Estimation of the Target Dose Corresponding To Pre-specified Toxicity Rate in Phase I Clinical Trials

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Abstract

In this project we review the developments of several variations of the up-and-down design utilized in Phase I clinical trials to estimate the maximum tolerated dose (MTD) of a drug which corresponds to a fixed probability of response or the pre-specified toxicity rate in the target population. In these designs selection of dose levels is restricted to one level higher, one level lower or the same. Several methods of estimation of the MTD are investigated. Some comparison of the designs by Monte Carlo simulation are carried out by the quality of the estimator of the target dose using the isotonic estimator. The designs are investigated under the generalized logistic (for different values of the power) and the gamma distributions. The NR is found to perform best on the basis of the quality of estimator under these distributions. The BCD is found to perform best on the basis of the average proportion of toxicity for a pre-specified toxicity rate of 0.2 whereas the KROW performs best for a toxicity rate of 0.3.

Key words: Phase I trial, up-and-down design, quantile targeting, toxicity.

Contents

Acronyms

MTD	-	Maximum Tolerated Dose
UD	-	Up-and-Down method
NR	-	Narayana
KROW	-	k-in-a-row
BCD	-	Biased Coin Design
CRM	-	Continual Reassessment Method
SM	-	Standard Method
RMSE	-	Root Mean Squared Error
TBIAS	-	Targeting bias
TOX	-	Average Proportion of the Toxic Responses in the Trial
TE	-	Targeting error
MLE	-	Maximum Likelihood Estimator
EM	-	Empirical Mean
WLS	-	Weighted Least Square
IR	-	Isotonic Regression

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Chapter 1

Introduction

One of the main objectives in a Phase I clinical trial, a study in which a new drug is initially given to humans to determine its maximum tolerated dose (MTD), e.g., an oncology or acute toxicity trial, is to estimate the dose level of a drug which will produce toxicity with a prescribed probability in the target population. Exceeding the MTD could be fatal to human lives. Often, in these studies low doses of more benign drugs are administered to healthy volunteers, typically, some of the investigators who developed the new drug, either some employees of a pharmaceutical company or some members of the research team at a university or patients who have no effective treatment available to them [13]. The doses are increased gradually until some biological activity is observed. Later, when the pharmacologic and safety information are available the drug is introduced to the patient population, again with an emphasis on safety. Observations can then be made on efficacy of the drug in subsequent Phase II trials (trials on persons having a specific disease or medical condition,

to determine whether the drug has some level of therapeutic effect).

Phase II clinical trials are usually carried out with a treatment group, who receive the drug, and a matched control group, who receive a placebo. These clinical trials provide information on the efficacy of different dose levels, the schedule for administering the drug, and the short-term safety of the drug in patients [13] after the MTD has been carefully determined in a Phase I clinical trial. In the context of life-threatening illness, given the hoped-for benefit, we must aim for an 'acceptable' level of toxic response [16]. Due to ethical reasons, it is imperative that the estimation of the MTD is determined using as few subjects as possible while making sure that the estimate is accurate [19]. This is accomplished by using experimental designs.

In these studies, an experimental design is a set of rules that assign subjects to different dose levels. Such designs are called dose-response designs. For practical considerations, the dose levels are usually fixed in advance. From a design point of view, one may note that very little is known about the appropriate dose range that will be efficacious with tolerable toxicity. Furthermore, simple random assignment of subjects to dose levels does not seem to be advisable because some subjects may receive low doses that will result in little or no efficacy and some of those who may receive high doses are likely to be exposed to severe, often fatal toxicity.

In order to avoid such problems, the MTD should be determined using as few subjects as possible. This is best done through sequential designs. A sequential design in this context

is one in which the assignment of a dose to the next subject depends on the outcome(s) of the previous subject(s). The level the next subject(s) receive is never more than one level away from the prior level. The responses are assumed to be binary - toxic or non-toxic, simply success or failure.

In dealing with such discrete levels and binary responses, Dixon and Mood [6] introduced a sequential design called the *Up-and-Down* (UD) method for obtaining and analyzing sensitivity data. Anderson, McCarthy and Tukey [1] first brought the UD design into the statistical community. The objective of the design was to estimate the mean of a normal distribution and the maximum likelihood estimation procedure was used for this purpose. The UD method which was originally used for explosive trials has been of interest in Phase I clinical trials. We describe it below.

Let the levels be $\ldots, d_{-2}, d_{-1}, d_0, d_1, d_2, \ldots$. The levels are equally spaced. Assign the first subject to level d_0. Suppose the m^{th} trial is performed at the d_j^{th} level. Then the next trial will be at the level d_{j-1} or d_{j+1} according to whether there was a success or a failure respectively. The design is illustrated in Fig. 1.1 below where the x's represent successes and the o's represent failures.

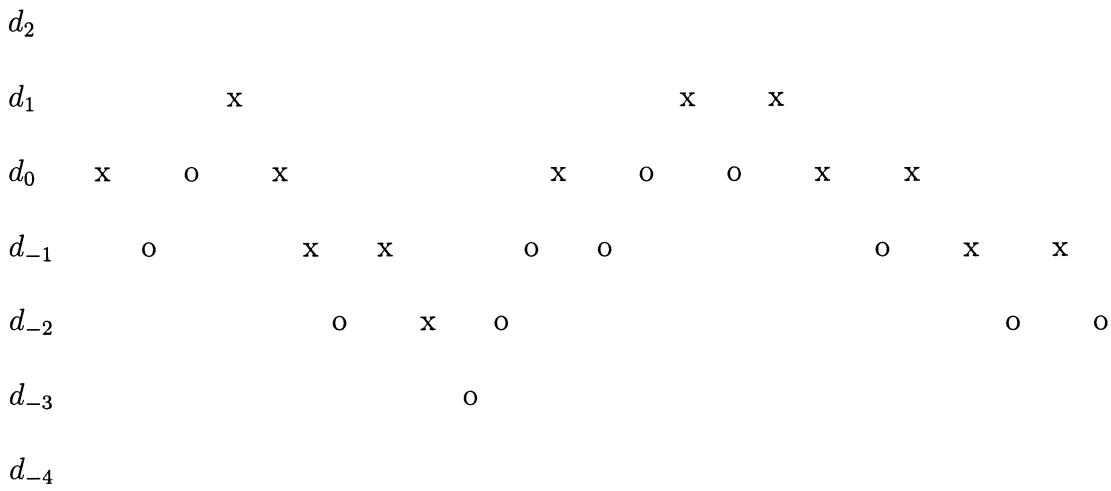

Fig. 1.1: Representation of the UD method of a sample of twenty-five tests.

The UD method automatically concentrates testing around the mean. Observe that the method uses only the outcome of the last trial in order to determine where the next trial is taken. Narayana in his thesis [15] introduced two alternative sequential designs in which the selection of the next level depends, not only on the outcome of the last trial, but also on all previous outcomes on the current level. These designs were meant to estimate the "median effective dose" (ED50) which happens to be the same as the mean in a normal population. Narayana [15] also considered the uniform distribution. The two rules are called the *1-rule* and the *3-rule* and these are explained below.

The 1-rule

As earlier, suppose the m^{th} trial is performed at the d_j^{th} level. Denote the total number of successes and failures on the level d_j by X_j and Y_j, respectively. Set $N_j = X_j + Y_j$. If $X_j > Y_j$, then assign the next subject (i.e., at the $(m+1)^{th}$ trial) to level d_{j-1} or d_j if the last trial was a success or a failure respectively. If $X_j < Y_j$, then assign the next subject to

level d_j or d_{j+1} if the last trial was a success or a failure respectively. If $X_j = Y_j$ then we take a further observation on level d_j. The rule is illustrated as in Fig. 1.2 below.

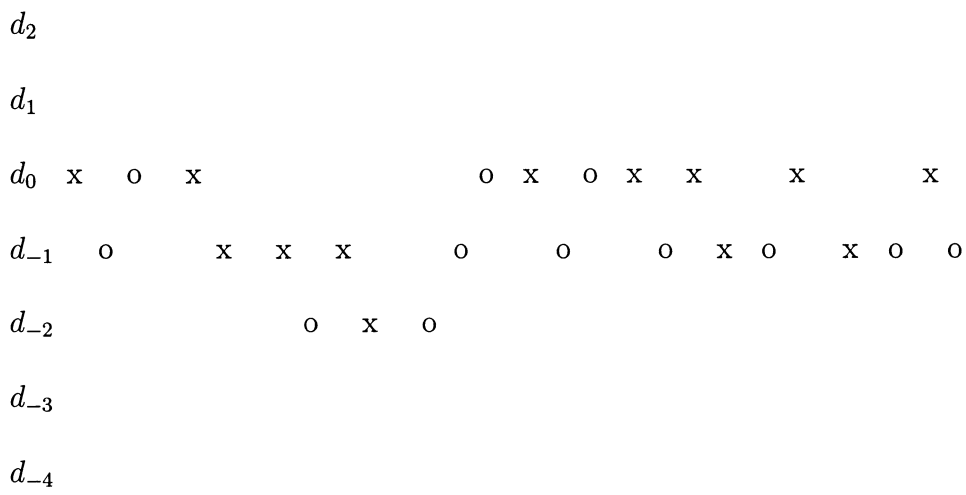

Fig. 1.2: Representation of the *1-rule.*

Note that the condition $X_j > Y_j$ is equivalent to $X_j/N_j > 0.5$.

The 3-rule

This rule uses information on three levels, d_{j-1}, d_j, d_{j+1} and is defined as follows:

If $X_{j-1} + X_j + X_{j+1} > Y_{j-1} + Y_j + Y_{j+1}$, then the next trial is taken at level d_{j-1} or d_j, according to whether the last observation was a success or a failure, respectively.

If $X_{j-1} + X_j + X_{j+1} < Y_{j-1} + Y_j + Y_{j+1}$, then the next trial is taken at level d_{j+1} or d_j if the last observation was a failure or a success.

In the case where $X_{j-1} + X_j + X_{j+1} = Y_{j-1} + Y_j + Y_{j+1}$, the observations on the levels d_{j-1}, d_j, d_{j+1} give us no idea whether to move up, down or stay on the current level, d_j. So we just consider the observations on the current level, X_j and Y_j, and follow the *1-rule.* The

3-Rule is illustrated as in Fig. 1.3 below.

