Data Combination in Seamless Phase II/III Designs

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In seamless Phase II/III trials multiple treatments are compared against a control. One of k treatments is selected in Phase II for further study in Phase III. The final decision rule for declaring the selected treatment superior to control must protect the family-wise type I error rate for k comparisons against the control. In adaptive seamless designs, combination rules are applied to P-values from data in the two Phases. This data combination does not necessarily lead to greater power than an analysis which simply ignores the Phase II data, raising the question of how one should combine information optimally to maximise power while protecting family-wise type I error.

We shall present a formulation of the problem which is amenable to analysis by decision theory. Hence, we derive optimal data combination rules for particular objectives. The results of this exercise are somewhat surprising. While Simes' rule reacts positively to low P-values for the treatments eliminated in Phase II, under some assumptions, the optimal inference treats such low P-values as detracting from the evidence for efficacy in the treatment selected for Phase III.

We shall endeavour to present a decision rule with robust efficiency across a variety of scenarios. We believe the results supporting this conclusion have broader implications for other multiple comparison problems and the methodology we have developed may be adapted for wider use.