Sequential Analysis of Cox Model under Response Dependent Allocation

Xiaolong Luo, Gongjun Xu and Zhiliang Ying

Celgene Corporation, Columbia University and Columbia University

Abstract: Sellke and Siegmund (1983) developed the Brownian approximation to the Cox partial likelihood score as a process of calendar time, laying the foundation for group sequential analysis of survival studies. We extend their results to cover situations in which treatment allocations may depend on observed outcomes. The new development makes use of the entry time and calendar time along with the corresponding $\sigma$-filtrations to handle the natural information accumulation. Large sample properties are established under suitable regularity conditions.

Key words and phrases: Survival analysis, group sequential methods, outcome dependent allocation, proportional hazards regression, clinical trials, staggered entry, Brownian approximation, weak convergence.

1 Introduction

The Cox (1972) proportional hazards model along with the partial likelihood (Cox, 1975) has been extensively applied to survival data. The theoretical properties of the maximum partial likelihood estimator can be easily derived by expressing the partial likelihood score as a counting process based martingale integral; see Andersen and Gill (1982), Fleming and Harrington (1991), and Kalbfleisch and Prentice (2002).

For sequential analysis, the partial likelihood score needs to be evaluated along the calendar time and its asymptotic behavior is crucial to deriving the corresponding group sequential methods. Due to the staggered entry of patients, the partial likelihood score as a process of calendar time is no longer a martingale integral. In a pioneering paper, Sellke and Siegmund (1983) showed that the score process can still be approximated by the Brownian motion process, thereby laying the foundation for group sequential analysis of survival studies. Slud