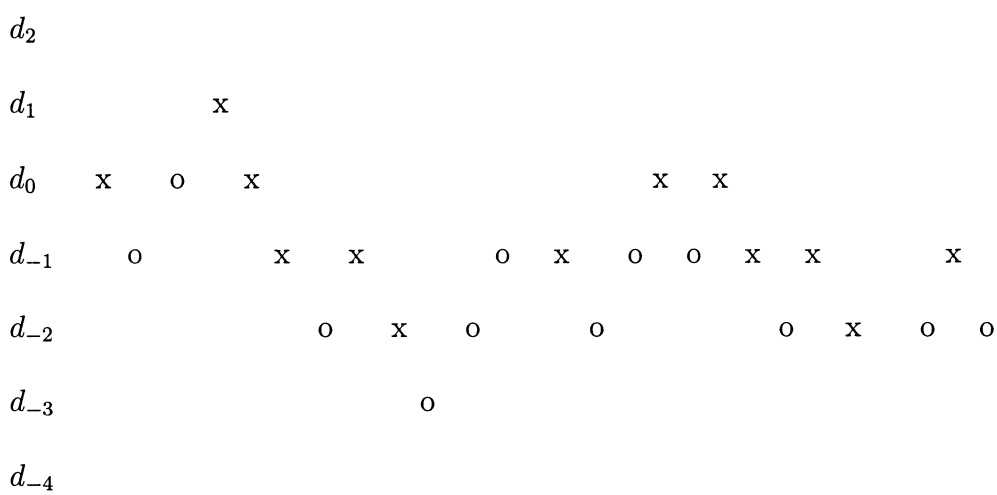

Fig. 1.3: Representation of the *3-rule*.

Subsequently, the UD method has been the focus of dose-response studies. In contrast, neither Narayana's contribution in his thesis has been published nor any further study on it has been conducted. However, two designs namely the *k-in-a-row* (KROW) rule and the *Continual Reassessment Method* (CRM), have the same feature as Narayana's rule (NR) in the sense that the decision for selection of the next level takes into account earlier information. These developments will be discussed in detail in chapter 2. Several estimators of the target dose in Phase I clinical trials have been proposed. For instance, Dixon and Mood [6] considered the maximum likelihood estimator (MLE). The other estimators include the weighted least squares (WLS) estimator, the empirical mean (EM), and the isotonic regression (IR) estimator. A detailed discussion of the estimators will be given in chapter 3. In chapter 4, some comparison of the designs by Monte Carlo simulation will be carried out and discussed.

Chapter 2

Designs

Designs considered for use in Phase 1 clinical trials have largely been based on Dixon and Mood's UD method. In these designs, d_j, $j = 1, 2, \ldots, L$, is a set of finite, ordered, fixed dose levels which are equally spaced on the logarithmic scale. For practical reasons, there should be only a finite number of levels on which to conduct the experiment. In this situation, if the rule suggests to go below d_1, then the next dose level will be d_1. Similarly, we stay on d_L if the rule suggests to go above d_L. Assume that we stop experimentation after the M^{th} trial. Let $Y(m)$, $m = 1, 2, \ldots, M$, be 1 or 0, according to the resulting success or failure of the M^{th} trial. Also, let $Q(d) = Pr\{Y = 1|d\}$ for dose d where $Q(d)$ is assumed to be a non-decreasing function of the dose and thus, can be considered as a distribution function. For a given probability of toxicity Γ, our objective is to estimate the corresponding quantile μ, such that $Q(\mu) = \Gamma$. Dixon and Mood [6]estimated μ for $\Gamma = 0.5$ when $Q(d)$ is the distribution function of the normal distribution. The estimation of μ for $\Gamma \neq 0.5$, specifically for

$\Gamma < 0.5$, is of practical importance. For example, in Phase 1 clinical trials in oncology, Γ is usually small, say 0.2. This is because we do not want to subject a high percentage of the target population to high toxic levels.

To estimate any quantile which imposes no parametric assumptions on $Q(d)$, a general scheme was suggested by Monro and Robbins [17]. However, this scheme assumes that the possible experimental values of dose levels is on the real line, which may not necessarily coincide with the fixed dose levels and therefore of little use in our case. In the rest of the chapter, designs related to the UD method are described and for that purpose we assume that the last trial was on dose level d_j.

2.1 Variations of The Up-and-Down Design

Derman [4] suggested a procedure for any given Γ. The design is described below.

Let $0.5 \leq \Gamma \leq 1$. At dose level d_j, if the outcome was a success, assign the next subject to d_{j-1} with a probability $\frac{1}{2\Gamma}$ or to d_{j+1} with a probability $1 - \frac{1}{2\Gamma}$. On the other hand, if the outcome was a failure then assign the next subject to level d_{j+1}. Suppose $0 \leq \Gamma \leq 0.5$. If the outcome was a success, then assign the next subject to d_{j-1}. If the outcome was a failure, assign the next subject to level d_{j+1} with probability $\frac{1}{2\Gamma}$ or to d_{j-1} with probability $1 - \frac{1}{2\Gamma}$. Observe that when $\Gamma = 0.5$, the design becomes a UD design. Then based on a fixed number of observations, the estimate of μ, $\hat{\mu}$, is the most frequent value of d, if unique, or

the arithmetic average of the most frequent levels, if not unique. This design asymptotically results in a unimodal distribution of dose level assignments with mode as close to μ as is possible given the discreteness of the dose levels permitted.

A block UD method which involves taking a number of observations per trial at sequentially determined levels has also been introduced by Tsutakawa [21]. This method was used to study the estimation of the median of an unknown continuous distribution function from quantal response (i.e. each outcome is classified merely as a response or non-response) data obtained sequentially in blocks of $K \geq 1$ subject(s) per trial.
Let the block size be, $K \geq 1$ and s be a predetermined integer such that $0 \leq s < K - s$ and $J(d_j)$ be the number of responses at the last trial. According to the rule, assign the next K subjects to d_{j+1}, d_j, d_{j-1} as determined by $0 \leq J(d_j) \leq s$, $s \leq J(d_j) \leq K - s$, $K - s \leq J(d_j) \leq K$, respectively. Note that this design with $K = 1$ and $s = 0$ is the same as the Dixon and Mood's UD method.

We also note that the use of $K > 1$ conveniently reduces the number of trials. For example, for a sample size of, say, 15 and $K = 3$, there would be only 5 trials instead of 15 trials for the other designs which assign one subject at a time.

Durham and Flournoy [7] introduced two designs along the line of Derman, the Biased Coin Design (BCD) I and II, which were again based on the UD method. The two rules are as follows:

Biased Coin Design (BCD) I:

For $0 \leq \Gamma \leq 1$, toss a coin with probability of heads equal to $b = \Gamma/(1+\Gamma)$, $0 \leq b \leq 0.5$. If the toss results in heads, assign the next subject to level d_{j+1}. If it results in tails and the last outcome was a failure, assign the next subject to level d_j, whereas if the outcome was a success, assign the subject to level d_{j-1}.

Biased Coin Design (BCD) II:

For $0 \leq \Gamma \leq 0.5$, let the bias $b = \Gamma/(1-\Gamma)$, equal the odds at the target quantile. If the outcome was a failure and the toss of a biased coin results in heads, then assign the next subject to level d_{j+1}; if the toss yielded tails, assign the next subject to dose level d_j; if a success was observed, then assign the next subject to level d_{j-1}. Note that when $\Gamma = 0.5$, both designs are the same as the UD design.

These two designs also asymptotically result in a unimodal distribution of dose level assignments with mode as close to μ as is possible given the discreteness of the dose levels permitted. Giovagnoli and Pintacuda [10] showed that, for large samples sizes, the BCD is optimal within the class of random walk designs (designs that move to neighboring points with certain probabilities) that use randomization for targeting. The distribution of the dose levels is most peaked around the target dose μ.

Storer [19], in determining an MTD that stops close to the 33rd percentile in a small-sampling setting (as in Phase 1 clinical trials), suggested several simple alternatives below to the previously described designs as given below.

Design A: Groups of three subjects are assigned each time. Assign the next three subjects to level d_{j+1} if no success is observed in all three; otherwise, an additional three patients are treated at the same dose level. If only one of six is a success, escalation again continues; otherwise, the trial stops.

Design B: Single subjects are assigned to the dose levels. The next subject is assigned to level, d_{j-1} or d_{j+1} if a success or a failure is observed respectively. We note that this design is the same as the UD method given earlier. It is included here to define the two two-staged designs described in the next section.

Design C: This design is similar to design B, except that two consecutive failures must be observed before the next subject is assigned to d_{j+1}, that is, if a failure is observed, the next subject is assigned to the current dose and if another failure is observed then the next subject is assigned to d_{j+1} as said but to level d_{j-1} if a success is observed.

Design D: Groups of three subjects are assigned at a time. Assign the next group to d_{j+1} if no success is observed. If more than one success is observed assign the next group to d_{j-1}. If only one success is observed, assign the next group to d_j. This design could be considered a discretized version of the Robbins-Monro [17] procedure.

2.2 Designs Using Previous Observations

Storer [19] also proposed two two-stage designs because the single-stage designs described above could not be expected to perform well in an arbitrary dose-response setting when employed with fixed sample sizes. The two-stage designs, denoted by BC and BD, combine single-stage designs. The first stage of a two-stage design, B in BC or BD, starts with design B above (section 2.1) until a success is observed, then the next subject is assigned to d_{j-1}; the second stage design, C or D, as explained above, is then implemented, again with fixed sample size.

Korn *et al* [14] introduced what they called the 'Standard Method' (SM). In this design, three subjects are assigned to dose level d_j. If there is no success among the three subjects, assign the next three to d_{j+1}. If one success is observed, assign an additional three subjects to the current dose level. If 1 out of 6 success is observed at the dose level, assign the next three to d_{j+1}. If 2 out of 6 successes are observed, or ≥ 2 out of 3 successes are observed in the initial subjects assigned at a dose level then the MTD has been exceeded. In some cases the previous dose level is chosen to be the MTD. A more common requirement, however, is to assign 3 more subjects to the previous level if there were only three already assigned. In this design the MTD is defined as the highest level in which six patients have been assigned with ≤ 1 instances of toxicity.

