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Continuous covariate imbalance and conditional power for clinical trial interim analyses

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ABSTRACT

Oftentimes valid statistical analyses for clinical trials involve adjustment for known influential covariates, regardless of imbalance observed in these covariates at baseline across treatment groups. Thus, it must be the case that valid interim analyses also properly adjust for these covariates. There are situations, however, in which covariate adjustment is not possible, not planned, or simply carries less merit as it makes inferences less generalizable and less intuitive. In this case, covariate imbalance between treatment groups can have a substantial effect on both interim and final primary outcome analyses. This paper illustrates the effect of influential continuous baseline covariate imbalance on unadjusted conditional power (CP), and thus, on trial decisions based on futility stopping bounds. The robustness of the relationship is illustrated for normal, skewed, and bimodal continuous baseline covariates that are related to a normally distributed primary outcome. Results suggest that unadjusted CP calculations in the presence of influential covariate imbalance require careful interpretation and evaluation.

1. Introduction

In a randomized setting, clinical trial treatment arms will be comparable on average with respect to covariate distributions. Thus, the expected level of covariate imbalance in a randomized clinical trial is zero and adjusted and unadjusted analyses will generally result in the same overall conclusions, but observed imbalance in a single clinical trial is one realization of all possible random levels of imbalance. Therefore, a single clinical trial may exhibit some form of nontrivial covariate imbalance for which adjustment should be made in analyses. The statistical literature argues that adjustment is essential in clinical trial analysis for known influential baseline covariates in order to ensure statistical efficiency and unbiased treatment effect estimates [1–7], but according to the International Conference on Harmonization (ICH) guidelines, adjustment in statistical analysis for covariates known to affect primary outcome must be pre-specified in the trial's statistical analysis plan (SAP) [8]. Unplanned adjusted analyses are thus considered secondary and carry less merit than planned unadjusted primary analyses.

However, choosing covariates to include in a final statistical model for primary outcome can be a difficult task for clinicians and statisticians designing clinical trials as situations arise in which influential covariates are unknown ahead of time. For example, the original analysis of the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) study for ischemic stroke [9] failed to account for baseline NIH Stroke Scale (NIHSS) score, a measure of baseline disease severity, resulting in controversy surrounding the efficacy of tPA in the treatment of ischemic stroke as well as the need for reanalysis of these data [10–13].

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Hauck [2], Hernández [3], and Peduzzi et al. [4] discuss the ease of interpretation and generalizability of unadjusted treatment effect estimates when compared to the adjusted estimates based on models. As a result, clinical trial reports often place emphasis on simple, unadjusted treatment effect estimates [2,3,14]. Austin et al. [14] suggest that a larger percentage of unadjusted analysis results are reported in clinical trial articles when compared to adjusted results. Although validity of analysis in the presence of known influential covariates requires proper adjustment [15], balance in influential baseline covariates may serve as a compromise between the complex, but more appropriate adjusted analyses and the more readily interpretable and accepted unadjusted analysis in some cases.

Senn [16] shows that imbalance in continuous normal covariate distributions across treatment groups as measured by the *Z*- or *t*-statistic is directly associated with type I error inflation in an unadjusted analysis for continuous primary outcome. Ciolino et al. [17,18] illustrate the robustness of the t-statistic in predicting power, type I error rate, and bias in unadjusted analyses for several continuous covariate distributions. The impact of imbalance on these statistical parameters for unadjusted analyses depends on the level of covariate influence on primary outcome.

If imbalance in continuous baseline covariate distributions is predictive of statistical parameters in the final analysis, then such is the case for an interim point of a trial and this imbalance may thus indirectly affect trial decisions based on unadjusted interim analyses. For example, the data monitoring committee (DMC) for a clinical trial may decide to terminate the trial prematurely because conditional power (CP) at an interim point falls below a pre-specified stopping boundary [19]. Presence of covariate imbalance in the case of unadjusted CP can therefore potentially have an indirect effect on the DMC's decision to terminate enrollment. This paper aims to determine the relationship between continuous baseline covariate imbalance and unadjusted CP at interim analysis for a normally distributed primary outcome and to illustrate the potential effect this imbalance may have on trial decisions based on unadjusted CP. We argue that unadjusted CP calculations require careful interpretation, and one should consider calculating CP based on a test statistic adjusted for influential and/or imbalanced covariates.

