ADAPTIVE MODEL-BASED APPROACH FOR DESIGNING DOSE-FINDING STUDIES

V. Dragalin[†], V. Fedorov, Y. Wu

Research Statistics Unit, GlaxoSmithKline, Collegeville, PA, USA

[†] E-mail: *Vladimir.2.Dragalin@gsk.com*

We have developed a flexible framework for designing dose-finding studies based on efficacy and toxicity response. Optimal experimental design methodology is used to construct efficient dose allocation procedures for estimation of parameters of the dose-response relationship as accurately as possible given ethical concerns of treating patients in the study at doses that are both safe and efficacious. The bivariate probit model is used to derive optimal designs and study their comparative performance.

Conventional locally optimal design can provide the most accurate parameter estimation if the guess on the unknown parameters are very close to the true value. These designs are used to add rigor and clarify the optimality properties for other practical designs as well as to provide a building block for constructing the adaptive designs. The latter are more appealing in practice since they do not rely on the unknown parameters, but converge to the optimal design if enough patients are available. In situations where there is an additional cost for performing interim analysis, the two-stage composite design has practical advantages over fully adaptive designs.

Greater flexibility can be achieved by using an appropriate penalty function, tailored to the desired goal of the study. We have shown that the penalized optimal designs achieve a reasonable balance between individual and collective ethics in dose-finding studies.