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TESTING HYPOTHESES OF COVARIATE-ADAPTIVE RANDOMIZED CLINICAL TRIALS WITH TIME-TO-EVENT OUTCOMES UNDER THE AFT MODEL

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Abstract: Covariate adaptive randomization (CAR) designs, including the stratified permuted block randomization design, are popular in clinical trials. However, clinical trialists usually ignore the unique feature of the CAR that the treatment assignment of the current subject depends not only on his or her covariate information, but also on the covariates and treatment assignments of all prior subjects. They often analyze the data as if complete randomization was used. As a result, the inferential conclusions of many clinical trials are open to question. This paper provides the theoretical foundation for trials using CAR designs and the accelerated failure time (AFT) model for time-to-event outcomes. We derive the asymptotic properties of the test statistics and explain the effect of the CAR design on the variability of the estimated treatment effect and the type I error rate. We also obtain the consistency and asymptotic normality of the estimators. Based on the theoretical results, we propose new test statistics to control the type I error rate. Numerical studies demonstrate our theoretical findings and show that our methods successfully protect the type I error rate. Our theoretical and numerical results provide practical guidance for future clinical trials employing CAR designs and time-to-event outcomes.

Key words and phrases: Accelerated failure time model, conservative tests, covariate adaptive design, type I error.

1. Introduction

Covariate adaptive randomization (CAR) is popular in clinical trials (Rosenberger and Lachin, 2015) and development economics research (Duflo, Glennerster and Kremer, 2007; Bruhn and McKenzie, 2009). However, the validity of the inference following CAR has been questioned (Weir and Lees, 2003; Hagino et al., 2004). In this paper, we study the validity of inference in clinical trials with CAR and the accelerated failure time (AFT) model for time-to-event outcomes.

We first introduce the importance and advantages of CAR designs. It is well accepted that many covariates (biomarkers) are associated with certain diseases

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