Gezmu [9] introduced the *Geometric UD* design which can be used to avoid highly toxic dose levels. The design is as follows when $\Gamma = 1 - (0.5)^{1/k}$:

The next subject is assigned to

(i) dose level d_{j-1} if the last observation was a success;

(ii) dose level d_{j+1} if the k most recent subjects all received dose level d_j and there were no successes, that is, $Y(m) = Y(m-1) = \ldots = Y(m-k+1) = 0$

(iii) otherwise assign subject to dose level d_j.

This rule has come to be called the *k-in-a-row* (KROW) rule. It targets any $\Gamma = 1-(0.5)^{1/k}$. The design is similar to the BCD design introduced by Durham and Fluornoy [7] in the sense that it centres the treatment distribution around μ but it uses the information on previous observations instead of a biased coin.

Another design that takes into consideration the information on all previous outcomes is the *continual reassessment method* (CRM), which was proposed by O'Quigley, Pepe and Fisher [16]. The CRM employs Bayes' theorem. The design uses a working model for the dose-response relationship, for example, the one-parameter model

$$\Pr\{Y = 1|d_r, a\} = [(\tanh d_r + 1)/2]^a \tag{2.1}$$

where d_r, $r = 1, 2, \ldots, S$ is a set of dose levels and the parameter a is to be estimated. Let the prior distribution for a be $g(a) = \exp(-a)$, which is updated using Bayes' theorem as data become available. The design estimates the MTD sequentially by estimating a. The first subject is assigned to the lowest dose level d_1. The mean posterior density of a after each subject is computed. For example, the estimate of a, $\hat{a}_m$ after the outcome of the m^{th} subject is given by

$$\hat{a}_m = \mathrm{E}(a|\Omega_m) = \int_0^\infty a f(a|\Omega_m) da$$

where $f(a|\Omega_m) = \frac{L_{\Omega_m}(a)g(a)}{\int_0^\infty L_{\Omega_m}(u)g(u)du}$ is the posterior density of a, $L_{\Omega_m}(a)$ is the likelihood function, and $\Omega_m = \{(x_1, Y(1)), \ldots, (x_m, Y(m))\}$ are the data accumulated up to m assignments. Assuming that $m-1$ subjects have been assigned so far, the next subject is assigned to dose level x_m such that $\left| Pr\{Y = 1|x_m, \hat{a}_m\} - \Gamma \right|$ is minimized. The next dose level is chosen from (d_{j-1}, d_j, d_{j+1}), when $x_m = d_j$.

Ivanova, Montazer-Haghighi, Mohanty, and Durham [12] considered the NR, which is nothing but a modified version of Narayana's *1-rule* and compared it to the BCD, the KROW, the CRM and the *Moving Average Up-and-Down* (MAU) rule. We describe the MAU rule and the NR below.

The MAU rule is as follows:

Assign the next subject to d_{j-1} if there is at least one success among the k most recent observations on the current dose level; or to level d_{j+1} if there are no successes observed among the k most recent observations on the current dose level.

This design is similar to the KROW rule in the sense that it looks at the k most recent observations at the current dose level but it only moves up or down each time. It also targets dose levels with probability of toxicity, $\Gamma = 1 - (0.5)^{1/k}$, where $k = 1, 2, 3, \ldots$.

The NR is modified to accommodate any $\Gamma = 1 - (0.5)^{1/k}$, where $k = 1, 2, \ldots$, and is given as follows:

Recall that X_j and N_j are the number of toxic observations and the number of assignments to the dose level d_j up to and including the m^{th} subject, respectively. The ratio X_j/N_j gives the estimate of the probability of toxicity at dose d_j if N_j is not zero.

Suppose the m^{th} subject was assigned to dose level d_j, $j = 1, 2, \ldots L$. The next subject is assigned to:

(i) dose level d_{j-1} if $X_j/N_j > \Gamma$ and if at least there is one success in the last k most recent observations on the current dose level;

(ii) dose level d_{j+1} if $X_j/N_j < \Gamma$ and if there are no successes in the k most recent observations;

(iii) otherwise assign subject to dose level d_j.

Note that the extra conditions are stipulated by the MAU rule.

A clarification of the NR is in order. Consider the case where $\Gamma = 0.29$ for which $k = 2$. Suppose the m^{th} subject in the trial was the first to receive dose d_j, where $d_j \in \{d_1, \ldots, d_L\}$ and the assignments and observations for the subjects $m, \ldots, m+3$ are (d_j, d_j, d_{j+1}, d_j) and $(Y(m), Y(m+1), Y(m+2), Y(m+3)) = (0, 0, 1, 0)$ respectively. The subject $m+4$ will receive dose d_{j+1} and subject $m+5$ will receive dose d_j no matter what the outcome of subject $m+4$ is. This type of anomaly occurs when there is insufficient experience with the dose level thus making X_j/N_j a bad estimate of the probability of toxicity at a dose level.

2.3 Start-Up Rule

Storer [19] suggested using a *Start-Up* rule where, starting at the lowest dose, subjects are assigned one per dose at increasing dose levels until a success is observed. The next subject is then entered at the next lower dose level and the primary design chosen for the study is then used to determine the subsequent assignments. The primary design here refers to, for example, the BCD, the NR, etc. Korn et al. [14] found Storer's scheme too aggressive and suggested assigning two subjects instead of one at a time at increasing dose levels until the first success is observed and then reverting to the primary design. We note here that the *Start-Up* rules suggested by Storer [19] and Korn *et al* [14] are the KROW rules for $k = 1$, $\Gamma = 1 - (0.5)^{1/k} = 0.5$ and for $k = 2$, $\Gamma = 1 - (0.5)^{1/k} = 0.3$ respectively. The purpose of the *Start-Up* rule is to bring the starting point of the primary design closer to the target dose thereby conserving resources. Ivanova *et al* [12] suggested that for trials where severe toxicity events are expected, the *Start-Up* rule should depend on Γ, the probability of toxicity at a target dose and defined the *Start-Up* rule as follows:

Starting at the lowest dose, for $\Gamma = 1 - (0.5)^{1/k} = 0.5$, $k = 1$, so assign one subject per dose; for $\Gamma = 1 - (0.5)^{1/k} = 0.3$, $k = 2$, so assign two per dose; and for, $\Gamma = 1 - (0.5)^{1/k} = 0.2$, $k = 3$, therefore assign three subjects per dose. If no success is observed, go to the next higher dose. If a success is observed go to the next lower dose level and revert to the primary design. It is possible that the *Start-Up* rule will use up all subjects in the sample; in this case one cannot attribute the results to a particular design.

Chapter 3

Estimators

Several estimators of μ have been proposed. Examples include the maximum likelihood estimator (MLE), weighted least squares (WLS) estimator, the empirical mean (EM) and the isotonic regression (IR) estimator. Durham and Fluornoy [7] used the empirical mode of the treatment distribution as an estimate of μ but the mode seems not to do well and so was not considered by Stylianou and Fluornoy. Stylianou and Fluornoy [20] considered Durham and Flournoy's BCD for the estimation of μ by using the MLE, WLS, EM, IR and a modified IR using linear interpolation. A detailed presentation of the MLE, WLS, EM, and IR is given below.

3.1 The Maximum Likelihood Estimator (MLE)

Let the equally-spaced dose levels be d, the variate of the distribution under consideration with mean and variance, μ and σ^2 respectively; also let q be a rough estimate of σ. Then the distance between dose levels is taken to be q, i.e., the trials are conducted at

$$d_j = d_0 \pm jq, \qquad j = -L, \ldots, L$$

where d_0 is the initial dose level. Recall that the number of successes and failures are X_j and Y_j respectively at the m^{th} level. Let $X = \sum X_j$ and $Y = \sum Y_j$. The probability of obtaining such a sample is

$$\mathrm{P}(X, Y|d_0) = a \prod_{j=-L}^{L} p_j^{X_j}(1-p_j)^{Y_j} \tag{3.1}$$

where p_j = the probability of success at the m^{th} level and a is not a function of μ and σ.

In the case of the normal distribution, d is the normally distributed variate with mean and variance, μ and σ^2, respectively and p_j is given by

$$p_j = \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{y_j} \exp\left(-\frac{1}{2}\frac{(t-\mu)^2}{\sigma^2}\right) dt = 1 - (1 - p_j) \tag{3.2}$$

We note that

$$|X_j - Y_{j-1}| = 0 \text{ or } 1. \tag{3.3}$$

Therefore either one of the sets (X_j) or (Y_j) contain practically all the information given by the sample. The smaller $X = \sum X_j$ or $Y = \sum Y_j$ is used for the analysis. Let us assume that $X \leq Y$. Now $Y - X$ is expected to be small according to the equation (3.3) above. In the case where the initial dose level, d_0, was poorly selected, a number of observations have

to be expended to get to the region of the mean and thus these observations contribute little to a precise location of the mean. We neglect this portion of the information and simply take the likelihood function to be maximized as

$$\mathrm{P}(X_j, Y_j | d_0, Y - X) = a' \prod_j p_j^{X_j} (1 - p_{j-1})^{X_j}. \tag{3.4}$$

If we apply the principle of maximum likelihood for the estimation of μ and σ^2, the derivatives of log P with respect to μ and σ are equated to zero to obtain the relation,

$$\Sigma X_j \left(\frac{z_{j-1}}{(1 - p_{j-1})} - \frac{z_j}{p_j} \right) = 0, \tag{3.5}$$

$$\Sigma X_j \left(\frac{x_{j-1} z_{j-1}}{(1 - p_{j-1})} - \frac{x_j z_j}{p_j} \right) = 0, \tag{3.6}$$

respectively where x_j is the standardized variable $\frac{d_j - \mu}{\sigma}$ and z_j is the ordinate of the distribution of d at d_j. For example,

$$z_j = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{1}{2} \left(\frac{d_j - \mu}{\sigma} \right)^2 \right)$$

is the ordinate of the distribution of d at d_j if the distribution is $N(\mu, \sigma^2)$.

