Symposium Program on Dose Selection for Cancer Treatments: May 12, 2017

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Title: Characterizing Efficacy Risk Profiles via a Bayesian Monotone Concavex Model

Abstract:
Dose response characterization, particularly in early clinical development, is playing an increasingly important role in the pharmaceutical and biotech industries, where such a characterization is needed to select a dose to test in confirmatory phase 3 studies. Good dose selection accounts for the tradeoff between efficacy versus safety, tolerability, patient burden, and manufacturability. A poorly chosen dose can lead to unnecessary safety and patient burden issues or even a phase 3 study failure due to efficacy.

Historically, dose ranging studies have been designed like mini phase 3 trials, with 2 (sometimes 3) dose groups spanning a narrow range. In order to better find doses to take to phase 3, there is increasing consensus that the number of dose groups should be increased and that they span a wider dynamic range. In addition, data from such designs should be analyzed via dose response models, rather than using more traditional pairwise comparisons approaches.

Such modeling approaches often pre-specify several potential model families to account for uncertainty in the underlying dose response shape. For example, hyperbolic Emax, linear, and exponential model families may be specified for the dose response analysis of a particular trial where it is believed that the true dose response curve is monotone and concave, linear or convex. This approach requires a method for final selection of a model or model averaging. Rather than specifying several candidate model families, we propose a single model with highly interpretable parameters that spans such dose response shapes. We illustrate a Bayesian application of the model that focuses on obtaining a meaningful characterization of the efficacy risk profile.