

# Improving efficiency of inferences in randomized clinical trials using auxiliary covariates

Min Zhang\*, Anastasios A. Tsiatis, and Marie Davidian

Department of Statistics, North Carolina State University, Raleigh, North Carolina  
27695-8203, U.S.A.

\**email*: mzhang4@stat.ncsu.edu

**SUMMARY.** The primary goal of a randomized clinical trial is to make comparisons among two or more treatments. For example, in a two-arm trial with continuous response, the focus may be on the difference in treatment means; with more than two treatments, the comparison may be based on pairwise differences. With binary outcomes, pairwise odds-ratios or log-odds ratios may be used. In general, comparisons may be based on meaningful parameters in a relevant statistical model. Standard analyses for estimation and testing in this context typically are based on the data collected on response and treatment assignment only. In many trials, auxiliary baseline covariate information may also be available, and it is of interest to exploit these data to improve the efficiency of inferences. Taking a semiparametric theory perspective, we propose a broadly-applicable approach to adjustment for auxiliary covariates to achieve more efficient estimators and tests for treatment parameters in the analysis of randomized clinical trials. Simulations and applications demonstrate the performance of the methods.

**KEY WORDS:** Covariate adjustment; Hypothesis test;  $k$ -arm trial; Kruskal-Wallis test; Log-odds ratio; Longitudinal data; Semiparametric theory.

## 1. Introduction

In randomized clinical trials, the primary objective is to compare two or more treatments on the basis of an outcome of interest. Along with treatment assignment and outcome, baseline auxiliary covariates may be recorded on each subject, including demographical and physiological characteristics, prior medical history, and baseline measures of the outcome. For example, the international Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) study (Harrington, 1998) in subjects with acute coronary syndromes compared the anti-coagulant Integrilin plus heparin and aspirin to heparin and aspirin alone (control) on the basis of the binary endpoint death or myocardial infarction at 30 days. Similarly, AIDS Clinical Trials Group (ACTG) 175 (Hammer et al., 1996) randomized HIV-infected subjects to four antiretroviral regimens with equal probabilities, and an objective was to compare measures of immunological status under the three newer treatments to those under standard zidovudine (ZDV) monotherapy. In both studies, in addition to the endpoint, substantial auxiliary baseline information was collected.

Ordinarily, the primary analysis is based only on the data on outcome and treatment assignment. However, if some of the auxiliary covariates are associated with outcome, precision may be improved by “adjusting” for these relationships (e.g., Pocock et al., 2002), and there is an extensive literature on such covariate adjustment (e.g., Senn, 1989; Hauck, Anderson, and Marcus, 1998; Koch et al., 1998; Tangen and Koch, 1999; Lesaffre and Senn, 2003; Grouin, Day, and Lewis, 2004). Much of this work focuses on inference on the difference of two means and/or on adjustment via a regression model for mean outcome as a function of treatment assignment and covariates. In the special case of the difference of two treatment means, Tsiatis et al. (2007) proposed an adjustment method that follows from application of the theory of semiparametrics (e.g., van der Laan and Robins, 2003; Tsiatis, 2006) by Leon, Tsiatis, and Davidian (2003) to the related problem of “pretest-posttest” analysis,

from which the form of the “optimal” (most precise) estimator for the treatment mean difference, adjusting for covariates, emerges readily. This approach separates estimation of the treatment difference from the adjustment, which may lessen concerns over bias that could result under regression-based adjustment because of the ability to inspect treatment effect estimates obtained simultaneously with different combinations of covariates and “to focus on the covariate model that best accentuates the estimate” (Pocock et al., 2002, p. 2925).

In this paper, we expand on this idea by developing a broad framework for covariate adjustment in settings with two or more treatments and general outcome summary measures (e.g., log-odds ratios) by appealing to the theory of semiparametrics. The resulting methods seek to use the available data as efficiently as possible while making as few assumptions as possible. In Section 2, we present a semiparametric model framework involving parameters relevant to making general treatment comparisons. Using the theory of semiparametrics, we derive the class of estimating functions for these parameters in Section 3 and in Section 4 demonstrate how these results lead to practical estimators. This development suggests a general approach to adjusting any test statistic for making treatment comparisons to increase efficiency, described in Section 5. Performance of the proposed methods is evaluated in simulation studies in Section 6 and is shown in representative applications in Section 7.

## 2. Semiparametric Model Framework

Denote the data from a  $k$ -arm randomized trial,  $k \geq 2$ , as  $(Y_i, X_i, Z_i)$ ,  $i = 1, \dots, n$ , independent and identically distributed (iid) across  $i$ , where, for subject  $i$ ,  $Y_i$  is outcome;  $X_i$  is the vector of all available auxiliary baseline covariates; and  $Z_i = g$  indicates assignment to treatment group  $g$  with known randomization probabilities  $P(Z = g) = \pi_g$ ,  $g = 1, \dots, k$ ,  $\sum_{g=1}^k \pi_g = 1$ . Randomization ensures that  $Z \perp\!\!\!\perp X$ , where “ $\perp\!\!\!\perp$ ” means “independent of.”

Let  $\beta$  denote a vector of parameters involved in making treatment comparisons under a specified statistical model. For example, in a two-arm trial, for a continuous real-valued

response  $Y$ , a natural basis for comparison is the difference in means for each treatment,  $E(Y | Z = 2) - E(Y | Z = 1)$ , represented directly as  $\beta_2$  in the model

$$E(Y | Z) = \beta_1 + \beta_2 I(Z = 2), \quad \beta_1 = E(Y | Z = 1), \quad \beta = (\beta_1, \beta_2)^T. \quad (1)$$

In a three-arm trial, we may consider the model

$$E(Y | Z) = \beta_1 I(Z = 1) + \beta_2 I(Z = 2) + \beta_3 I(Z = 3), \quad \beta = (\beta_1, \beta_2, \beta_3)^T. \quad (2)$$

In contrast to (1), we have parameterized (2) equivalently in terms of the three treatment means rather than differences relative to a reference treatment, and treatment comparisons may be based on pairwise contrasts among elements of  $\beta$ . For binary outcome  $Y = 0$  or  $1$ , where  $Y = 1$  indicates the event of interest, we may consider for a  $k$ -arm trial

$$\text{logit}\{E(Y | Z)\} = \text{logit}\{P(Y = 1 | Z)\} = \beta_1 + \beta_2 I(Z = 2) + \dots + \beta_k I(Z = k), \quad (3)$$

where  $\text{logit}(p) = \log\{p/(1 - p)\}$ ;  $\beta = (\beta_1, \dots, \beta_k)^T$ ; and the log-odds ratio for treatment  $g$  relative to treatment 1 is  $\beta_g$ ,  $g = 2, \dots, k$ .

If  $Y_i$  is a vector of continuous longitudinal responses  $Y_{ij}$ ,  $j = 1, \dots, m_i$ , at times  $t_{i1}, \dots, t_{im_i}$ , response-time profiles in a two-arm trial might be described by the simple linear mixed model

$$Y_{ij} = \alpha + \{\beta_1 + \beta_2 I(Z_i = 2)\}t_{ij} + b_{0i} + b_{1i}t_{ij} + e_{ij}, \quad (b_{0i}, b_{1i})^T \stackrel{iid}{\sim} \mathcal{N}(0, D), \quad e_{ij} \stackrel{iid}{\sim} \mathcal{N}(0, \sigma_e^2), \quad (4)$$

where  $\beta = (\beta_1, \beta_2)^T$ , and  $\beta_2$  is the difference in mean slope between the two treatments; extension to  $k > 2$  treatment groups is straightforward. Alternatively, instead of considering the fully parametric model (4), one might make no assumption beyond

$$E(Y_{ij} | Z_i) = \alpha + \{\beta_1 + \beta_2 I(Z_i = 2)\}t_{ij}, \quad j = 1, \dots, m_i, \quad (5)$$

leaving remaining features of the distribution of  $Y$  given  $Z$  unspecified. For binary  $Y_{ij}$ , the marginal model  $\text{logit}\{E(Y_{ij} | Z_i)\} = \alpha + \{\beta_1 + \beta_2 I(Z_i = 2)\}t_{ij}$  might be adopted.

