

HIERARCHICAL WEIGHTED METHODS WHICH CONTROL THE FALSE DISCOVERY RATE CRITERION AND THEIR USE IN CLINICAL TRIALS

In clinical medical studies the problem of multiple comparisons is of importance. In Phase III trials, conducted for drug registering, attending to it is a major part of the statistical analysis. We show that the issue of multiplicity is dramatically lacking in usual clinical research, and is being addressed only by the division to primary endpoints (usually one) and many secondary endpoints.

The weighted FDR controlling method of Benjamini and Hochberg is used hierarchically, where in the first level the secondary endpoints are grouped into a single endpoint and tested jointly with the primary endpoints, while possibly being assigned a lower weight. If rejected the secondary endpoints are tested again using the same approach. The levels at which these two steps are conducted are adjusted to assure overall control of the error-rate.

The proposed hierarchic method may achieve greater power than competing methods for controlling the FDR, and even greater than other gatekeeper methods.

The main power of the proposed method can be materialized at Phase II of the clinical trial, when the investigator might consider changing the submittal protocol of Phase III of the trial for the drug-licensing authorities. Thus, its use may lead to the choice of one of the secondary endpoints that was found to be significant and which is on a sufficient level of importance so that it can serve as the primary endpoint at Phase III of the trial. In some cases, this change may make all the difference between the success of the trial and its failure.

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