Substituting the expected value of d_j, $E(d_j)$, for d_j, the left hand sides of equations (3.5) and (3.6) are readily found to be zero. If we let

$$w_0 = 1$$

and

$$w_j = \begin{cases} \prod_{t=0}^{j-1} \frac{1-p_t}{p_t} & \text{if } j > 0; \\ \prod_{t=-j}^{1} \frac{p_t}{1-p_t} & \text{if } j < 0 \end{cases}$$

then from the relation

$$\frac{\mathrm{E}(X_j)}{p_j} = \frac{\mathrm{E}(X_{j+1})}{1-p_j},$$

it follows that

$$\mathrm{E}(X_j) = \frac{Xw_j}{\sum_{-\infty}^{\infty} w_j}.$$

The roots of equations (3.5) and (3.6) are the maximum likelihood estimates of μ and σ. A close approximations of the roots can be obtained when $q \leq 2\sigma$. We consider the function

$$\alpha(\mu) = \frac{z(x)}{1-p(x)} - \frac{z(x+q/\sigma)}{p(x+q/\sigma)}$$

where $\mu = x + q/2\sigma$. This expression is nearly linear in μ when $q \leq 2\sigma$; similarly

$$\beta(\mu) = \frac{xz(x)}{1-p(x)} - \frac{(x+q/\sigma)z(x+q/\sigma)}{p(x+q/\sigma)}$$

is nearly quadratic in μ. If we let

$$\mu_1 = \frac{1}{X}\sum X_j d_j \tag{3.7}$$

and

$$\mu_2 = \frac{1}{X}\sum X_j d_j^2, \tag{3.8}$$

we have

$$\mathrm{E}(\mu_1) = \mu - q/2$$

and

$$\mathrm{E}(\mu_2) - \mathrm{E}^2(\mu_1) + \frac{q^2}{4} = \frac{\sigma^2 \sum w_j x_j^2}{\sum w_j}.$$

The MLE of μ is

$$\hat{\mu}_1 = d' + q\left(\frac{\sum jX_j}{X} \pm \frac{1}{2}\right)$$

where d' is the normalized level corresponding to the lowest level on which the less frequent event between successes and failures occurs. When analysis is based on failures, we use the plus sign whereas the negative sign is used when the analysis is based on successes.

However, the sample sizes in oncology or acute toxicity trials are too small and the distribution is usually not normal. The MLE is also very unstable because it does not exist for small samples [17].

3.2 The Empirical Mean (EM) Estimator

Brownlee, Hodges, and Rosenblatt [3] proposed the empirical mean estimator. According to them, the MLE proposed by Dixon and Mood for normal distribution is asymptotically equivalent to the empirical mean of all observations. The distribution of the dose assignments tends to vary unimodally around the target quantile μ. Thus the empirical mean estimator is simply the average of all the doses that have been administered.

Likewise, Stylianou and Fluornoy [20] presented a simple nonparametric estimator of μ which is the truncated simple average of all the doses that have been administered given by

$$\hat{\mu}_3 = \frac{1}{n}\sum_{i=t}^{N+1} d_j \tag{3.9}$$

where $n = N - t + 2$ and $t = \max\{i$: the first i subjects having the same response$\}$. At the beginning of an UD design, a run may have all positive or all negative responses, i.e. all successes or all failures, which are usually ignored and truncated. The last dose of the

run is kept and the dose to be assigned after the last dose of the study is also recorded. Stylianou and Flournoy [20] found this estimator to be superior to the estimator of the dose level mean, particularly when the difference between the starting dose and the target dose is large.

Several others who have studied the use of the empirical mean together with modifications, as the estimator of the μ when $\Gamma = 0.50$, include Dixon [5], Hsi [11] and Tsutakawa [20]. Narayana estimated the ED50 in a normal population (which is the same as the mean) for the target quantile.

3.3 The Weighted Least Squares (WLS) Estimator

Stylianou and Flournoy [20] estimated the target quantile using the WLS method. Recall that X_j and N_j are the number of successes and the number of assignments to the dose level d_j up to and including the m^{th} subject, respectively; also $j = 1, 2, \ldots L$. Then, $\hat{Q}(d_j) = X_j/N_j$. The theory of generalized linear models (GLM) is used to obtain the WLS estimator. The probability of the outcome of the m^{th} subject is given by $Q(d_j) = Pr\{Y = 1|d_j\}$ and $1 - Q(d_j)$ for a success and a failure respectively. The logarithm of the odds of success verses failure $\frac{Q(d_j)}{1-Q(d_j)}$ is called the logit of the response function. Let z_j =logit$(Q(d_j))$ and the dose levels, d_j, $j = 1, 2, \ldots, L$, be the dependent and the explanatory (independent) variables respectively. Recall that $Q(d_j)$ is an increasing function of d_j. Assuming the underlying

distribution Q for dose-toxicity to be logistic with two parameters α and β, as given by

$$Q(d_j, \alpha, \beta) = \frac{\exp(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j)}{1 + \exp(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j)} \tag{3.10}$$

we find that the logit of the response function is a linear function of the dose, that is,

$$\text{logit } (Q(d_j)) = \ln \left(\frac{Q(d_j)}{1 - Q(d_j)} \right) = \beta^{-1}(d_j - \alpha) \tag{3.11}$$

For derivation see Appendix A.1.

Define

$$\mathbf{Z} = (z_1, \ldots, z_L)',$$

$$\mathbf{D} = \begin{pmatrix} 1 & \ldots & 1 \\ d_1 & \ldots & d_L \end{pmatrix}'$$

and

$$\theta = \begin{pmatrix} \alpha \\ \beta \end{pmatrix}$$

Then

$$\mathbf{Z} = \mathbf{D}\theta + \epsilon,$$

where the expectation and the covariance of ϵ are $\mathbf{0}$ and $\mathbf{\Sigma}$ and α and β are the intercept and slope parameters of the dose-response curve, respectively. The covariance is a KxK matrix with the r^{th} row and the l^{th} column element

$$\Sigma_{[r,l]} = \text{cov}\left(\ln\frac{Q_r}{1-Q_r}, \ln\frac{Q_l}{1-Q_l}\right) = \text{cov}\left(\ln\frac{X_r}{Y_r - X_r}, \ln\frac{X_l}{Y_l - X_l}\right)$$

for all $r, l = 1, 2, \ldots, L$. The WLS method requires that we minimize

$$(\mathbf{Z} - \mathbf{D}\theta)'\mathbf{\Sigma}^{-1}(\mathbf{Z} - \mathbf{D}\theta) \tag{3.12}$$

It is noted that the observations from the design are not independent due to the way the subjects are sampled. The value of θ that minimizes the above equation with $\hat{\mathbf{\Sigma}}$ replacing $\mathbf{\Sigma}$ is

$$\hat{\theta} = (\mathbf{D}'\hat{\mathbf{\Sigma}}^{-1}\mathbf{D})^{-1}\mathbf{D}'\hat{\mathbf{\Sigma}}^{-1}\mathbf{Z}.$$

We solve $\text{logit}(\Gamma) = \hat{\alpha} + \hat{\beta}\mu$ for μ and insert the WLS estimator $\hat{\theta} = (\hat{\alpha}, \hat{\beta})'$ to give the equation (3.13) below for the WLS estimator for μ

$$\hat{\mu}_4 = \frac{ln\left(\frac{\Gamma}{1-\Gamma}\right) - \hat{\alpha}}{\hat{\beta}} \tag{3.13}$$

In Phase I trials the WLS has been suggested for use under the logistic distribution since the response in these trials is binary.

3.4 The Isotonic Regression (IR) Estimator

Stylianou and Flournoy [20] suggested the IR estimator which was then used by Ivanova *et al.* [12] to estimate μ. Suppose h is the maximum index such that $N_j > 0$ where $h \leq L$.

Then estimate $Q(d_j)$ by, $\hat{Q}(d_j) = X_j/N_j$ for $j = 1, 2, \ldots h$. The problem with using this method for estimation is that $\{\hat{Q}(d_j), \ldots, \hat{Q}(d_h)\}$ may not be non-decreasing with dose levels. In cases like these the proportions $\hat{Q}(d_j)$ have to be put in a non-decreasing order by isotonic regression procedure. The most widely used algorithm for computing the isotonic regression is the pool-adjacent-violators algorithm (PAVA) [2, 22]. The estimate of μ is then obtained by interpolating between d_m and the next higher level, d_{m+1}. The estimate of μ is then found by interpolation based on the assumed distribution.

For instance, for the two-parameter logistic model as given in (3.10), for dose-toxicity, the estimate, $\hat{\mu}_4$, has the expression,

$$\hat{\mu}_4 = d_m + \frac{\log[\Gamma/(1-\Gamma)] - \log[Q^*(d_m)/(1-Q^*(d_m))]}{\log[Q^*(d_{m+1})/(1-Q^*(d_{m+1}))] - \log[Q^*(d_m)/(1-Q^*(d_m))]}(d_{m+1} - d_m) \quad (3.14)$$

where Q^*'s are the isotonic regression estimates of the Q's and $Q^*(d_m) < \Gamma \leq Q^*(d_{m+1)}$. In the case where Γ is less than $Q^*(d_1)$, $\hat{\mu}_4 = d_1$ and if Γ is greater than $Q^*(d_L)$, $\hat{\mu}_4 = d_L$. The derivation of (3.14) is done in Appendix A.2.

Remark: In some instances where the denominator, $Q^*(d_m)$, or $Q^*(d_{m+1})$ is zero, such data is excluded.

Chapter 4

Comparison Of Designs

As noted above in Dixon and Mood's UD method, the level to which the next subject is assigned depends only on the observation just prior to it. That is, only the very last observation is used to determine where the next trial is taken and thus, the information contained in the observations from $1, \ldots, m-1$ does not play any role in assigning the $(m+1)^{th}$ subject. By using all the information on previous observations on the current level, Narayana [15] states that we might conceivably concentrate assignments closer to the mean dose level and possibly get a better estimate of it. Thus, the NR is perceived to perform better than the UD method.

Unlike the UD method, the CRM updates the notion of the dose-response relationship as the observations on severe toxicity become available thereby using more information than the UD method. It also has been found to perform better than the UD method. On the other hand, Korn *et al.* [14] found that the CRM takes longer to complete and also assigns

more subjects to higher dose levels than the SM.