In all of (1)–(5),  $\beta$  ( $p \times 1$ ) is a parameter involved in making treatment comparisons in a model describing aspects of the conditional distribution of  $Y$  given  $Z$  and is of central interest. In addition to  $\beta$ , models like (4) and (5) depend on a vector of parameters  $\gamma$ , say;

e.g., in (4),  $\gamma = \{\alpha, \sigma_e^2, \text{vech}(D)^T\}^T$ ; and  $\gamma = \alpha$  in (5). In general, we define  $\theta = (\beta^T, \gamma^T)^T$  ( $r \times 1$ ), recognizing that models like (1)–(3) do not involve an additional  $\gamma$ , so that  $\theta = \beta$ .

For these and similar models, consistent, asymptotically normal estimators for  $\theta$ , and hence for  $\beta$  and functions of its elements reflecting treatment comparisons, based on the data  $(Y_i, Z_i)$ ,  $i = 1, \dots, n$ , only and thus “unadjusted” for covariates, are readily available. Unadjusted, large-sample tests of null hypotheses of “no treatment effects” are also well-established. The difference of sample means is the obvious such estimator for  $\beta_2$  in (1) and is efficient (i.e., has smallest asymptotic variance) among estimators depending only on these data, and a test of  $H_0 : \beta_2 = 0$  may be based on the usual  $t$  statistic. Similarly, the maximum likelihood estimator (MLE) for  $\beta_2$  in (4) and associated tests may be obtained from standard mixed model software. For  $k > 2$ , pairwise and global comparisons are possible; e.g., in (2), the sample means are efficient estimators for each element of  $\beta$ , and a test of  $H_0 : \beta_1 = \beta_2 = \beta_3$  may be based on the corresponding two-degree-of-freedom Wald statistic.

As noted in Section 1, the standard approach in practice for covariate adjustment, thus using all of  $(Y_i, X_i, Z_i)$ ,  $i = 1, \dots, n$ , is based on regression models for mean outcome as a function of  $X$  and  $Z$ . E.g., for  $k = 2$  and continuous  $Y$ , a popular such estimator for  $\beta_2$  in (1) is the ordinary least squares (OLS) estimator for  $\phi$  in the analysis of covariance model

$$E(Y | X, Z) = \alpha_0 + \alpha_1^T X + \phi I(Z = 2); \quad (6)$$

extension to  $k > 2$  treatments is immediate. See Tsiatis et al. (2007, Section 3) for discussion of related estimators for  $\beta_2$  in the particular case of (1). If (6) is the correct model for  $E(Y | X, Z)$ , then  $\phi$  and  $\beta_2$  in (1) coincide, and, moreover, the OLS estimator for  $\phi$  in (6) is a consistent estimator for  $\beta_2$  that is generally more precise than the usual unadjusted estimator, even if (6) is not correct (e.g., Yang and Tsiatis, 2001). For binary  $Y$ , covariate adjustment is often carried out based on the logistic regression model

$$\text{logit}\{E(Y | X, Z)\} = \text{logit}\{P(Y = 1) | X, Z\} = \alpha_0 + \alpha_1^T X + \phi I(Z = 2), \quad (7)$$

where the MLE of  $\phi$  is taken as the adjusted estimator for the log-odds ratio  $\beta_2$  in (3) with  $k = 2$ . In (7),  $\phi$  is the log-odds ratio conditional on  $X$ , assuming this quantity is constant for all  $X$ . This assumption may or may not be correct; even if it were,  $\phi$  is generally different from  $\beta_2$  in (3). Tsiatis et al. (2007, Section 2) discuss this point in more detail.

To derive alternative methods, we begin by describing our assumed semiparametric statistical model for the full data  $(Y, X, Z)$ , which is a characterization of the class of all joint densities for  $(Y, X, Z)$  that could have generated the data. We seek methods that perform well over as large a class as possible; thus, we assume that densities in this class involve no restrictions beyond the facts that  $Z \perp\!\!\!\perp X$ , guaranteed by randomization; that  $\pi_g = P(Z = g)$ ,  $g = 1, \dots, k$ , are known; and that  $\beta$  is defined through a specification on the conditional distribution of  $Y$  given  $Z$  as in (1)–(5). We thus first describe the conditional density of  $Y$  given  $Z$ . Under (3) and (4), this density is completely specified in terms of  $\theta$ , while (5) describes only one aspect of the conditional distribution, the mean, in terms of  $\theta$ , and (1) and (2) make no restrictions on the conditional distribution of  $Y$  given  $Z$ . To represent all such situations, we assume that this conditional density may be written as  $p_{Y|Z}(y|z; \theta, \eta)$ , where  $\eta$  is an additional nuisance parameter possibly needed to describe the density fully. For (3) and (4),  $\eta$  is null, as the density is already entirely characterized. For (1), (2), and (5),  $\eta$  is infinite-dimensional, as these specifications do not impose any additional constraints on what the density might be, so any density consistent with these models is possible.

Under the above conditions, we assume that all joint densities for  $(Y, X, Z)$  may be written, in obvious notation, as  $p_{Y,X,Z}(y, x, z; \theta, \eta, \psi, \pi) = p_{Y,X|Z}(y, x | z; \theta, \eta, \psi)p_Z(z; \pi)$ , where  $p_Z(z; \pi)$  is completely specified, as  $\pi = (\pi_1, \dots, \pi_k)^T$  is known, and satisfy the constraints

$$(i) \quad \int p_{Y,X|Z}(y, x | z; \theta, \eta, \psi) dx = p_{Y|Z}(y|z; \theta, \eta), \quad (8)$$

$$(ii) \quad \int p_{Y,X|Z}(y, x | z; \theta, \eta, \psi) dy = p_X(x). \quad (9)$$

The joint density involves an additional, possibly infinite-dimensional nuisance parameter

$\psi$ , needed to include in the class all joint densities satisfying (i) and (ii). Here,  $p_X(x)$  is any arbitrary marginal density for the covariates, and (ii) follows because  $Z \perp\!\!\!\perp X$ . In Web Appendix A, we demonstrate that a rich class of joint distributions for  $(Y, X, Z)$  may be identified such that  $X$  is correlated with  $Y$  and  $Z \perp\!\!\!\perp X$  [condition (ii)] that also satisfy condition (i). Because the joint density involves both finite (parametric) and infinite-dimensional components, it represents a semiparametric statistical model (see Tsiatis, 2006, Section 1.2).

### 3. Estimating Functions for Treatment Parameters Using Auxiliary Covariates

We now derive consistent, asymptotically normal estimators for  $\theta$ , and hence  $\beta$ , in a given  $p_{Y|Z}(y|z; \theta, \eta)$  and using the iid data  $(Y_i, X_i, Z_i)$ ,  $i = 1 \dots, n$ , under the semiparametric framework satisfying (8) and (9). To do this, we identify the class of all estimating functions for  $\theta$  based on  $(Y, X, Z)$  leading to all estimators for  $\theta$  that are consistent and asymptotically normal under this framework. An estimating function is a function of a single observation and parameters used to construct estimating equations yielding an estimator for the parameters.

