# Model-assisted Adaptive Designs for Dose-ranging Clinical Trials

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**Abstract**

The overall goal of dose-ranging studies is to establish the existence, nature, and extent of dose effect. Recently, a great effort has been made to investigate and develop designs and methods for efficient learning about dose response and more accurate and faster decision making on dose. The focus is on adaptive model-assisted optimal designs of experiments modeling safety, efficacy, or both efficacy and safety endpoints. The proposed dose allocation rules are based on a combination of D- and c-optimality criteria in optimal design of experiments.

**Keywords:** adaptive design, design of experiments, response-adaptive allocation, sequential analysis, stopping rule.

## 1 Overview

When a new molecular entity is being developed as a potential drug, a dose-ranging study is a critical part of the drug development process before going in to confirmatory clinical trials. The dose-response relationship describes the change in effect on patient caused by differing levels of exposure to a drug. The primary purpose of dose-ranging studies is to determine the dose of a drug for further study in large scale trials. Essentially, the design problem is to allocate efficiently, the limited number of participants at hand to the candidate doses, in order to maximize learning about the dose-response relationship. Traditionally, patients have been allocated to a few selected doses in fixed

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proportion and the decisions about the best doses were made at the end of the study, based on pairwise comparisons to a control (usually, placebo).

In contrast, an adaptive dose ranging trial design allows for opportunities to learn about the dose-response relationship more fully and efficiently. By adaptive design, we refer to a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial (see [16]). The goal of adaptive designs is to learn from the accumulating data and to apply what is learned as quickly as possible. A lot of research has been conducted in the field of the statistical methodology for adaptive designs (see reviews in [3, 8, 9, 11]).

The primary goal of a dose-finding study is to establish the dose-response relationship. The optimal experimental design framework provides enough structure to make this goal attainable. It is assumed that the available doses (the design region) and the response variables have been defined and there exists a known structure for the mathematical model describing the dose-response relationship (the model). The objective is on choosing the dose levels in some optimal way to enhance the process of estimating the unknown parameters of the model $\theta$. The experimental designs are represented by a set of design points and a corresponding set of weights representing the allocations to the design points: $\xi = \{(d_i, w_i), i = 1, k\}$. An important element in optimal design is the Fisher information matrix, say $M(\xi, \theta)$, which is an expression of the accuracy of the $\theta$ estimate based on observations at $k$ design points of design $\xi$. A "larger" value of $M$ reflects more information (more precision, lower variability) in the estimate. A natural goal in picking the design $\xi$ is to find the design that "maximizes" the determinant of matrix $M$, the so-called the D-optimal criterion.

A major challenge in design for nonlinear (in $\theta$) models is that the optimal design $\xi^*$ depends on $\theta$ – a conundrum: one is looking for the design $\xi$ with the aim of estimating the unknown $\theta$, and yet one has to know $\theta$ to find the best $\xi$. This conundrum leads to various ways of coping with the dependence on $\theta$. These include the locally-optimal

design based on one's best guess at $\theta$, Bayesian design by augmenting the criterion to reflect the uncertainty in a prior knowledge about $\theta$, minimax design by finding the design that is optimal under the worst parameter $\theta$ value.

The widely used approach in practice is adaptive design that alternates between forming estimates of $\theta$ and choosing a locally-optimal design for that value of the parameter at different stages of the trial. Initial design is chosen and preliminary parameter estimates are obtained. Then, the next doses are selected from the available range of doses that satisfy the efficacy and safety constraints and provide the maximal improvement of the design with respect to the selected criterion of optimality and current parameter estimates. The next available cohort of patients is allocated to these doses. The estimates of unknown parameters are refined given these additional observations. These design-estimation steps are repeated until either the available resources are exhausted or the set of acceptable doses is empty. Such an approach is efficient from the perspective of both time and patient resources.

A critical step in the model-assisted approach is positing a model for the data to be observed in the trial. The model can be flexible and have many parameters. In fitting dose-response models, it is only the data that contain information; the model is just an intermediary that is chosen for its flexibility to follow the data. Therefore, the choice of design is far more important than the choice of the model.

The general framework is that a response $Y$ is observed for a given set of parallel groups of subjects corresponding to doses $d_1, d_3, \ldots, d_K$, with $d_1$ as placebo or active control, for a total of $K$ groups. We consider a one-way layout for the model specification

$$Y_{ij} = \mu_{d_i} + \epsilon_{ij}, \tag{1}$$

where the mean response at dose $d_i$ can be represented as $\mu_{d_i} = f(d_i, \theta)$ for some dose-response model $f(d, \theta)$ parameterized by a vector of parameters $\theta$, and $\epsilon_{ij}$ is the error term for patient $j$ within dose group $i$. We assume for simplicity that $\epsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$ are independent identi-

cally normally distributed.

The sigmoid $E_{max}$ model is flexible enough to adequately approximate many different families of parametric monotone dose-response models and has been investigated in many recent publications on dose-ranging studies (see [10, 15] and references therein). The mean response has the form

$$f(d,\theta) = \theta_1 + (\theta_2 - \theta_1)\frac{d^{\theta_4}}{d^{\theta_4} + \theta_3^{\theta_4}}. \tag{2}$$

Here $\theta_1 < \theta_2$ and $\theta_3 > 0$. The parameter $\theta_3$, called $ED_{50}$, is the dose that corresponds to a mean response halfway between the minimum and maximum. The slope parameter $\theta_4$ controls the steepness of the curve. A steeper curve has a slope factor with higher absolute value (the slope is negative for downhill curves) and a shallower curve has a slope factor with lower absolute value of $\theta_4$. This is a highly flexible nonlinear model that captures the essential features of many dose-response relationships such as an apparent threshold dose below which little, if any, treatment effect is observed, an approximately log-linear dose versus mean treatment effect at higher doses, and sometimes a plateau or ceiling effect at relatively high doses. Note that by changing the values of $\theta_1$ and $\theta_2$ and the sign of $\theta_4$, the same model can be used to describe both monotonically increasing and decreasing dose-response curves.

There are several generalizations of the methodology that address different practical situations: two binary endpoints, one for efficacy one for safety ([12, 14, 17], combination of continuous endpoint and binary endpoint [7], combination of two drugs [1, 13], delay response models [2, 6]. Some of these innovative methods have been used in practice, see a short list here [4, 5, 7].

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