Comparing BCD I and BCD II, Durham and Flournoy [7] found that both designs centre the stationary assignment distribution around the unknown targeted percentile (the probability of toxicity that corresponds to μ) in the sense that the mode occurs as close to μ as is possible given the distance between dose levels.

Ivanova *et al.* [12] compared several improved UD designs which included the NR, the CRM, the BCD, the KROW and the MAU rule by the quality of the estimation of μ using the isotonic estimator only for the logistic model given by

$$Q(d_j, \alpha, \beta) = \left[\frac{\exp(\alpha + \beta d_j)}{1 + \exp(\alpha + \beta d_j)} \right]^{\gamma} \tag{4.1}$$

where $\gamma = 1$. The comparison was done by simulation. They observed that the NR and the KROW performed better than the BCD with the NR performing the best, especially in large sample sizes when the distribution was logistic.

In this project, we use simulation by exactly following [12] and compare the KROW, BCD, and the NR, when the distribution function Q is the generalized logistic as in (4.1), specifically, for $\gamma = 1, 2, 3,$ and 6, and the gamma as given by

$$Q(x, \alpha, \beta) = \frac{1}{\Gamma(\alpha)\beta^{\alpha}} \int_0^{d_j} d_j^{\alpha-1} \exp(-d_j/\beta) dx \tag{4.2}$$

where $x = d_j$. The results are presented in Tables 4.2 - 4.5. The purpose is to examine the performance of these designs when the unknown distribution is not logistic but a similar one.

4.1 Simulation Set-up

In comparing the designs, we look at the quality of the estimator of μ using the isotonic estimator. We calculate the root mean square error (RMSE) for the isotonic estimator to see which one gives more precision in estimating the target dose; we also look at how tightly the dose assignments tend to concentrate around μ by calculating the average squared targeting error (ASTE), which is given by $\frac{1}{N}\sum_{i=t}^{N}(x_i-\mu)^2$ for each run where N is the sample size and t is the first dose in the primary design, and we report TE, the square root of the mean of the values of ASTE over 4000 replications. In addition, we calculate the targeting bias (TBIAS) which is the average difference between the mean dose and μ, and the average proportion of toxic responses observed in the trial (TOX). We do not investigate the CRM due to the fact that it assigns subjects to high, toxic dose levels. The results of the Start-Up rule are not counted in the calculation of the TE and TBIAS. As in [12], we use the following for the computer simulation (see Appendix C) study:

1. Sample size, $N = 15, 25, 35, 100$;

2. Two target probabilities, $\Gamma = 0.2, 0.3$;

3. Number of replications, 4000; and

4. The isotonic regression estimator, $\hat{\mu}_4$, based on the logistic model.

5. (a) The form of Q is (4.1), $\gamma = 1, 2, 3$ and 6;

   The three scenarios to select (α, β) for each γ (see Tables 4.1 for values) :

- Scenario I represents the case where the probability of toxicity at the first three doses is small and rapidly increases at subsequent doses,
- Scenario II represents the case where the probability of toxicity moderately increases from dose to dose; this scenario would be the ideal case,
- Scenario III represents the case where the target doses (doses corresponding to $\Gamma = 0.2, 0.3$) are far away from the start than the first two scenarios.

(b) The form of Q is Gamma (4.2) with similar three scenarios. The dose-toxicity curves illustrating all possible cases are presented in Appendix B.

Table 4.1: *Values of α and β for scenarios I, II, III under the logistic and the Gamma distributions.*

Distribution	Value of γ	Scenario	α	β
Logistic	1	I	-6.0	1.0
		II	-3.0	0.5
		III	-4.0	0.5
	2	I	-2.9	0.75
		II	-1.3	0.40
		III	-2.2	0.35
	3	I	-1.99	0.70
		II	-0.66	0.38
		III	-1.3	0.32
	6	I	-0.79	0.65
		II	0.29	0.36
		III	-0.20	0.28
Gamma		I	4.0	1.0
		II	4.0	1.5
		III	2.5	6.0

4.2 Results

The results obtained from the computer simulations are presented below.

Table 4.2: *Targeting Performance of the designs under the logistic model with* $\gamma = 1$.

N	Design	Scenario I				Scenario II				Scenario III			
		RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE
$\Gamma = 0.2$													
N=15	BCD	1.43	-1.19	0.05	3.02	**1.41**	-0.99	0.07	2.09	2.26	-2.08	0.07	8.10
	KROW	**1.15**	-0.82	0.06	2.01	1.42	-0.66	0.08	1.50	2.01	-1.77	0.07	6.31
	NR	1.22	-0.30	0.10	1.94	1.70	0.10	0.12	2.39	**1.82**	-0.86	0.11	5.11
N=25	BCD	1.35	-0.63	0.07	1.80	1.37	-0.59	0.11	1.99	1.77	-1.62	0.04	5.47
	KROW	**1.25**	-0.32	0.08	1.27	**1.36**	-0.30	0.12	1.57	**1.43**	-1.17	0.05	3.74
	NR	1.39	0.25	0.13	1.61	1.72	0.47	0.17	2.75	1.73	-0.07	0.09	3.49
N=35	BCD	1.17	-0.52	0.10	1.64	**1.12**	-0.47	0.14	1.93	1.49	-1.30	0.08	4.67
	KROW	**1.04**	-0.29	0.12	1.19	1.20	-0.22	0.15	1.58	**1.33**	-0.85	0.09	3.18
	NR	1.52	0.20	0.17	1.32	1.32	0.45	0.20	2.37	1.57	0.19	0.14	3.24
N=100	BCD	0.41	-0.37	0.17	1.39	0.74	-0.25	0.18	1.83	0.85	-0.65	0.15	3.04
	KROW	**0.37**	-0.21	0.18	1.07	0.71	-0.11	0.19	1.55	0.75	-0.36	0.17	2.22
	NR	0.38	0.06	0.21	0.74	**0.70**	0.25	0.21	1.46	**0.73**	0.12	0.20	1.72
$\Gamma = 0.3$													
N=15	BCD	1.12	-0.79	0.06	2.06	1.46	-1.09	0.11	3.16	2.10	-2.14	0.06	7.89
	KROW	1.26	-0.63	0.07	1.85	1.79	-1.26	0.11	3.79	2.11	-1.99	0.06	6.83
	NR	**1.11**	-0.20	0.11	1.58	**1.24**	-0.42	0.15	2.72	**1.69**	-1.34	0.08	5.02
N=25	BCD	**1.07**	-0.51	0.15	1.69	**1.31**	-0.76	0.18	2.79	1.46	-1.40	0.11	5.33
	KROW	1.09	-1.18	0.10	2.79	1.57	-1.76	0.12	5.11	2.03	-1.88	0.09	7.02
	NR	1.29	-0.08	1.20	1.31	1.46	-0.18	0.22	2.43	**1.33**	-0.52	0.15	3.56
N=35	BCD	1.03	-0.40	0.19	1.55	**1.11**	-0.59	0.21	2.60	1.26	-1.03	0.16	4.22
	KROW	0.98	-1.63	0.09	4.05	1.55	-2.18	0.12	6.45	2.00	-2.40	0.09	9.01
	NR	**0.97**	-0.05	0.24	1.10	1.13	-0.07	0.25	0.09	**1.21**	-0.32	0.20	0.97
N=100	BCD	0.33	-0.27	0.26	1.35	0.66	-0.31	0.27	2.27	0.71	-0.46	0.25	2.89
	KROW	0.95	-2.87	0.04	9.58	1.52	-2.95	0.09	9.49	1.99	-4.37	0.06	22.2
	NR	**0.32**	-0.01	0.29	0.67	**0.61**	-0.03	0.29	1.25	**0.61**	-0.08	0.27	1.53

The smallest RMSE is indicated in **bold**.

Table 4.3: *Targeting Performance of the designs under the logistic model with* $\gamma = 2$.

N	Design	Scenario I				Scenario II				Scenario III			
		RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE
$\Gamma = 0.2$													
N=15	BCD	1.32	-0.83	0.03	1.50	**1.31**	-0.59	0.08	1.28	2.01	-1.90	0.06	6.65
	KROW	1.37	-0.47	0.04	0.99	1.53	-0.28	0.09	1.07	**1.75**	-1.53	0.07	4.98
	NR	**1.22**	0.06	0.09	1.41	1.72	0.39	0.13	0.23	1.88	-0.63	0.99	4.25
N=25	BCD	**1.29**	-0.43	0.09	1.32	**1.27**	-0.30	0.12	1.44	1.58	-1.32	0.05	4.32
	KROW	1.39	-0.17	0.11	1.02	1.34	-0.10	0.14	1.28	**1.34**	-0.89	0.06	2.93
	NR	1.79	0.34	0.16	1.51	1.80	0.63	0.18	2.62	1.82	0.12	0.10	3.54
N=35	BCD	**1.02**	-0.37	0.12	1.30	**1.05**	-0.22	0.15	1.47	1.45	-1.02	0.08	3.77
	KROW	1.06	-0.17	0.14	1.00	1.13	-0.05	0.16	1.26	**1.28**	-0.62	0.10	2.58
	NR	1.59	0.25	0.19	1.27	1.21	0.55	0.20	2.23	1.56	0.30	0.15	3.20
N=100	BCD	0.38	-0.28	0.17	1.23	0.64	-0.08	0.19	1.48	0.86	-0.50	0.16	2.76
	KROW	**0.35**	-0.14	0.19	0.98	**0.60**	-0.01	0.20	1.29	**0.75**	-0.26	0.17	2.07
	NR	0.36	0.09	0.21	0.70	**0.60**	0.29	0.22	1.29	0.76	0.23	0.20	1.79
$\Gamma = 0.3$													
N=15	BCD	**1.11**	-0.53	0.09	1.55	**1.34**	-0.80	0.13	2.37	1.92	-2.02	0.05	6.82
	KROW	1.29	-0.56	0.10	1.71	1.54	-0.97	0.12	2.85	1.52	-0.66	0.06	3.07
	NR	1.21	-0.02	0.14	1.49	1.44	-0.17	0.17	2.30	**1.61**	-1.12	0.08	4.28
N=25	BCD	1.10	-0.38	0.18	1.46	**1.29**	-0.51	0.19	2.21	1.58	-1.28	0.11	5.13
	KROW	**0.96**	-1.21	0.10	2.70	1.33	-1.53	0.13	3.94	1.67	-0.82	0.08	4.03
	NR	1.36	0.02	0.22	1.23	1.51	0.02	0.23	2.14	**1.12**	-0.42	0.16	3.47
N=35	BCD	**0.82**	-0.31	0.21	1.41	1.15	-0.40	0.22	2.11	**1.25**	-0.91	0.16	3.95
	KROW	0.91	-1.61	0.086	3.79	1.29	-1.90	0.12	4.90	1.91	-2.41	0.09	8.79
	NR	1.07	-0.00	0.25	1.04	**1.11**	0.04	0.26	1.89	1.38	-0.24	0.20	2.90
N=100	BCD	0.34	-0.21	0.27	1.32	0.69	-0.20	0.28	2.05	0.79	-0.37	0.25	2.87
	KROW	0.85	-2.52	0.04	7.20	1.28	-2.46	0.09	6.60	1.91	-4.20	0.06	20.3
	NR	**0.32**	0.01	0.29	0.66	**0.59**	0.06	0.29	1.18	**0.69**	-0.02	0.28	1.64

Table 4.4: *Targeting Performance of the designs under the logistic model with* $\gamma = 3$.