When the data on auxiliary covariates  $X$  are not taken into account, estimating functions for  $\theta$  based only on  $(Y, Z)$  in models like those in (1)–(5) leading to consistent, asymptotically normal estimators are well known. For example, the OLS estimator for  $\theta = \beta$  in the linear regression model (1) may be obtained by considering the estimating function

$$m(Y, Z; \theta) = \{1, I(Z = 2)\}^T \{Y - \beta_1 - \beta_2 I(Z = 2)\}, \quad \theta = \beta = (\beta_1, \beta_2)^T. \quad (10)$$

and solving the estimating equation  $\sum_{i=1}^n m(Y_i, Z_i; \theta) = 0$  in  $\theta$ . The OLS estimator for  $\beta_2$  so obtained equals the usual difference in sample means. Likewise, with  $\theta = \beta = (\beta_1, \dots, \beta_k)^T$  and  $\text{expit}(u) = \exp(u)/\{1+\exp(u)\}$ , the usual logistic regression MLE for  $\beta$  in (3) is obtained by solving  $\sum_{i=1}^n m(Y_i, Z_i; \theta) = 0$ , where the estimating function  $m(Y, Z; \theta)$  is equal to

$$\{1, I(Z = 2), \dots, I(Z = k)\}^T [Y - \text{expit}\{\beta_1 + \beta_2 I(Z = 2) + \dots + \beta_k I(Z = k)\}]. \quad (11)$$

The estimating functions (10) and (11) are unbiased; i.e., have mean zero assuming that (1) and (3), respectively, are correct. Under regularity conditions, unbiased estimating functions

lead to consistent, asymptotically normal estimators (e.g., Carroll et al., 2006, Section A.6).

Our key result is that, given a semiparametric model  $p_{Y,X,Z}(y, x, z; \theta, \eta, \psi, \pi)$  based on a specific  $p_{Y|Z}(y|z; \theta, \eta)$  and satisfying (8) and (9), and given a fixed unbiased estimating function  $m(Y, Z; \theta)$  ( $r \times 1$ ) for  $\theta$ , such as (10) or (11), members of the class of all unbiased estimating functions for  $\theta$ , and hence  $\beta$ , using all of  $(Y, X, Z)$  may be written as

$$m^*(Y, X, Z; \theta) = m(Y, Z; \theta) - \sum_{g=1}^k \{I(Z = g) - \pi_g\} a_g(X), \quad (12)$$

where  $a_g(X)$ ,  $g = 1, \dots, k$ , are arbitrary  $r$ -dimensional functions of  $X$ . Because  $Z \perp\!\!\!\perp X$ , the second term in (12) has mean zero; thus, (12) is an unbiased estimating function based on  $(Y, X, Z)$ . When  $a_g(X) \equiv 0$ ,  $g = 1, \dots, k$ , (12) reduces to the original estimating function, which does not take account of auxiliary covariates, and solving  $\sum_{i=1}^n m(Y_i, Z_i; \theta) = 0$  leads to the unadjusted estimator  $\hat{\theta} = (\hat{\beta}^T, \hat{\gamma}^T)^T$  to which it corresponds. Otherwise, (12) ‘‘augments’’  $m(Y, Z; \theta)$  by the second term. With appropriate choice of the  $a_g(X)$ , the augmentation term exploits correlations between  $Y$  and elements of  $X$  to yield an estimator for  $\theta$  solving  $\sum_{i=1}^n m^*(Y_i, X_i, Z_i; \theta) = 0$  that is relatively more efficient than  $\hat{\theta}$ . The proof of (12) is based on applying principles of semiparametric theory and is given in Web Appendix B.

Full advantage of this result may be taken by identifying the optimal estimating function within class (12), that for which the elements of the corresponding estimator for  $\theta$  have smallest asymptotic variance. This estimator for  $\beta$  thus yields the greatest efficiency gain over  $\hat{\beta}$  among all estimators with estimating functions in class (12) and hence more efficient inferences on treatment comparisons. By standard arguments for M-estimators (e.g., Stefanski and Boos, 2002), an estimator for  $\theta$  corresponding to an estimating function of form (12) is consistent and asymptotically normal with asymptotic covariance matrix

$$\Delta^{-1} \Gamma (\Delta^{-1})^T, \quad \Gamma = E \left( \left[ m(Y, Z; \theta_0) - \sum_{g=1}^k \{I(Z = g) - \pi_g\} a_g(X) \right]^{\otimes 2} \right), \quad (13)$$

where  $\theta_0$  is the true value of  $\theta$ ,  $u^{\otimes 2} = uu^T$ , and  $\Delta = E \{ -\partial / \partial \theta^T m(Y, Z; \theta) \} |_{\theta = \theta_0}$ . Thus, to find the optimal estimating function, one need only consider  $\Gamma$  in (13) and determine

$a_g(X)$ ,  $g = 1, \dots, k$ , leading to  $\Gamma_{opt}$ , say, such that  $\Gamma - \Gamma_{opt}$  is nonnegative definite. For given  $m(Y, Z; \theta)$ , it is shown in Web Appendix C that  $\Gamma_{opt}$  takes  $a_g(X) = E\{m(Y, Z; \theta) | X, Z = g\}$ ,  $g = 1, \dots, k$ . Thus, in general, the optimal estimator in class (12) is the solution to

$$\sum_{i=1}^n \left[ m(Y_i, Z_i; \theta) - \sum_{g=1}^k \{I(Z_i = g) - \pi_g\} E\{m(Y, Z; \theta) | X_i, Z = g\} \right] = 0. \quad (14)$$

In the case of  $\beta_2$  in (1), (14) yields the optimal estimator in (16) of Tsiatis et al. (2007).

#### 4. Implementation of Improved Estimators

The optimal estimator in class (12) solving (14) depends on the conditional expectations  $E\{m(Y, Z; \theta) | X_i, Z = g\}$ ,  $g = 1, \dots, k$ , the forms of which are of course unknown. Thus, to obtain practical estimators, we first consider a general adaptive strategy based on postulating regression models for these conditional expectations, which involves the following steps:

- (1) Solve the original estimating equation  $\sum_{i=1}^n m(Y_i, Z_i; \theta) = 0$  to obtain the unadjusted estimator  $\hat{\theta}$ . For each subject  $i$ , obtain the values  $m(Y_i, g; \hat{\theta})$  for each  $g = 1, \dots, k$ .
- (2) Note that the  $m(Y_i, g; \hat{\theta})$  are  $(r \times 1)$ . For each treatment group  $g = 1, \dots, k$  separately, based on the  $r$ -variate “data”  $m(Y_i, g; \hat{\theta})$  for  $i$  in group  $g$ , develop a parametric regression model  $E\{m(Y, g; \hat{\theta}) | X, Z = g\} = q_g(X, \zeta_g) = \{q_{g1}(X, \zeta_{g1}), \dots, q_{gr}(X, \zeta_{gr})\}^T$ , where  $\zeta_g = (\zeta_{g1}^T, \dots, \zeta_{gr}^T)^T$ ; i.e., such that  $q_{gu}(X, \zeta_{gu})$ ,  $u = 1, \dots, r$ , are regression models for each component of  $m(Y, g; \hat{\theta})$ . We recommend an approach analogous to that in Leon et al. (2003, Section 4) where the  $q_{gu}(X, \zeta_{gu})$  are represented as  $\{1, c_{gu}^T(X)\}^T \zeta_{gu}$ ,  $u = 1, \dots, r$ , and  $c_{gu}(X)$  are vectors of basis functions in  $X$  that may include polynomial terms in elements of  $X$ , interaction terms, splines, and so on. This offers considerable latitude for achieving representations that can approximate the true conditional expectations, and hence predictions derived from them, well. We also recommend obtaining estimates  $\hat{\zeta}_g = (\hat{\zeta}_{g1}^T, \dots, \hat{\zeta}_{gr}^T)^T$  via OLS separately for each  $u = 1, \dots, r$ , as, by a generalization of the argument in Leon et al. (2003, Section 4), this will yield the most efficient estimator for  $\theta$  in step (3) below when the  $q_g(X, \zeta_g)$  are of this form.

