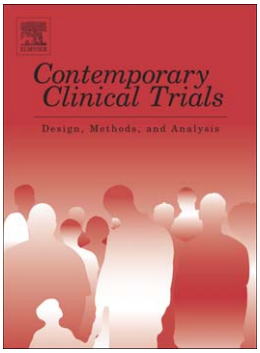

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Adaptive Choice of Patient Subgroup for Comparing Two Treatments

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Abstract

This paper is motivated by a randomized controlled trial to compare an endovascular procedure with conventional medical treatment for stroke patients, in which the endovascular procedure may be effective only in a subgroup of patients. Since the subgroup is not known at the design stage but can be learned statistically from the data collected during the course of the trial, we develop a novel group sequential design that incorporates adaptive choice of the patient subgroup among several possibilities which include the entire patient population as a choice. We define the type I and type II errors of a test in this design and show how a prescribed type I error can be maintained by using the closed testing principle in multiple testing. We also show how asymptotically optimal tests can be constructed by using generalized likelihood ratio statistics for parametric problems and analogous standardized or Studentized statistics for nonparametric tests such as Wilcoxon's rank sum test commonly used for treatment comparison in stroke patients.

Keywords: adaptive selection, generalized likelihood ratio statistics, group sequential design, Kullback-Leibler information, multiple testing, normalized Wilcoxon statistic.

1. Introduction

It is widely recognized that the comparative efficacy of a new treatment can depend on certain characteristics of the patients that are difficult to pre-specify at the design stage. In a randomized trial, ignoring characteristics that account for patient heterogeneity in response may yield a false negative result. On the other hand, narrowly defining the patient characteristics for inclusion and exclusion limits the proven usefulness of the treatment to a small patient subpopulation. A trial may also encounter difficulties in patient accrual when relatively few patients satisfy the stringent inclusion/exclusion criteria. Adaptive (data-dependent) choice of the patient subgroup to compare the new and control treatments is a natural compromise between ignoring patient heterogeneity and using stringent inclusion/exclusion criteria in the

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