N	Design	Scenario I				Scenario II				Scenario III			
		RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE
$\Gamma = 0.2$													
N=15	BCD	1.31	-0.73	0.04	1.31	**1.35**	-0.58	0.08	1.24	1.88	-1.72	0.06	5.60
	KROW	1.45	-0.37	0.05	0.90	1.54	-0.27	0.09	1.01	1.70	-1.35	0.06	4.11
	NR	**1.22**	0.15	0.10	1.35	1.70	0.41	0.13	2.17	**1.64**	-0.52	0.09	3.67
N=25	BCD	**1.21**	-0.38	0.10	1.23	1.27	-0.31	0.12	1.35	1.50	-1.12	0.06	2.54
	KROW	1.41	-0.15	0.11	0.97	1.38	-0.09	0.14	1.21	**1.36**	-0.71	0.07	2.54
	NR	1.81	0.35	0.17	1.47	**1.17**	0.59	0.19	2.44	1.79	0.32	0.11	3.40
N=35	BCD	1.44	-0.35	0.12	1.23	1.38	-0.22	0.15	1.39	1.29	-0.91	0.09	3.19
	KROW	1.11	-0.15	0.14	0.96	1.06	-0.06	0.16	1.22	**1.26**	-0.55	0.11	2.32
	NR	**1.07**	0.28	0.19	1.21	**0.99**	0.50	0.21	1.07	1.85	0.42	0.16	3.15
N=100	BCD	0.35	-0.25	0.17	1.16	0.59	-0.10	0.19	1.42	0.81	-0.42	0.16	2.51
	KROW	**0.33**	-0.13	0.19	0.95	0.58	-0.01	0.20	1.24	0.76	-0.21	0.17	1.97
	NR	**0.33**	0.10	0.21	0.68	**0.57**	0.23	0.22	1.17	**0.73**	0.25	0.20	1.77
$\Gamma = 0.3$													
N=15	BCD	1.09	-0.46	0.10	1.43	1.29	-0.77	0.13	2.25	1.76	-1.75	0.06	5.59
	KROW	1.21	-0.57	0.10	1.63	1.52	-0.96	0.12	2.76	1.90	-1.63	0.06	5.07
	NR	**1.02**	0.03	0.15	1.5	**1.41**	-0.09	0.17	2.21	**1.60**	-0.97	0.09	3.73
N=25	BCD	1.05	-0.33	0.18	1.40	1.18	-0.52	0.20	2.07	1.44	-1.14	0.13	4.22
	KROW	**0.95**	-1.16	0.10	2.54	1.29	-1.50	0.13	3.76	1.87	-1.80	0.10	6.26
	NR	1.21	0.05	0.23	1.20	**1.13**	0.01	0.24	2.01	**1.22**	-0.33	0.17	3.25
N=35	BCD	0.90	-0.26	0.21	1.31	**1.03**	-0.37	0.23	2.03	**1.28**	-0.85	0.17	3.70
	KROW	**0.88**	-1.54	0.09	3.52	1.25	-1.84	0.12	4.62	1.83	2.36	0.10	8.38
	NR	1.16	0.07	0.26	1.03	1.43	0.03	0.26	1.79	1.39	-0.17	0.21	2.70
N=100	BCD	0.35	-0.18	0.27	1.27	0.62	-0.19	0.28	1.94	0.81	-0.35	0.25	2.81
	KROW	0.82	-2.37	0.04	6.32	1.22	-2.38	0.09	6.15	1.81	-4.04	0.06	18.6
	NR	**0.33**	0.02	0.29	0.65	**0.58**	0.00	0.29	1.14	**0.70**	0.00	0.28	1.58

Table 4.5: *Targeting Performance of the designs under the logistic model with* $\gamma = 6$.

N	Design	Scenario I				Scenario II				Scenario III			
		RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE
$\Gamma = 0.2$													
N=15	BCD	1.36	-0.60	0.04	1.10	**1.39**	-0.44	0.08	1.06	1.73	-1.55	0.05	4.67
	KROW	1.69	-0.24	0.06	0.80	1.57	-0.14	0.09	0.92	2.21	-2.35	0.06	7.64
	NR	**1.33**	0.26	0.11	1.34	1.73	0.50	0.14	2.16	**1.71**	-0.37	0.09	3.37
N=25	BCD	1.30	-0.34	0.10	1.12	1.27	-0.19	0.13	1.24	**1.47**	-0.99	0.06	3.29
	KROW	1.34	-0.15	0.12	0.91	1.28	-0.01	0.14	1.11	1.74	-1.77	0.07	5.14
	NR	**1.24**	0.32	0.17	1.33	**1.23**	0.61	0.19	2.32	1.90	0.44	0.12	3.50
N=35	BCD	1.04	-0.31	0.13	1.11	**0.99**	-0.14	0.15	1.26	**1.29**	-0.70	0.10	2.82
	KROW	**1.03**	-0.15	0.15	0.90	1.10	0.02	0.16	1.12	1.51	-1.60	0.11	4.47
	NR	1.36	0.22	0.19	1.08	1.33	0.53	0.21	1.99	1.58	0.51	0.16	3.23
N=100	BCD	0.33	-0.25	0.18	1.08	0.58	-0.02	0.19	1.32	0.81	-0.33	-0.16	2.43
	KROW	**0.29**	-0.14	0.19	0.89	**0.54**	0.05	0.20	1.14	1.30	-1.33	0.17	3.62
	NR	0.30	0.10	0.22	0.65	0.55	0.26	0.22	1.15	**0.72**	0.31	0.20	1.75
$\Gamma = 0.3$													
N=15	BCD	**1.10**	-0.35	0.12	1.29	1.25	-0.64	0.14	1.93	1.72	-1.65	0.07	5.19
	KROW	1.16	-0.46	0.11	1.44	1.42	-0.84	0.13	2.38	1.87	-1.50	0.07	4.76
	NR	1.24	0.10	0.17	1.37	**1.12**	-0.02	0.18	2.13	**1.56**	-0.86	0.09	3.53
N=25	BCD	1.10	-0.22	0.19	1.25	1.20	-0.38	0.20	1.91	1.46	-1.02	0.13	3.87
	KROW	**0.86**	-1.04	0.10	2.18	**1.17**	-1.37	0.13	3.24	1.83	-1.77	0.10	6.07
	NR	1.42	0.12	0.23	1.14	1.52	0.10	0.24	1.91	**1.24**	-0.24	0.17	3.20
N=35	BCD	0.88	-0.17	0.22	1.23	1.21	-0.29	0.23	1.86	1.32	-0.73	0.18	3.45
	KROW	**0.82**	-1.43	0.08	3.06	1.16	-1.70	0.12	3.94	1.77	-2.35	0.10	8.18
	NR	1.09	0.12	0.26	0.97	**1.03**	0.08	0.26	1.67	**1.31**	-0.10	0.21	2.75
N=100	BCD	0.34	-0.09	0.27	1.20	0.61	-0.14	0.28	1.84	0.82	-0.29	0.26	2.80
	KROW	0.76	-2.13	0.04	5.07	1.14	-2.15	0.09	5.06	1.72	-3.92	0.06	17.5
	NR	**0.29**	0.08	0.29	0.59	**0.57**	0.07	0.29	1.07	**0.71**	0.05	0.28	1.60