For each subject  $i = 1, \dots, n$ , form predicted values  $q_g(X_i, \widehat{\zeta}_g)$  for each  $g = 1, \dots, k$ .

(3) Using the predicted values from step (2), form the augmented estimating equation

$$\sum_{i=1}^n \left[ m(Y_i, Z_i; \theta) - \sum_{g=1}^k \{I(Z_i = g) - \pi_g\} q_g(X_i, \widehat{\zeta}_g) \right] = 0 \quad (15)$$

and solve for  $\theta$  to obtain the final, adjusted estimator  $\widetilde{\theta}$ . We recommend substituting  $\widehat{\pi}_g = n^{-1} \sum_{i=1}^n I(Z_i = g)$  for  $\pi_g$ ,  $g = 1, \dots, k$ , in (15).

The foregoing three-step algorithm applies to very general  $m(Y, Z; \theta)$ . Often,

$$m(Y, Z; \theta) = A(Z, \theta) \{Y - f(Z; \theta)\} \quad (16)$$

for some  $A(Z, \theta)$  with  $r$  rows and some  $f(Z, \theta)$ , as in (10) and (11). Here, a simpler, “direct” implementation strategy is possible. Note that  $E\{m(Y, Z; \theta) | X, Z = g\} = A(g, \theta) \{E(Y | X, Z = g) - f(g; \theta)\}$ ; thus, for each  $g = 1, \dots, k$ , based on the data  $(Y_i, X_i)$  for  $i$  in group  $g$ , we may postulate parametric regression models  $E(Y | X, Z = g) = q_g^*(X, \zeta_g) = \{1, c_g^T(X)\} \zeta_g$ , for a vector of basis functions  $c_g(X)$ , and obtain OLS estimators  $\widehat{\zeta}_g$ ,  $g = 1, \dots, k$ . Then form for each  $i = 1, \dots, n$  the corresponding predicted values for  $E\{m(Y, Z; \theta) | X, Z = g\}$  as  $q_g(X_i, \widehat{\zeta}_g, \theta) = A(g, \theta) \{q_g^*(X_i, \widehat{\zeta}_g) - f(g, \theta)\}$ , where we emphasize that, here,  $q_g(X_i, \widehat{\zeta}_g, \theta)$ ,  $g = 1, \dots, k$ , are functions of  $\theta$ . Substituting the  $q_g(X_i, \widehat{\zeta}_g, \theta)$  (and  $\widehat{\pi}_g$ ,  $g = 1, \dots, k$ ) in (15), solve the resulting equation in  $\theta$  directly to obtain  $\widetilde{\theta}$ .

Several observations follow from semiparametric theory. Although we advocate representing  $E\{m(Y, Z; \theta) | X, Z = g\}$  or  $E(Y | X, Z = g)$ ,  $g = 1, \dots, k$ , by parametric models, consistency and asymptotic normality of  $\widetilde{\theta}$  hold regardless of whether or not these models are correct specifications of the true  $E\{m(Y, Z; \theta) | X, Z = g\}$  or  $E(Y | X, Z = g)$ . Thus, the proposed methods are not parametric, as their validity does not depend on parametric assumptions. The theory also shows that, in either implementation strategy, if the  $q_g$  are specified and fitted via OLS as described above, then, by an argument similar to that in Leon

et al. (2003, Section 4),  $\tilde{\theta}$  is guaranteed to be relatively more efficient than the corresponding unadjusted estimator. Moreover, under these conditions, although  $\zeta_g$  and  $\pi_g$ ,  $g = 1, \dots, k$ , are estimated,  $\tilde{\theta}$  will have the same properties asymptotically as the estimator that could be obtained if the limits in probability of the  $\hat{\zeta}_g$  were known and substituted in (14) and if the true  $\pi_g$  were substituted, regardless of whether the  $q_g$  are correct or not. In the direct strategy, if  $Y$  is discrete, it is natural to instead posit the  $q_g^*(X, \zeta_g)$  as generalized linear models; e.g., logistic regression for binary  $Y$ , and fit these using iteratively reweighted least squares (IRWLS). Although the previous statements do not necessarily hold exactly, in our experience, they hold approximately. Regardless of whether or not the  $q_g$  are represented by parametric linear models and fitted by OLS, if the representation chosen contains the true form of  $E\{m(Y, Z; \theta) | X, Z = g\}$  or  $E(Y | X, Z = g)$ , respectively, then  $\tilde{\theta}$  is asymptotically equivalent to the optimal estimator solving (14). In general, the closer the predictions from these models are to the true functions of  $X$ , the closer  $\tilde{\theta}$  will come to achieving the precision of the optimal estimator. Because  $\beta$  is contained in  $\theta$ , all of these results apply equally to  $\tilde{\beta}$ .

Because in either implementation strategy  $\tilde{\theta}$  solving (15) is an M-estimator, the sandwich method (e.g., Stefanski and Boos, 2002) may be used to obtain a sampling covariance matrix for  $\tilde{\theta}$ , from which standard errors for functions of  $\tilde{\beta}$  may be derived. This matrix is of form (13), with expectations replaced by sample averages evaluated at the estimates and  $a_g(X)$  replaced by the predicted values using the  $q_g$ ,  $g = 1, \dots, k$ .

The regression models  $q_g$  in either implementation, which are the mechanism by which covariate adjustment is incorporated, are determined separately by treatment group and are developed independently of reference to the adjusted estimator  $\tilde{\beta}$ . Thus, estimation of  $\beta$  could be carried out by a generalization of the “principled” strategy proposed by Tsiatis et al. (2007, Section 4) in the context of a two-arm trial and inference on  $\beta_2$  in (1), where development of the models  $q_g$  would be undertaken by analysts different from those responsible

for obtaining  $\tilde{\theta}$  to lessen concerns over possible bias, as discussed in Section 1.

## 5. Improved Hypothesis Tests

The principles in Section 3 may be used to construct more powerful tests of null hypotheses of no treatment effects by exploiting auxiliary covariates. The key is that, under a general null hypothesis  $H_0$  involving  $s$  degrees of freedom, a usual test statistic  $T_n$ , say, based on the data  $(Y_i, Z_i)$ ,  $i = 1, \dots, n$ , only is asymptotically equivalent to a quadratic form; i.e.,

$$T_n \approx \left\{ n^{-1/2} \sum_{i=1}^n \ell(Y_i, Z_i) \right\}^T \Sigma^{-1} \left\{ n^{-1/2} \sum_{i=1}^n \ell(Y_i, Z_i) \right\}, \quad (17)$$

where  $\ell(Y, Z)$  is a  $(s \times 1)$  function of  $(Y, Z)$ , discussed further below, such that  $E_{H_0}\{\ell(Y, Z)\} = 0$ , with  $E_{H_0}$  denoting expectation under  $H_0$ ; and  $\Sigma = E_{H_0}\{\ell(Y, Z)^{\otimes 2}\}$ .

When the notion of “treatment effects” may be formulated in terms of  $\beta$  in a model like (1)–(5), the null hypothesis is typically of the form  $H_0 : C\beta = 0$ , where  $C$  is a  $(s \times p)$  contrast matrix. E.g., in (2),  $C$  is  $(2 \times 3)$  with rows  $(1, -1, 0)$  and  $(1, 0, -1)$ . When inference on  $H_0$  is based on a Wald test of the form  $T_n = (C\hat{\beta})^T (n^{-1}\hat{\Sigma})^{-1} C\hat{\beta}$ , where  $\hat{\beta}$  is an unadjusted estimator corresponding to an estimating function  $m(Y, Z; \theta)$ , and  $n^{-1}\hat{\Sigma}$  is an estimator for the covariance matrix of  $C\hat{\beta}$ ,  $\ell(Y, Z) = CBm(Y, Z, \theta_0)$ . Here,  $B$  is the  $(p \times r)$  matrix equal to the first  $p$  rows of  $[E_{H_0}\{-\partial/\partial\theta^T m(Y_i, Z_i; \theta)\}|_{\theta=\theta_0}]^{-1}$ , and  $\theta_0$  is the value of  $\theta$  under  $H_0$ .

