Optimal rejection regions for multi-arm clinical trials

Niewczas J., Burman C.-F., Hampson L., Posch M., König F.*

*Medical University of Vienna, Section for Medical Statistics, Vienna, Austria,

In phase II and phase III clinical trials it is common to compare several treatment groups to a control. To adjust for multiplicity popular adjustments include e.g. Bonferroni and Dunnett tests. For these methods marginal tests are used splitting the alpha accordingly. Instead we propose a test statistic for the intersection null hypothesis (i.e., to test if there is any treatment effect) that is a weighted combination of the marginal test statistics of the individual treatment-control comparisons. We derive optimal rejection regions for the test of the intersection hypothesis by applying the Neyman-Pearson lemma for a clinical trial comparing two treatment arms to a common control. To allow for individual treatment-control comparisons this is further embedded into a full closed test by applying a truncated version of the optimal intersection test. Bayesian decision theoretic approaches based on discrete priors are used to derive optimal weights and rejection regions in the context of frequentist testing. We show that if the difference between the assumed effects in the two treatment group becomes larger, the optimal test coincides with a classical hierarchical test in the framework of a closed test. We compare the proposed tests with more conventional ones such as the weighted Dunnett test in terms of power (e.g., disjunctive power or assurance) and efficiency.

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