Table 4.6: *Performance of the designs under the Gamma distributions.*

N	Design	Scenario I				Scenario II				Scenario III			
		RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE	RMSE	TBIAS	TOX	TE
$\Gamma = 0.2$													
N=15	BCD	**1.49**	-0.27	0.07	0.78	**1.32**	-0.78	0.04	1.51	2.42	-2.22	0.08	9.44
	KROW	1.80	-0.02	0.09	0.72	1.43	-0.41	0.05	1.01	2.26	-1.82	0.08	7.44
	NR	1.97	0.46	0.14	1.46	1.40	0.16	0.08	1.60	**2.14**	-0.92	0.11	6.45
N=25	BCD	**1.35**	-0.20	0.12	0.87	1.33	-0.36	0.09	1.41	2.04	-1.96	0.04	6.83
	KROW	1.62	-0.04	0.14	0.76	**1.33**	-0.11	0.11	1.15	**1.63**	-1.46	0.04	4.71
	NR	2.12	0.37	0.19	1.21	1.77	0.54	0.15	2.08	2.09	-0.30	0.07	4.25
N=35	BCD	**1.00**	-0.16	0.15	0.86	**0.97**	-0.32	0.12	1.42	1.75	-1.54	0.07	5.78
	KROW	1.23	-0.05	0.16	0.74	1.09	-0.10	0.14	1.12	**1.56**	-1.02	0.08	4.04
	NR	1.63	0.30	0.21	0.98	1.33	0.44	0.19	1.69	2.03	0.25	0.11	4.48
N=100	BCD	0.30	-0.13	0.18	0.87	0.48	-0.19	0.17	1.35	1.21	-0.61	-0.15	4.01
	KROW	**0.28**	-0.05	0.20	0.74	0.42	-0.05	0.18	1.11	1.24	-0.25	0.16	3.06
	NR	0.29	0.15	0.22	0.59	**0.42**	0.20	0.21	0.91	**1.16**	0.45	0.19	2.97
$\Gamma = 0.3$													
N=15	BCD	1.13	-0.16	0.15	1.05	**1.20**	-0.47	0.09	1.70	3.15	-3.29	0.06	14.62
	KROW	**1.05**	-0.43	0.12	1.19	1.32	-0.48	0.09	1.84	3.08	-3.10	0.06	13.07
	NR	1.19	0.26	0.20	1.32	1.39	0.13	0.13	1.89	**1.65**	-2.46	0.07	9.23
N=25	BCD	1.19	-0.08	0.21	1.07	1.22	-0.25	0.17	1.69	2.12	-2.45	0.08	10.12
	KROW	**0.81**	-0.93	0.10	1.67	**1.06**	-1.12	0.10	2.77	2.91	-2.85	0.08	12.65
	NR	1.49	0.21	0.25	1.05	1.51	0.19	0.22	1.65	**1.98**	-1.40	0.12	6.52
N=35	BCD	0.90	-0.04	0.23	1.07	1.00	-0.16	0.21	1.65	1.68	-1.92	0.01	8.01
	KROW	**0.76**	-1.18	0.08	2.04	**0.97**	-1.57	0.09	3.87	2.90	-3.37	0.09	15.72
	NR	1.16	0.18	0.27	0.90	1.12	0.18	0.25	1.45	**1.49**	-0.98	0.16	5.04
N=100	BCD	**0.33**	0.02	0.28	1.08	0.48	-0.04	0.27	1.60	1.15	-0.92	0.22	4.51
	KROW	0.67	-1.53	0.04	2.60	0.94	-2.51	0.04	7.16	2.88	-5.50	0.06	34.18
	NR	0.35	0.12	0.29	0.58	**0.44**	0.15	0.29	0.90	**1.04**	-0.29	0.25	2.65

4.3 Discussion

The usual measure of precision is the standard error of the estimator. The results in Table 4.2 are found to be close to those obtained by Ivanova *et al.* [12]. We, in addition, investigate the designs under the generalized logistic distribution with higher powers and also the gamma distribution.

In Tables 4.2 - 4.5, except in Table 4.3, smallest RMSE values are observed for NR most of the time with NR performing best for large sample sizes. In addition, TE is smallest in most cases for NR indicating that the dose assignments concentrate more around the target dose for the NR. This suggests that the targeting ability is more effective for NR than for the BCD and the KROW. This confirms that the additional information enhances the targeting ability of the design. We also observe that the values of TBIAS for the KROW and the NR are smaller than those of the BCD indicating that they perform better than the BCD. However, we observe that the values of TOX are smallest for the KROW but highest for the NR. That is, lower average proportion of toxic responses are observed in the KROW than in the NR and the BCD.

Similar observations are noted under the Gamma distribution (see Table 4.6). This further confirms that the additional information enhances the targeting ability of the design.

4.4 Conclusion

In general, the NR performs best on the basis of the quality of the estimator under both the generalized logistic and the gamma distribution but it results in higher average proportion of toxic responses. In addition, since the Gamma distribution is similar to the generalized logistic distribution and the results are similar we can say that the gamma is as good as the logistic distribution.

Appendix A

Derivations

A.1 Derivation of the linear regression equation from the logistic distribution

From the logistic distribution with Q as (3.10),

$$Q(d_j, \alpha, \beta) = \frac{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right)}{1 + \exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right)}. \tag{A-1}$$

We have

$$\frac{1}{Q(d_j, \alpha, \beta)} = \frac{1}{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right)} + 1. \tag{A-2}$$

Therefore

$$\frac{1 - Q(d_j, \alpha, \beta)}{Q(d_j, \alpha, \beta)} = \frac{1}{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right)} \tag{A-3}$$

which implies

$$\frac{Q(d_j, \alpha, \beta)}{1 - Q(d_j, \alpha, \beta)} = \exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right). \tag{A-4}$$

Taking ln of both sides, gives

$$\ln\left[\frac{Q(d_j, \alpha, \beta)}{1 - Q(d_j, \alpha, \beta)}\right] = \left(\frac{-\alpha}{\beta} + \frac{1}{\beta} d_j\right). \tag{A-5}$$

In other words

$$\text{logit}(Q(d_j, \alpha, \beta)) = \ln\left(\frac{Q(d_j, \alpha, \beta)}{1 - Q(d_j, \alpha, \beta)}\right) = \beta^{-1}(d_j - \alpha). \tag{A-6}$$

which is the desired linear relation (3.11).

A.2 Derivation of $\hat{\mu}_4$

Assuming that Γ falls between $Q^*(d_m)$ and $Q^*(d_{m+1})$ with the corresponding dose levels d_m and d_{m+1} respectively, we have from (A-1)

$$Q^*(d_m) = \frac{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_m\right)}{1 + \exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_m\right)} \tag{B-1}$$

and

$$Q^*(d_{m+1}) = \frac{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_{m+1}\right)}{1 + \exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_{m+1}\right)}. \tag{B-2}$$

It follows that

$$\log\left(\frac{Q^*(d_m)}{1 - Q^*(d_m)}\right) = \left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_m\right) \tag{B-3}$$

and

$$\log\left(\frac{Q^*(d_{m+1})}{1 - Q^*(d_{m+1})}\right) = \left(\frac{-\alpha}{\beta} + \frac{1}{\beta}d_{m+1}\right). \tag{B-4}$$

From (B-3) and (B-4), $\frac{1}{\beta}$ is given by

$$\frac{1}{\beta} = \frac{1}{d_{m+1} - d_m}\left[\log\left(\frac{Q^*(d_{m+1})}{1 - Q^*(d_{m+1})}\right) - \log\left(\frac{Q^*(d_m)}{1 - Q^*(d_m)}\right)\right] \tag{B-5}$$

Substituting (B-5) into (B-3) gives

$$\frac{-\alpha}{\beta} = \log\left[\frac{Q^*(d_m)}{1 - Q^*(d_m)}\right] - \frac{d_m}{d_{m+1} - d_m}\left[\log\left(\frac{Q^*(d_{m+1})}{1 - Q^*(d_{m+1})}\right) - \log\left(\frac{Q^*(d_m)}{1 - Q^*(d_m)}\right)\right] \tag{B-6}$$

We obtain $\hat{\mu_4}$ by solving

$$\Gamma = \frac{\exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}\hat{\mu_4}\right)}{1 + \exp\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}\hat{\mu_4}\right)} \tag{B-7}$$

which implies that

$$\log\left(\frac{1 - \Gamma}{\Gamma}\right) = -\left(\frac{-\alpha}{\beta} + \frac{1}{\beta}\hat{\mu_4}\right). \tag{B-8}$$

Substituting the values of $\frac{1}{\beta}$ and $\frac{-\alpha}{\beta}$ in (B-5) and (B-6) respectively into (B-8) gives

$$\hat{\mu_4} = d_m + \left[\frac{\log[\frac{\Gamma}{(1-\Gamma)}] - \log[\frac{Q^*(d_m)}{(1-Q^*(d_m))}]}{\log[\frac{Q^*(d_{m+1})}{(1-Q^*(d_{m+1}))}] - \log[\frac{Q^*(d_m)}{(1-Q^*(d_m))}]}\right](d_{m+1} - d_m) \tag{B-9}$$

which is the same as (3.14).