In other situations, the null hypothesis may not refer to a parameter like  $\beta$  in a given model. For example, the null hypothesis for a  $k$ -arm trial may be  $H_0 : S_1(u) = \dots = S_k(u) = S(u)$ , where  $S_g(u) = 1 - P(Y \leq u | Z = g)$ , and  $S(u) = 1 - P(Y \leq u)$ . A popular test in this setting is the Kruskal-Wallis test, which reduces to the Wilcoxon rank sum test for  $k = 2$ . Letting  $n_g = \sum_{i=1}^n I(Z_i = g)$  and  $\bar{R}_g$  be the average of the overall ranks for subjects in group  $g$ , the test statistic is  $T_n = 12 \sum_{g=1}^k n_g \{\bar{R}_g - (n+1)/2\}^2 / \{n(n+1)\}$ . By results in van der Vaart (1998, Section 12.2), it may be shown that  $T_n$  is asymptotically equivalent to a statistic of the form (17), where  $\ell(Y, Z)$  is  $(k-1 \times 1)$  with  $g$ th element  $\{I(Z = g) - \pi_g\}\{S(Y) - 1/2\}$ .

To motivate the proposed more powerful tests, we consider the behavior of  $T_n$  in (17) under a sequence of local alternatives  $H_{1n}$  converging to  $H_0$  at rate  $n^{-1/2}$ . Typically, under suitable regularity conditions,  $n^{-1/2} \sum_{i=1}^n \ell(Y_i, Z_i)$  in (17) converges under the sequence  $H_{1n}$  to a  $\mathcal{N}(\tau, \Sigma)$  random vector for some  $\tau$ , so that  $T_n$  has asymptotically a noncentral  $\chi_s^2$  distribution with noncentrality parameter  $\tau^T \Sigma^{-1} \tau$ . To obtain a more powerful test, then, we wish to construct a test statistic with noncentrality parameter as large as possible. Based on the developments in Section 3, we consider test statistics of the form

$$T_n^* = \left\{ n^{-1/2} \sum_{i=1}^n \ell^*(Y_i, X_i, Z_i) \right\}^T \Sigma^{*-1} \left\{ n^{-1/2} \sum_{i=1}^n \ell^*(Y_i, X_i, Z_i) \right\}, \quad (18)$$

$$\ell^*(Y, X, Z) = \ell(Y, Z) - \sum_{g=1}^k \{I(Z = g) - \pi_g\} a_g(X), \quad (19)$$

where  $\Sigma^* = E_{H_0} \{\ell^*(Y, X, Z)^{\otimes 2}\}$ . The second term in (19) has mean zero by randomization under  $H_0$  or any alternative. Accordingly, it follows under the sequence of alternatives  $H_{1n}$  that  $n^{-1/2} \sum_{i=1}^n \ell^*(Y_i, X_i, Z_i)$  converges in distribution to a  $\mathcal{N}(\tau, \Sigma^*)$  random vector, so that  $T_n^*$  in (18) has an asymptotic  $\chi_s^2$  distribution with noncentrality parameter  $\tau^T \Sigma^{*-1} \tau$ .

These results suggest that, to maximize the noncentrality parameter and thus power, we wish to find the particular  $\Sigma^*$ ,  $\Sigma_{opt}^*$ , say, that makes  $\Sigma_{opt}^{*-1} - \Sigma^{*-1}$  non-negative definite for all  $\Sigma^*$ , which is equivalent to making  $\Sigma^* - \Sigma_{opt}^*$  non-negative definite for all  $\Sigma^*$ . This corresponds to finding the optimal choice of  $a_g(X)$ ,  $g = 1, \dots, k$ , in (19). By an argument similar to that leading to (14), the optimal choice is  $a_g(X) = E\{\ell(Y, Z)|X, Z = g\}$  for  $g = 1, \dots, k$ .

These developments suggest an implementation strategy analogous to that in Section 4:

- (1) For the test statistic  $T_n$ , determine  $\ell(Y, Z)$  and substitute sample quantities for any unknown parameters to obtain  $\widehat{\ell}(Y_i, Z_i)$ ,  $i = 1, \dots, n$ . E.g., for  $H_0 : C\beta = 0$  in model (2), with  $C$  ( $2 \times 3$ ) as above,  $m(Y, Z, \theta) = \{I(Z = 1), I(Z = 2), I(Z = 3)\}^T \{Y - \beta_1 I(Z = 1) - \beta_2 I(Z = 2) - \beta_3 I(Z = 3)\}$ ,  $\theta = (\beta_1, \beta_2, \beta_3)^T$ . Under  $H_0$ ,  $\theta_0 = (\mu, \mu, \mu)^T$ ,

say, so that  $m(Y, Z, \theta_0) = \{I(Z = 1), I(Z = 2), I(Z = 3)\}^T(Y - \mu)$ , and

$$\ell(Y, Z) = \begin{pmatrix} \pi_1^{-1}I(Z = 1) - \pi_2^{-1}I(Z = 2) \\ \pi_1^{-1}I(Z = 1) - \pi_3^{-1}I(Z = 3) \end{pmatrix} (Y - \mu). \quad (20)$$

As  $\mu$  is unknown,  $\widehat{\ell}(Y_i, Z_i)$  is obtained by substituting  $n^{-1} \sum_{i=1}^n Y_i$  for  $\mu$ . We recommend substituting  $\widehat{\pi}_g$  for  $\pi_g$ ,  $g = 1, 2, 3$ , in (20), as above. Similarly, for the Kruskal-Wallis test,  $\widehat{\ell}(Y_i, Z_i) = \{I(Z = g) - \widehat{\pi}_g\}\{\widehat{S}(Y_i) - 1/2\}$ ,  $\widehat{S}(u) = n^{-1} \sum_{i=1}^n I(Y_i \geq u)$ .

- (2) For each treatment group  $g = 1, \dots, k$  separately, treating the  $\widehat{\ell}(Y_i, Z_i)$  for subjects  $i$  in group  $g$  as  $s$ -variate “data,” develop a regression model  $E\{\widehat{\ell}(Y, g)|X, Z = g\} = q_g(X, \zeta_g) = \{q_{g1}(X, \zeta_{g1}) \dots, q_{gs}(X, \zeta_{gs})\}^T$  by representing each component  $q_{gu}(X, \zeta_{gu})$ ,  $u = 1, \dots, s$ , by the parametric “basis function” approach in Section 4; estimate each  $\zeta_{gu}$  by OLS to obtain  $\widehat{\zeta}_g$ ; and form predicted values  $q_g(X_i, \widehat{\zeta}_g)$ ,  $i = 1, \dots, n$ .

- (3) Using the predicted values from step (2), form

$$\widehat{\ell}^*(Y_i, X_i, Z_i) = \widehat{\ell}(Y_i, Z_i) - \sum_{g=1}^k \{I(Z_i = g) - \widehat{\pi}_g\} q_g(X_i, \widehat{\zeta}_g) \quad (21)$$

and substitute these values into (18). Estimate  $\Sigma^*$  in (18) by  $\widehat{\Sigma}^* = n^{-1} \sum_{i=1}^n \widehat{\ell}^*(Y_i, X_i, Z_i)^{\otimes 2}$ .

Compare the resulting test statistic  $\widehat{T}_n^*$  to the  $\chi_s^2$  distribution.

