

Incorporating population pharmacokinetics data for Phase I-II dose-schedule finding

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Abstract: In early phase clinical trials, incorporating PK information into dose finding process is an important thought. PK information could be considered as an appropriate indicator for evaluating the degree of drug intervention in humans. FDA has issued the population pharmacokinetics about the guidance for industry to guide the population analysis since it could be used to guide drug development and provide guidance about dose individualization. However, traditional clinical trial designs usually execute dose finding and PK analysis separately while the object of general dose finding is to identify an optimal dose of a treatment with a fixed schedule, which may cause over or under exposure of patients. Thus, we propose a novel Phase I-II dose-schedule finding design incorporating PK information to improve the design by taking advantage of the PK information collected from patients as well. The AUC indicator calculated from population pharmacokinetics is considered into the model to combine PK analysis with the probability models of both toxicity and efficacy, and construct the joint effects through utility function for combination allocation. Simulations illustrate that the design we proposed has a good ability of making the correct dose-schedule combination selection.