"Multi-arm Group Sequential Designs with a Simultaneous Stopping Rule" Statistics in Medicine – to appear

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Abstract

Multi-arm group sequential clinical trials are efficient designs to compare multiple treatments to a control. They allow one to test for treatment effects already in interim analyses and can have a lower average sample number than fixed sample designs. Their operating characteristics depend on the stopping rule: We consider simultaneous stopping, where the whole trial is stopped as soon as for any of the arms the null hypothesis of no treatment effect can be rejected, and separate stopping, where only recruitment to arms for which a significant treatment effect could be demonstrated is stopped, but the other arms are continued. For both stopping rules the family-wise error rate can be controlled by the closed testing procedure applied to group sequential tests of intersection and elementary hypotheses.

The group sequential boundaries for the separate stopping rule also control the family-wise error rate if the simultaneous stopping rule is applied. However, we show that for the simultaneous stopping rule one can apply improved, less conservative stopping boundaries for local tests of elementary hypotheses. We derive corresponding improved Pocock and O'Brien type boundaries as well as optimized boundaries to maximize the power or average sample number and investigate the operating characteristics and small sample properties of the resulting designs. To control the power to reject at least one null hypothesis, the simultaneous stopping rule requires a lower average sample number than the separate stopping rule. This comes at the cost of a lower power to reject all null hypotheses. Some of this loss in power can be regained by applying the improved stopping boundaries for the simultaneous stopping rule.

The procedures are illustrated with clinical trials in systemic sclerosis and narcolepsy.