As in Section 4, there is no effect asymptotically of estimating  $\zeta_g$  and  $\pi_g$ ,  $g = 1, \dots, k$ , so that  $\widehat{T}_n^*$  will achieve the same power asymptotically as if the limits in probability of  $\widehat{\zeta}_g$  and the true  $\pi_g$  were substituted. Notably, the test based on  $\widehat{T}_n^*$  will be asymptotically more powerful than the corresponding unadjusted test against any sequence of alternatives.

The approach of Tangen and Koch (1999) to modifying the Wilcoxon test for two treatments is in a similar spirit to this general approach.

## 6. Simulation Studies

### 6.1 Estimation

We report results of several simulations, each based on 5000 Monte Carlo data sets. Tsiatis et al. (2007, Section 6) carried out extensive simulations in the particular case of (1); thus, we focus here on estimation of quantities other than differences of treatment means.

In the first set of simulations, we considered  $k = 2$ , a binary response  $Y$ , and

$$\text{logit}\{E(Y|Z)\} = \beta_1 + \beta_2 I(Z = 2), \quad (22)$$

so that  $\beta_2$  is the log-odds ratio for treatment 2 relative to treatment 1, the parameter of interest; and  $\theta = \beta = (\beta_1, \beta_2)^T$ . For each scenario, we generated  $Z$  as Bernoulli with  $P(Z = 1) = P(Z = 2) = 0.5$  and covariates  $X = (X_1, \dots, X_8)^T$  such that  $X_1, X_3, X_8 \sim \mathcal{N}(0, 1)$ ;  $X_4$  and  $X_6$  were Bernoulli with  $P(X_4 = 1) = 0.3$  and  $P(X_6 = 1) = 0.5$ ; and  $X_2 = 0.2X_1 + 0.98U_1$ ,  $X_5 = 0.1X_1 + 0.2X_3 + 0.97U_2$ , and  $X_7 = 0.1X_3 + 0.99U_3$ , where  $U_\ell \sim \mathcal{N}(0, 1)$ ,  $\ell = 1, 2, 3$ . We then generated  $Y$  as Bernoulli according to  $\text{logit}\{P(Y = 1|Z = g, X)\} = \alpha_{0g} + \alpha_g^T X$ ,  $g = 1, 2$ , with  $\alpha_{0g}$  and  $\alpha_g$  chosen to yield mild, moderate, and strong association between  $Y$  and  $X$  within each treatment, as follows. Using the coefficient of determination  $R^2$  to measure the strength of association,  $R^2 = (0.18, 0.16)$  for treatments (1,2) in the “mild” scenario, with  $(\alpha_{01}, \alpha_{02}) = (0.25, -0.8)$ ,  $\alpha_1 = (0.8, 0.5, 0, 0, 0, 0, 0, 0)^T$ , and  $\alpha_2 = (0.3, 0.7, 0.3, 0.8, 0, 0, 0, 0)^T$ ;  $R^2 = (0.32, 0.33)$  in the “moderate” scenario, with  $(\alpha_{01}, \alpha_{02}) = (0.38, -0.8)$ ,  $\alpha_1 = (1.2, 1.0, 0, 0, 0, 0, 0, 0)^T$ , and  $\alpha_2 = (0.5, 1.3, 0.5, 1.5, 0, 0, 0, 0)^T$ ; and  $R^2 = (0.43, 0.41)$  in the “strong” scenario, with  $(\alpha_{01}, \alpha_{02}) = (0.8, -0.8)$ ,  $\alpha_1 = (1.5, 1.8, 0, 0, 0, 0, 0, 0)^T$  and  $\alpha_2 = (1.0, 1.3, 0.8, 2.5, 0, 0, 0, 0)^T$ . Thus, in all cases,  $X_1, \dots, X_4$  are covariates “important” for adjustment while  $X_5, \dots, X_8$  are “unimportant.” For each data set,  $n = 600$ , and, we fitted (22) by IRWLS to  $(Y_i, Z_i)$ ,  $i = 1, \dots, n$ , to obtain the unadjusted estimate of  $\beta$ . We also estimated  $\beta$  by the proposed methods using the direct implementation strategy, where the models  $q_g^*(X, \zeta_g)$  for each  $g = 1, 2$  in the augmentation term were developed six ways:

- Aug. 1  $q_g^*(X, \zeta_g) = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X) = \text{“true,”}$  fit by OLS
- Aug. 2  $q_g^*(X, \zeta_g) = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X) = X$ , fit by OLS
- Aug. 3  $\text{logit}\{q_g^*(X, \zeta_g)\} = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X) = \text{“true,”}$  fit by IRWLS
- Aug. 4  $\text{logit}\{q_g^*(X, \zeta_g)\} = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X) = X$ , fit by IRWLS
- Aug. 5  $q_g^*(X, \zeta_g) = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X)$  by OLS with forward selection
- Aug. 6  $\text{logit}\{q_g^*(X, \zeta_g)\} = \{1, c_g^T(X)\}^T \zeta_g$ ,  $c_g(X)$  by IRWLS with forward selection

where “true” means that  $c_g(X)$  contained only  $X_\ell$ ,  $\ell = 1, \dots, 4$ , for which the corresponding element of  $\alpha_g$  was not zero (i.e., using the “true important covariates” for each  $g$ ); and in Aug. 5 and 6 forward selection from linear terms in  $X_1, \dots, X_8$  for linear or logistic regression was used to determine each  $q_g^*(X, \zeta_g)$ , with entry criterion 0.05. Aug. 3, 4, and 6 demonstrate performance when nonlinear models and methods other than OLS are used. We also estimated  $\beta_2$  by estimating  $\phi$  in (7) via IRWLS two ways: Usual 1, where only the “important” covariates  $X_1, \dots, X_4$  were included in the model; and Usual 2, where the subset of  $X_1, \dots, X_8$  to include was identified via forward selection with entry criterion 0.05.

Table 1 shows modest to considerable gains in efficiency for the proposed estimators, depending on the strength of the association. The estimators are unbiased, and associated confidence intervals achieve the nominal level. In contrast, the usual adjustment based on (7) leads to biased estimation of  $\beta_2$ , considerable efficiency loss, and unreliable intervals. This is a consequence of the fact that  $\beta_2$  is an unconditional measure of treatment effect while  $\phi$  is defined conditional on  $X$ ; this distinction does not matter when the model for  $Y$  is linear but is important when it is nonlinear, as is (7) (see, e.g., Robinson et al., 1998).

In the second set of simulations, we again took  $k = 2$  and focused on  $\beta_2$ , the difference in treatment slopes in the linear mixed model (4). In each scenario, we generated for each  $i = 1, \dots, n = 200$   $Z_i$  as Bernoulli with  $P(Z = 1) = P(Z = 2) = 0.5$ ;  $X_{1i}, X_{2i}, X_{3i}$  as above; and subject-specific intercept  $\beta_{0i} = 0.5 + 0.2X_{1i} + 0.5X_{2i} + b_{0i}$  and slope  $\beta_{1i} = \alpha_{0g} + \alpha_{1g}X_{1i}^2 + \alpha_{2g}X_{2i} + \alpha_{13}X_{3i} + b_{1i}$ , where  $(\alpha_{01}, \alpha_{02}) = (1.0, 1.3)$ ,  $(b_{0i}, b_{1i})^T \sim \mathcal{N}(0, D)$ , with  $D_{11} = 1$ ,  $D_{12} = 0.2$ , and  $D_{22} = 0.4$ , so that  $\text{corr}(b_{0i}, b_{1i}) = 0.5$ . We generated  $m_i = 9, 10, 11$  with equal probabilities; took  $t_{ij} = 2(j - 1)$  for  $j = 1, \dots, m_i$ ; and generated  $Y_{ij} = \beta_{0i} + \beta_{1i}t_{ij} + e_{ij}$ ,  $j = 1, \dots, m_i$ , where  $e_{ij} \stackrel{iid}{\sim} \mathcal{N}(0, \sigma_e^2 = 16)$ . Writing  $\alpha_g = (\alpha_{1g}, \alpha_{2g}, \alpha_{3g})^T$ , we took  $\alpha_1 = (0.2, 0.2, 0)^T$  and  $\alpha_2 = (0.2, 0, 0.2)^T$ , yielding  $R^2$  values between subject-specific slopes and covariates of (0.11, 0.14) in the two groups, for “mild” association;  $\alpha_1 =$

