Dose selection in adaptive clinical trials based on pharmacokinetic and pharmacodynamic responses

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In this talk we present an adaptive design for dose finding in phase I/II clinical trials, where the probabilities of trinomial responses of efficacy, toxicity and 'no-response' as well as pharmacokinetic (PK) information are considered in the dose-selection procedure. The local D-optimal design for estimating population PK parameters is found and applied in each step of the adaptive trial, where the responses to the drug are measured and the models updated accordingly. A new optimum dose for next cohort of patients is then selected, based on the updated information. An ethical approach is considered in this case, where the dose is optimized for efficacy of the response with some constraints on toxicity. We also consider the total exposure to the drug as an additional constraint for dose selection. The area under the drug concentration curve reflects the population variability in the drug absorption and elimination and this fact is included in the procedure. This method gives efficient designs for dose finding from the point of view of population PK parameter estimation and ethical dose selection with maximum probability of efficacy while keeping the chances of toxicity under control.