Appendix B

Dose-toxicity curves

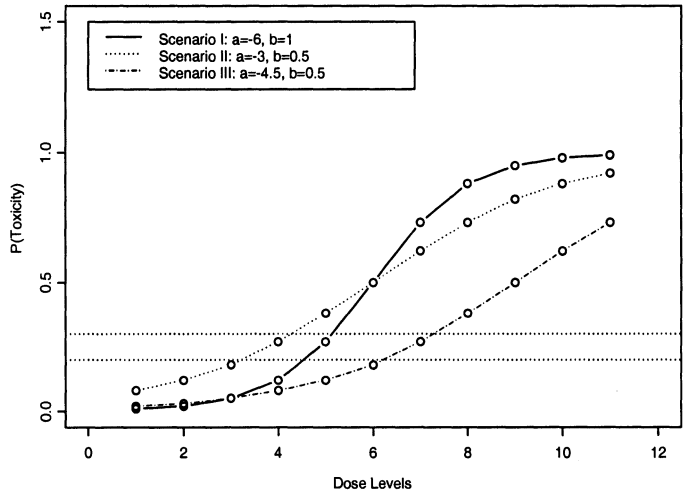

Fig. B.1: Dose-toxicity Curves for Scenarios I, II, III, $\gamma = 1$

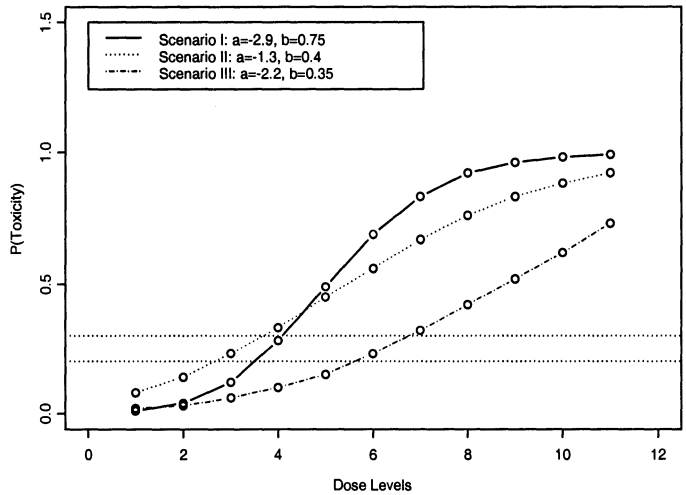

Fig. B.2: Dose-toxicity Curves for Scenarios I, II, III, $\gamma = 2$

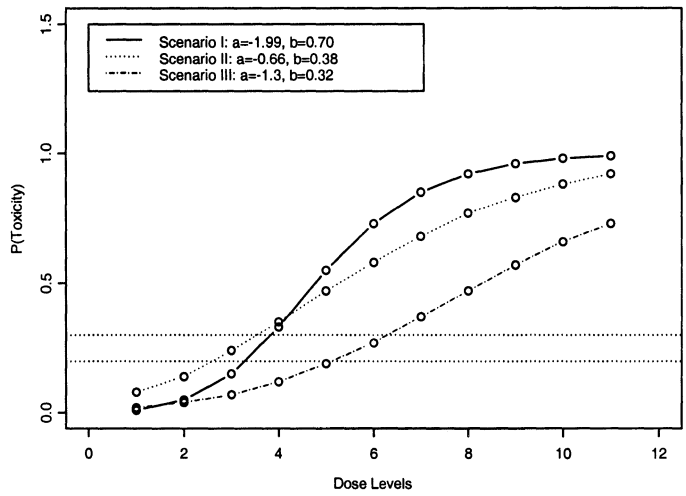

Fig. B.3: Dose-toxicity Curves for Scenarios I, II, III, $\gamma = 3$

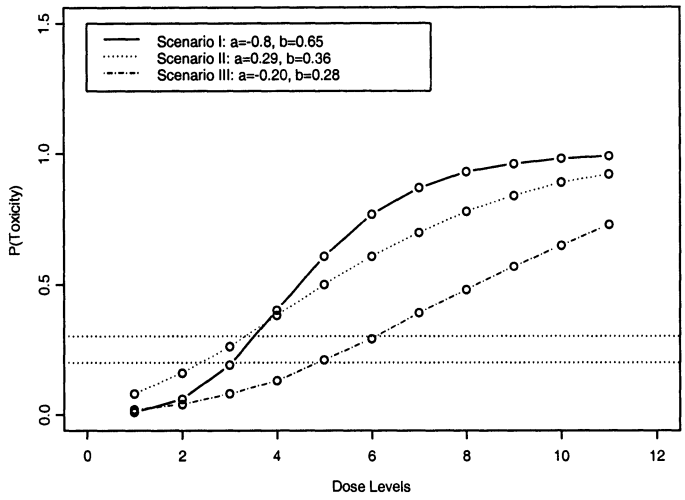

Fig. B.4: Dose-toxicity Curves for Scenarios I, II, III, $\gamma = 6$

Gamma Distribution Curve

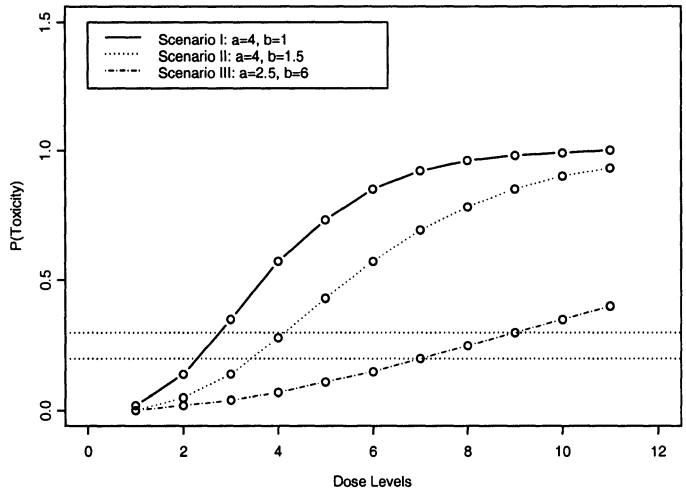

Fig. B.5: Dose-toxicity Curves for Scenarios I, II, III, under the Gamma Distribution

Appendix C

S-Plus functions' codes

Function pava.q[‡]

```
# #    Function 'pava.q' # # function(Q, w = NULL, long.out = F) {
# # Function 'pava.q', performs isotonic regression for a simple
#linear ordering using the ''pool adjacent violators
#algorithm''(PAVA). If long.out = T then the  result returned
#consists of a list containing the fitted values and the final
#weights. Otherwise only the fitted values are returned.

    nq <- length(Q)
    if(is.null(w))
        w <- rep(1, nq)
    r <- rep(1, nq)
    repeat {
        stble <- T
        i <- 1
        while(i < nq) {
            if(Q[i] > Q[i + 1]) {
                stble <- F
                www <- w[i] + w[i + 1]
                ttt <- (w[i] * Q[i] + w[
                    i + 1] * Q[i +
                    1])/www
                Q[i + 1] <- ttt
```

[‡]Thanks to Dr. Rolf Turner at the University of New Brunswick for this function.

```
                w[i + 1] <- www
                Q <- Q[ - i]
                w <- w[ - i]
                r[i + 1] <- r[i] + r[
                    i + 1]
                r <- r[ - i]
                nq <- nq - 1
            }
            i <- i + 1
        }
        if(stble)
            break
    }
    Q <- rep(Q, r)
    w <- rep(w, r)
    tr <- rep(tapply(1:length(Q), rep(1:length(r),
        r), min), r)
    if(long.out)
        list(Q = Q, w = w, tr = tr)
    else Q
} # # # # # # Funtion 'compbcd' # function(gam, ss, mu) {
    #  Complete program to run a BCD Design
    #
    #
    #  Computes the dose to start the primary design.
    #
    tts <- 0
    kval <- 3:1
    gamval <- c(0.2, 0.3, 0.5)
    k <- sum(kval[gamval == gam])
    p <- c(0., 0.05, 0.14, 0.28, 0.43, 0.57, 0.69, 0.78, 0.85, 0.9, 0.93)
    stats.startup <- matrix(c(0), 11, 3)
    stats.startup[, 1] <- 1:length(p)
    for(i in 1:length(p)) {
        u <- runif(k, 0, 1)
        tots <- sum(u <= p[i])
        stats.startup[i, (2:3)] <- c(tots, k)
        if(tots > 0) {
            dose <- max(i - 1, 1)
            tts <- max(i, 1)
            break
        }
        dose <- length(p)
    }
    count <- tts * k
```

```
rs <- ss - count
if(rs == 0) {
    print("results not due to a particular design")
    break
}
else results <- c(dose, p[dose], rs)
#
#
#
#  Computes the successes/failures and dose levels in actual
#  primary design.
#
prob <- gam/(1 - gam)
doseseq <- dose
sf <- c()
for(i in 1:(rs - 1)) {
    u1 <- runif(1, 0, 1)
    sf <- c(sf, (u1 <= p[dose]))
    if(u1 <= p[dose]) {
        dose <- max(dose - 1, 1)
    }
    else {
        u2 <- runif(1, 0, 1)
        if(u2 <= prob) {
            dose <- min(dose + 1, 11)
        }
    }
    doseseq <- c(doseseq, dose)
}
sf <- c(sf, (u1 <= p[dose]))
res <- rbind(sf, doseseq)
#
#  Computation of probability of success at each dose level.
#
stats.prim <- matrix(c(0), 11, 3)
for(i in (1:11)) {
    a <- sum(sf[doseseq == i])
    b <- sum(doseseq == i)
    stats.prim[i,  ] <- c(i, a, b)
}
stats <- stats.startup
stats[, (2:3)] <- stats.startup[, (2:3)] + stats.prim[, (2:3)]
stats.prim <- stats.prim[stats.prim[, 3] > 0,  ]
if(is.matrix(stats.prim) == F) {
    stats.prim <- t(as.matrix(stats.prim))
```

```
}
stats.prim <- cbind(stats.prim, stats.prim[, 2]/stats.prim[, 3])
tei <- sum((stats.prim[, 3] * ((stats.prim[, 1] - mu)^2))/sum(stats.prim[, 3]))
Tbiasi <- (sum(stats.prim[, 1] * stats.prim[, 3])/sum(stats.prim[, 3])) - mu
#
#    Computation of the estimate involving all the start-up
#    and primary results
#
stats <- stats[stats[, 3] > 0,  ]
if(is.matrix(stats) == F) {
    stats <- t(as.matrix(stats))
}
stats <- cbind(stats, stats[, 2]/stats[, 3])
dose <- stats[, 1]
Q <- stats[, 4]
Q <- pava.q(Q)
nq <- length(Q)
if((gam > Q[1]) & (gam <= Q[nq])) {
    for(m in (1:(nq - 1))) {
        if((gam > Q[m]) & (gam <= Q[m + 1])) {
            a1 <- log(gam/(1 - gam))
            a3 <- log(Q[m + 1]/(1 - Q[m + 1]))
            a4 <- dose[m + 1] - dose[m]
            a2 <- log(Q[m]/(1 - Q[m]))
            if(Q[m] == 0) {
                est1 <- dose[m] + ((a1/a3) * a4)
            }
            else {
#
#
# Calculation of the estimate
#
                est1 <- dose[m] + (((a1 - a2)/(a3 - a2)) * a4)
#
#
            }
            break
        }
    }
}
else {
    est1 <- ((gam <= Q[1]) * dose[1]) + ((gam > Q[nq]) * dose[nq])
}
tox <- sum(sf)/ss
c(est1, tox, tei, Tbiasi)
```

```
} # # # # # Function 'master' # function(gam, ss, n, mu) {
    #  Simulates n estimates of mu and computes the RSME, TBIAS, TOX and TE
    #
    print(c(gam, ss, n, mu))
    esti <- c()
    toxi <- c()
    tei <- c(0)
    Tbiasi <- c(0)
    for(i in 1:n) {
        est <- compbcd(gam, ss, mu)
        esti <- c(esti, est[1])
        toxi <- c(toxi, est[2])
        tei <- c(tei, est[3])
        Tbiasi <- c(Tbiasi, est[4])
        print("i, est1, tox, te, Tbias:")
        print(c(i, est))
    }
    ind <- (esti != "NA") & (esti != "-Inf") & (esti != "Inf")
    vest <- esti[ind]
    vtox <- toxi[ind]
    vte <- tei[ind]
    vTbias <- Tbiasi[ind]
    vrep <- length(vest)
    print("Valid number of replications:")
    print(vrep)
    mse <- sum((vest - mu)^2)/vrep
    rmse <- mse^0.5
    print("MSE,RMSE:")
    print(c(mse, rmse))
    Tbias <- sum(vTbias)/vrep
    print("TBIAS:")
    print(Tbias)
    toxave <- sum(vtox)/vrep
    print("TOX:")
    print(toxave)
    TE <- sum(vte)/vrep
    print("TE:")
    print(TE)
}
```

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