$(0.13, 0.1, 0)^T$  and  $\alpha_2 = (0.13, 0, 0.15)^T$ ,  $R^2 = (0.24, 0.24)$ , for “moderate” association; and  $\alpha_1 = (0.28, 0.25, 0)^T$  and  $\alpha_2 = (0.28, 0, 0.25)^T$ ,  $R^2 = (0.36, 0.36)$ , for “strong” association. For each data set, we obtained the unadjusted estimate for  $\theta$  by fitting (4) using SAS `proc mixed` (SAS Institute, 2006). For (4),  $m(Y, Z; \theta)$  has components of form (16) for  $\alpha$  and  $\beta$  and more complicated components quadratic in  $Y$  for  $D$  and  $\sigma_e^2$ . For simplicity, because the estimators for  $(\alpha, \beta)$  and  $(D, \sigma_e^2)$  are uncorrelated, we fixed  $D$  and  $\sigma_e^2$  at the unadjusted analysis estimates in the components of  $m(Y, Z; \theta)$  for  $(\alpha, \beta)$ , as asymptotically this will not impact precision of the estimators for  $(\alpha, \beta)$ , and used the direct implementation strategy based on the components for  $(\alpha, \beta)$  only. We considered three variants on the proposed methods, all with each element of  $q_g^*(X, \zeta_g) = \{1, c_g^T(X)\}\zeta_g$  fitted by OLS: Aug 1., taking  $c_g(X) = (1, X_1^2, X_2, X_3)^T$ , corresponding to the form of the true relationship; Aug 2., with  $c_g(X) = (1, X_1, X_2, X_3)^T$ , so not exploiting the quadratic relationship in  $X_1$ ; and Aug 3., with  $c_g(X) = (1, X_1, X_1^2, X_2, X_3)^T$ , including an unneeded linear effect of  $X_1$ . Writing now  $X_i = (X_{1i}, X_{2i}, X_{3i})^T$ , we also estimated  $\beta_2$  by the estimate of  $\phi$  from fitting via `proc mixed` the linear mixed model  $Y_{ij} = \alpha_{00} + \alpha_{01}^T X_i + (\alpha_{10} + \alpha_{11}^T X_i + \phi Z_i)t_{ij} + b_{0i} + b_{1i}t_{ij} + e_{ij}$ , denoted as Usual; such a model, with linear covariate effects only, might be prespecified in a trial protocol (e.g., Grouin et al., 2004). Table 2 shows that the proposed methods lead to relatively more efficient estimators when quadratic terms in  $X_1$  are included in the  $q_g^*(X, \zeta_g)$ .

## 6.2 Testing

We carried out simulations based on 10,000 Monte Carlo data sets involving  $k = 3$  and the Kruskal-Wallis test. For each data set, we generated for each of  $n = 200$  or 400 subjects  $Z$  with  $P(Z = g) = 1/3$ ,  $g = 1, 2, 3$ , and  $(Y, X)$  with joint distribution of  $(Y, X)$  given  $Z$  bivariate normal with mean  $\{\beta_1 I(Z = 1) + \beta_2 I(Z = 2), 0\}^T$  and covariance matrix  $\text{vech}(1, \rho, 1)$ , where  $\rho = 0.25, 0.50, 0.75$  corresponds to mild, moderate, and strong association between covariate and response. Under the null hypothesis, we set  $\beta_1 = \beta_2 = 0$ ; simulations

under the alternative involved  $\beta_1 = 0.25$ ,  $\beta_2 = 0.4$ . For each data set, we calculated the unadjusted Kruskal-Wallis test statistic  $T_n$  and the proposed statistic  $\widehat{T}_n^*$  using the strategy in Section 5, with each component of the  $s = 2$ -dimensional models  $q_g(X, \zeta_g)$  in (21) represented as  $q_{gu}(X, \zeta_{gu}) = \{1, c_{gu}^T(X)\}^T \zeta_{ug}$ ,  $u = 1, 2$ ,  $c_{gu}(X) = (X, X^2)^T$ . Each statistic was compared to the 0.95 quantile of the  $\chi_2^2$  distribution. Table 3 shows that the proposed procedure yields greater power than the unadjusted test while achieving the nominal level, where the extent of improvement depends on the strength of the association between  $Y$  and  $X$ , as expected.

## 7. Applications

### 7.1 PURSUIT Clinical Trial

We consider data from 5,710 patients in the PURSUIT trial introduced in Section 1 and focus on the log-odds ratio for Integrilin relative to control. The 35 baseline auxiliary covariates are listed in Web Appendix D.

The unadjusted estimate of the log-odds ratio based on (22),  $\widehat{\beta}_2$ , is  $-0.174$  with standard error 0.073. To calculate the augmented estimator based on (22), we used the direct implementation strategy and took  $q_g^*(X, \zeta_g) = \{1, c_g^T(X)\}^T \zeta_g$ ,  $g = 1, 2$ , with  $c_g(X)$  including main effects of all 35 covariates, and fitted the models by OLS. The resulting estimate  $\widetilde{\beta}_2 = -0.163$ , with standard error 0.071. For these data, the relative efficiency of the proposed estimator to the unadjusted, computed as the square of the ratio of the estimated standard errors, is 1.06. For binary response, substantial increases in efficiency via covariate adjustment are not likely; thus, this admittedly modest improvement is encouraging.

### 7.2 AIDS Clinical Trials Group Protocol 175

We consider data on 2139 subjects from ACTG 175, discussed in Section 1, where the  $k = 4$  treatments were zidovudine (ZDV) monotherapy ( $g = 1$ ), ZDV+didanosine (ddI,  $g = 2$ ), ZDV+zalcitabine ( $g = 3$ ), and ddI monotherapy ( $g = 4$ ). The continuous response is CD4 count (cells/mm<sup>3</sup>,  $Y$ ) at  $20 \pm 5$  weeks, and we focus on the four treatment means, with

the same 12 auxiliary covariates considered by Tsiatis et al. (2007, Section 5).

We consider the extension of model (2) to  $k = 4$  treatments, so that  $\theta = \beta = (\beta_1, \dots, \beta_4)^T$ ,  $\beta_g = E(Y|Z = g)$ ,  $g = 1, \dots, 4$ . The standard unadjusted estimator for  $\beta$  is the vector of sample averages; these are  $(336.14, 403.17, 372.04, 374.32)^T$  for  $g = (1, 2, 3, 4)$ , with standard errors  $(5.68, 6.84, 5.90, 6.22)^T$ . Using the direct implementation strategy with each element of  $q_g^*(X, \zeta_g)$  represented using  $c_g(X)$  containing all linear terms in the 12 covariates, the proposed methods yield  $\tilde{\beta} = (333.85, 403.83, 370.43, 376.45)^T$ , with standard errors obtained via the sandwich method as  $(4.61, 5.93, 4.89, 5.11)^T$ . This is of course one realization of data; however, it is noteworthy that the standard errors for the proposed estimator correspond to relative efficiencies of 1.51, 1.33, 1.46 and 1.48, respectively.

