Testing effect of a drug using multiple nested models for the dose-response

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During development of a drug, typically the choice of dose is based on a Phase II dose-finding trial, where selected doses are included with placebo. Two common statistical dose-finding methods to analyze such trials are separate comparisons of each dose to placebo (using a multiple comparison procedure) or a model-based strategy (where a model is fitted to all data). The first approach works best when patients are concentrated on few doses, but cannot conclude on doses not tested.

Model-based methods allow for interpolation between doses, but the validity depends on the correctness of the assumed dose-response model. Bretz et al. (2005; Biometrics 61, 738-748) suggested a combined approach, which selects one or more suitable models from a set of candidate models using a multiple comparison procedure. The method initially requires a priori estimates of any non-linear parameters of the candidate models, such that there is still a degree of model misspecification possible and one can only evaluate one or several restrictions of a general model.

We propose an alternative multiple testing procedure, which evaluates a candidate set of plausible dose-response models against each other to select one final model. The method does not require any a priori parameter estimates and controls the Type I error rate of selecting a too complex model.