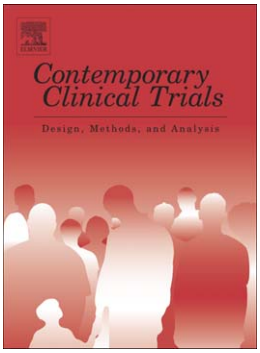

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OPTIMAL ADAPTIVE GROUP SEQUENTIAL DESIGN WITH FLEXIBLE TIMING OF SAMPLE SIZE DETERMINATION

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Abstract. Flexible sample size designs, including group sequential and sample size re-estimation designs, have been used as alternatives to fixed sample size designs to achieve more robust statistical power and better trial efficiency. In this work, a new representation of sample size re-estimation design suggested by Cui et al is introduced as an adaptive group sequential design with flexible timing of sample size determination. This generalized adaptive group sequential design allows one time sample size determination either before the start of or in the mid-course of a clinical study. The new approach leads to possible design optimization on an expanded space of design parameters. Its equivalence to sample size re-estimation design proposed by Cui et al provides further insight on re-estimation design and helps to address common confusions and misunderstanding. Issues in designing flexible sample size trial, including design objective, performance evaluation and implementation are touched upon with an example to illustrate.

Key words: sample size, interim analysis, information fraction, type I error rate, power

1. Introduction

Flexible sample size design has been used in clinical trials as an alternative to traditional fixed sample size design to achieve robust power and trial efficiency. Unlike a fixed sample size trial, for a flexible sample size trial, the total trial sample size may not be chosen upfront but determined at a later time through interim analysis.

Flexible sample size design can be traced back to Stein's two-stage design proposed in 1940s ([1]). In early 1990s, Wittes and Britain proposed to use interim trial data for internal piloting to improve trial efficiency and reliability ([2]). The idea triggered waves of research on adaptive clinical trial designs including design with sample size re-estimation base on unblinded interim data. A method to analyze data from a two-stage study through combining stage-wise p-values was proposed by Bauer and Köhne ([3]). A method was proposed by Proschan and Hunsberger ([4]) to allow direct combination of the data from the two stages with modified critical value to control type I error rate. Simple but more flexible methods were proposed by Cui et. al ([5], [6]) and by Lehmarcher and Wassmer ([7]), extending two-stage design into group sequential (GS) design allowing mid-course sample size change. The former is often termed as weighted sample size re-estimation method