We also carried out the standard unadjusted three-degree-of-freedom Wald test for  $H_0 : \beta_1 = \beta_2 = \beta_3 = \beta_4$  and Kruskal-Wallis test for  $H_0 : S_1(u) = \dots = S_4(u) = S(u)$ , as well as their adjusted counterparts using  $c_{gu}(X)$  containing linear and quadratic terms in the continuous components of  $X$  and linear terms in the binary elements. The unadjusted and adjusted Wald statistics are 59.40 and 109.58, respectively; the unadjusted and adjusted Kruskal-Wallis statistics are 49.04 and 100.53; and all are to be compared to  $\chi_3^2$  critical values. Again, although the evidence against the null hypotheses is overwhelming even without adjustment, the proposed test statistics are considerably larger.

See Web Appendix D for further results for these data.

## 8. Discussion

We have proposed a general approach to using auxiliary baseline covariates to improve the precision of estimators and tests for general measures of treatment effect and general null hypotheses in the analysis of randomized clinical trials by using semiparametric theory.

We identify the optimal estimating function involving covariates within the class of such estimating functions based on a *given*  $m(Y, Z; \theta)$ . For differences of treatment means or

measures of treatment effect for binary outcomes, this estimating function in fact leads to the efficient estimator for the treatment effect. In more complicated models, e.g., repeated measures models, we do not identify the optimal estimating function among *all* possible. Our experience in other problems suggests that gains over the methods here would be modest.

The use of model selection techniques, such as forward selection in our simulations, to determine covariates to include in the augmentation term models should have no effect asymptotically on the properties of the estimators for  $\theta$ . However, such effects may be evident in smaller samples, requiring a “correction” to account for failure of the asymptotic theory to represent faithfully the uncertainty due to model selection. Investigation of how approaches to inference after model selection (e.g., Hjort and Claeskens, 2003; Shen, Huang and Ye, 2004) may be adapted to this setting would be a fruitful area for future research.

#### SUPPLEMENTARY MATERIALS

Web Appendices A–D, referenced in Sections 2, 3, and 7, are available under the Paper Information link at the *Biometrics* website <http://www.tibs.org/biometrics>.

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**Table 1**

*Simulation results for estimation of the log-odds ratio  $\beta_2$  for treatment  $Z = 2$  relative to  $Z = 1$  in (22) based on 5,000 Monte Carlo data sets. “Unadjusted” refers to the unadjusted estimator based on the data on  $(Y, Z)$  only, “Aug.  $a$ ” for  $a = 1, \dots, 6$  refers to estimators based on the data on  $(Y, X, Z)$  using the strategy in Section 4, and “Usual  $b$ ” for  $b = 1, 2$  refers to direct logistic regression adjustment, as described in the text. MC bias is Monte Carlo bias, MC SD is Monte Carlo standard deviation, Ave. SE is the average of estimated standard errors obtained using the sandwich formula (13), Cov. Prob. is the MC coverage probability of 95% Wald confidence intervals, and Rel. Eff. is the Monte Carlo mean squared error for the unadjusted estimator divided by that for the indicated estimator.*

Method	True	MC Bias	MC SD	Ave. SE	Cov. Prob	Rel. Eff.
Mild Association						
Unadjusted	-0.494	0.002	0.168	0.166	0.948	1.00
Aug. 1	-0.494	-0.001	0.156	0.153	0.948	1.16
Aug. 2	-0.494	0.000	0.156	0.153	0.944	1.15
Aug. 3	-0.494	0.000	0.156	0.153	0.946	1.16
Aug. 4	-0.494	0.000	0.156	0.152	0.943	1.15
Aug. 5	-0.494	-0.001	0.156	0.153	0.945	1.16
Aug. 6	-0.494	0.000	0.156	0.153	0.946	1.16
Usual 1	-0.494	-0.091	0.185	0.182	0.922	0.66
Usual 2	-0.494	-0.090	0.185	0.182	0.922	0.66
Moderate Association						
Unadjusted	-0.490	0.001	0.165	0.165	0.948	1.00
Aug. 1	-0.490	-0.002	0.140	0.139	0.950	1.39
Aug. 2	-0.490	-0.002	0.141	0.139	0.949	1.38
Aug. 3	-0.490	-0.001	0.139	0.138	0.948	1.41
Aug. 4	-0.490	-0.001	0.140	0.137	0.945	1.40
Aug. 5	-0.490	-0.002	0.140	0.139	0.949	1.39
Aug. 6	-0.490	-0.001	0.140	0.138	0.946	1.40
Usual 1	-0.490	-0.218	0.203	0.201	0.813	0.31
Usual 2	-0.490	-0.219	0.204	0.201	0.813	0.31
Strong Association						
Unadjusted	-0.460	0.004	0.164	0.165	0.954	1.00
Aug. 1	-0.460	0.000	0.132	0.131	0.952	1.55
Aug. 2	-0.460	0.000	0.132	0.131	0.950	1.54
Aug. 3	-0.460	0.001	0.129	0.128	0.948	1.61
Aug. 4	-0.460	0.001	0.130	0.127	0.945	1.60
Aug. 5	-0.460	0.000	0.132	0.131	0.951	1.55
Aug. 6	-0.460	0.001	0.129	0.127	0.947	1.61
Usual 1	-0.460	-0.321	0.223	0.220	0.695	0.18
Usual 2	-0.460	-0.322	0.224	0.220	0.695	0.17

**Table 2**

*Simulation results for estimation of  $\beta_2$  in the linear mixed model (4) using the usual unadjusted method, the proposed augmented methods denoted by “Aug. a” for  $a=1,2,3$ , and the “Usual” method, as described in the text, based on 5,000 Monte Carlo data sets.*

*Entries are as in Table 1.*

Method	True	MC Bias	MC SD	Ave. SE	Cov. Prob	Rel. Eff.
Mild Association						
Unadjusted	0.300	0.000	0.100	0.099	0.951	1.00
Aug. 1	0.300	-0.001	0.095	0.094	0.951	1.10
Aug. 2	0.300	-0.001	0.100	0.097	0.945	1.00
Aug. 3	0.300	-0.001	0.096	0.094	0.950	1.08
Usual	0.300	-0.001	0.100	0.097	0.944	1.00
Moderate Association						
Unadjusted	0.300	0.000	0.107	0.106	0.949	1.00
Aug. 1	0.300	-0.001	0.097	0.095	0.951	1.22
Aug. 2	0.300	0.000	0.106	0.103	0.945	1.02
Aug. 3	0.300	-0.001	0.097	0.095	0.952	1.21
Usual	0.300	-0.001	0.105	0.101	0.946	1.04
Strong Association						
Unadjusted	0.300	0.000	0.116	0.115	0.950	1.00
Aug. 1	0.300	-0.001	0.098	0.096	0.951	1.41
Aug. 2	0.300	0.000	0.114	0.111	0.943	1.03
Aug. 3	0.300	-0.001	0.098	0.096	0.951	1.39
Usual	0.300	-0.001	0.113	0.109	0.944	1.06

**Table 3**

*Empirical size and power of the usual Kruskal-Wallis test  $T_n$  (unadjusted) and the proposed test  $\hat{T}_n^*$  based on 10,000 Monte Carlo replications. Each entry in the columns labeled  $T_n$  and  $\hat{T}_n^*$  is the number of times out of 10,000 that each test rejected the null hypothesis of “no treatment effects” under the corresponding scenario.*

$\rho$	$n$	Null		Alternative	
		$T_n$	$\hat{T}_n^*$	$T_n$	$\hat{T}_n^*$
0.25	200	0.05	0.05	0.51	0.54
	400	0.05	0.05	0.83	0.85
0.50	200	0.05	0.05	0.51	0.64
	400	0.05	0.05	0.83	0.92
0.75	200	0.05	0.05	0.51	0.85
	400	0.05	0.05	0.83	0.99