Adaptive Alpha Allocation Methods for Analyzing Multiple Endpoints

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In a typical late-stage clinical trial comparing a new treatment with a control, there are 1 or 2 primary endpoints and a few (say, 1 to 4) secondary endpoints. Results for the secondary endpoints are used to either support additional "label claims", or, in some cases, to "rescue" the trial if no statistical benefit of the new treatment is demonstrated for any primary endpoint. Because multiple endpoints are involved, regulators often require sponsors to ensure that the familywise error rate (FWER), i.e., the probability of falsely claiming a statistical benefit of the new treatment over the control for even a single primary or secondary endpoint, is controlled at a pre-set low level (typically 5%). Standard methods to control the FWER include Hochberg's (1988) procedure, and various "gate keeping" approaches. In this presentation, we will propose alternate FWER-controlling methods that improve the power for primary and/or secondary endpoints relative to the standard methods. All the proposed methods use the idea of "adaptive alpha allocation" which capitalizes on the fact that primary endpoints are generally well-powered by design. We will use simulation results and real examples to illustrate the utility of the new methods.