2. Background

2.1. Statistical framework

The basic statistical ideas outlined here adopt those of Lan and Wittes [20] and Lan et al. [21] for CP and Brownian Motion properties. Consider a randomized clinical trial with two arms: an active treatment group and a placebo group with 1:1 allocation. Assume n out of the total N subjects have been enrolled in each arm, and let $t = n / N$ denotes the trial fraction at an interim point. Further, assume the primary outcome, $Y \sim N(\mu_Y, \sigma_Y^2)$, and planned analysis fails to adjust for an influential covariate, $X \sim N(\mu_X, \sigma_X^2)$.

Let $Z_X(t) = \frac{\mu_{X_{tx}} - \mu_{X_{pbo}}}{\sigma_X\sqrt{2/n}}$ (where $\mu_{X_{tx}}$ is the mean covariate value for the active treatment group and $\mu_{X_{pbo}}$ is the mean covariate value for the placebo group) and $Z_Y(t) = \frac{\mu_{Y_{tx}} - \mu_{Y_{pbo}}}{\sigma_Y\sqrt{2/n}}$ (where $\mu_{Y_{tx}}$ is the mean primary outcome value for the active treatment group and $\mu_{Y_{pbo}}$ is the mean primary outcome value for the placebo group) represent the *Z*-scores at trial fraction t comparing mean covariate and primary outcome values across treatment groups, respectively. Following the notation of Lan and Wittes [20], the *B*-values used in calculating CP are equivalent to $B_X(t) = \sqrt{t}Z_X(t)$ and $B_Y(t) = \sqrt{t}Z_Y(t)$, respectively.

Let θ be the expected Z-score for the primary outcome at the end of the trial (i.e., $\theta = E[Z_Y(1)]$). Under random allocation, treatment groups are expected to be balanced with respect to continuous covariates, and the expected *Z*-score for the covariate at the end of the trial is zero (i.e., $E[Z_X(1)] = 0$). Assume that $\theta > 0$ such that the treatment has a positive effect on primary outcome.

It should be noted that in the calculation of $Z_X(t)$ and $Z_Y(t)$, the numerators are calculated in the same direction (mean value in the treatment group minus mean value in the placebo group), and the results to follow rely heavily on this fact. In the hypothetical clinical trial scenario discussed here, assume that larger values of outcome correspond to more favorable clinical prognosis and situations in which the placebo group is "favored" at baseline suggest a better baseline prognosis in the placebo group (i.e., the placebo group is predisposed for better clinical outcome).

It can be shown that if the $corr(X, Y) = \rho$, then the $corr(B_X(t), B_Y(t)) = \rho$. Given this information and the properties of Brownian Motions (as related to the *B*-values here), we can determine the distribution of $B_Y(1)|B_X(t) = b_{X_t}$. This distribution can, in turn, be used to calculate unadjusted CP given only covariate imbalance for an influential covariate at trial fraction t.

2.2. The distribution of $B_Y(t)$ $B_X(t) = b_{Xt}$

The properties of Brownian Motions and their relationship to the *B*-value in clinical trial data monitoring [20] allow for the following assumptions:

- $B_X(t) \sim N(0, t)$
- $B_Y(t) \sim N(\theta t, t)$
- $corr(B_X(t), B_X(1)) = corr(B_Y(t), B_Y(1)) = \sqrt{t}$
- $corr(B_X(t), B_Y(t)) = \rho$.

By the definition of the conditional normal distribution, it can be shown that

$$\left(B_X(1)|B_X(t) = b_{X_t}\right) \sim N\left(b_{X_t}, 1-t\right),$$

and

$$\left(B_Y(1)|B_X(1) = b_{X_1}\right) \sim N\left(\theta + \rho b_{X_1}, 1-\rho^2\right).$$

However, $B_X(1)$ is a random variable that depends on $B_X(t) = b_{X_t}$. Therefore,

$$E\left(B_Y(1)|B_X(t) = b_{X_t}\right) = \theta + \rho b_{X_t}.$$