

**SRA Dose-Response Specialty Group**  
**2008 Student Merit Award—Extended Abstract**  
**Adaptive Optimal designs for dose-finding based on the Sigmoid Emax model**  
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When a new drug is under development, a conventional dose-finding study involves learning about the dose-response curve in order to bring forward right doses of the drug to late-stage development. Traditionally, dose-finding studies have involved randomizing subjects equally to a pre-chosen set of doses (which may include a placebo arm additionally) and learning about the doses at the end of the trial, after the data has been analyzed using an appropriate statistical model. This method of determining optimal doses has quite a few limitations. Subjects can be allocated to doses that have no effect or to the doses that are too high and potentially unsafe. An alternative way of learning about a drug's true dose-response will be to learn from the study as it is ongoing and make changes to the design in a pre-planned manner. An adaptive clinical trial design is one in which data accumulated during the course of the trial is used to learn about the drug and this information is used to modify the trial with a pre-specified set of rules so that the statistical validity and ethical integrity of the study is preserved. The advantages in learning about the drug early can be substantial in terms of both resources and time required to develop the drug. This can translate to a benefit to the patients in terms of having a drug available to treat a disease much earlier than would have been possible otherwise. Here, we propose an adaptive procedure for dose-finding in clinical trials when the primary efficacy endpoint is continuous. We model the mean of the efficacy endpoint, given the dose, according to a four-parameter logistic function. The efficacy endpoint at each dose is distributed according to either a normal or a gamma distribution. We consider the cases of fixed variance and fixed coefficient of variation, both known and unknown. The analytic formulae for the Fisher information matrix are obtained. We build adaptive D-optimal and c-optimal designs (for different goals of the experiment). We show that this procedure of learning about the dose-response for a drug leads to greater efficiencies (translating to smaller sample sizes required) and higher precision of estimation of the dose-response relationship. We show results of simulation studies conducted to investigate these designs. We further extend the concept of optimal experimental designs to bivariate endpoints by introducing a toxicity parameter (normally distributed, with an exponentially increasing mean, as a function of the dose) which will be informative in picking doses based both on efficacy and toxicity. We build the Information matrices using the joint likelihood and derive the utilities of interest, when targeting an optimal dose (with an ideal trade-off between efficacy and toxicity). Quantities of interest for optimal dose are derived using conditional and truncated conditional densities of the joint distributions for efficacy and toxicity. We also build in penalties by deriving appropriate penalty functions for ineffective or toxic doses, from the corresponding probability distributions. We also show how to incorporate these penalty functions into the D-optimality criteria to build penalized optimal designs. This is compared with the traditional fixed allocation design in terms of allocation of subjects and precision of the identified dose-response curve. For all the new designs proposed (c-, D- and penalized D-optimal designs), we show that they perform better than the traditional fixed allocation designs. The operating characteristics for these designs show advantages both in terms of better identification of the dose-response curve and in terms of allocation of subjects to safe and effective doses. The advantage is not just in terms of better estimation of parameters, but these designs also also more 'ethical' by using penalty functions to minimize allocation to doses that

are either too ineffective or toxic. In summary, we have proposed methods for adaptively allocating subjects, using optimal experimental designs, to various candidate doses for typical dose finding studies. These methodologies can be used when we have observable endpoints for efficacy or toxicity or both. Although Normal and Gamma distributed data were considered, these can be easily extended to any distribution by writing out the log-likelihood and deriving the information matrix. Also, these methods can be tailored to the goals of a particular study, according to whether the target is a particular dose (c-optimality) or optimal learning about the dose-response curve (D-optimality) - with or without constraints for allocation to doses, achieved via penalty functions.