Adaptive Selection and Multiple Testing of Effective and Safe Treatments

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We consider the situation that during a multiple treatment (dose) control comparison experiment low doses are truncated because of lack of efficacy and high doses are truncated because of lack of safety, e.g., by decisions of a data safety monitoring committee in multiple interim looks. We investigate the property of a hierarchical test procedure for the efficacy outcome in the set of treatments carried on until to the end of the trial, starting with the highest selected treatment to be compared with the control at the full level alpha and going down to the next lower dose-control comparison if significance has been achieved. This step is repeated till one of the comparisons fails to reach significance. Obviously, left truncation, i.e., dropping doses in a sequence starting with the smallest dose, does not inflate the type I error rate. Two right truncation rules based on safety data are investigated, one based on the mean treatment-control differences, the other based on the absolute treatment means at the interim looks. It is shown, that the right truncated hierarchical testing procedure controls the multiple level alpha, if there is a non-negative correlation between efficacy and toxicity (assuming a bivariate normal distribution between both). This holds true if different monitoring boundaries are used at the different interim look, which may also vary between the treatments. In case of a negative correlation we show that the multiple level may be violated for specific safety patterns among the doses, particularly when the selection is done late in the trial. An increase in power can be achieved if sample sizes saved for the truncated treatment (dose) groups are reallocated to the remaining treatments and control at the following stages.