Optimizing Confirmatory Clinical Trial Designs for Targeted Therapies

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Abstract

An important objective in the development of targeted therapies is the identification of subgroups, where the treatment is effective. Disregarding relevant subpopulations, a treatment option may be missed due to a dilution of the treatment effect in the full population. Furthermore, even if the diluted treatment effect can be demonstrated in an overall population, it is not ethical to treat patients that do not benefit from the treatment when they can be identified in advance. On the contrary, selecting a spurious subpopulation increases the risk to restrict an efficacious treatment to a too narrow fraction of a potentially benefiting population. We quantify these risks with utility functions in a decision theoretic approach and compare the efficiency of three different designs: the classical trial design, where the treatment effect is tested only in the full population (disregarding the biomarker status), the stratified design, which incorporates a multiplicity adjusted subgroup analysis, and the enrichment design, focusing on the biomarker defined subgroup only. We optimize these trial designs by maximizing expected utility functions that reflect either a sponsor's view (maximizing the expected revenue) or a public health view (maximizing the expected total treatment effect adjusted by trial costs).