2007

An Adaptive Dose Finding Design (DOSEFIND) Using A Nonlinear Dose Response Model

James Michael Davenport
Virginia Commonwealth University

AN ADAPTIVE DOSE FINDING DESIGN (DOSEFIND) USING A NONLINEAR DOSE RESPONSE MODEL

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

JAMES MICHAEL DAVENPORT
Master of Science, University of Arkansas, 1984
Bachelor of Science, University of Arkansas 1982

Co-Directors: RONALD K. ELSWICK, JR., CHRIS GENNINGS AND RAMESH RAMAKRISHNAN
INTERIM DEPARTMENT CHAIR, PROFESSOR AND ASSOCIATE PROFESSOR, BIOSTATISTICS

Virginia Commonwealth University
Richmond, Virginia
May 2007

Table of Contents

List of Tables

Page

List of Figures

Page

Abstract

AN ADAPTIVE DOSE FINDING DESIGN (DOSEFIND) USING A NONLINEAR DOSE RESPONSE MODEL
By James Michael Davenport, PhD

A Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2007

Major Director: R. K. Elswick
Interim Department Chair, Biostatistics

First-in-man (FIM) Phase I clinical trials are part of the critical path in the development of a new compound entity (NCE). Since FIM clinical trials are the first time that an NCE is dosed in human subjects, the designs used in these trials are unique and geared toward patient safety. We develop a method for obtaining the desired response using an adaptive non-linear approach. This method is applicable for studies in which MTD, NOEL, NOAEL, PK, PD effects or other such endpoints are evaluated to determine the desired dose. The method has application whenever a measurable PD marker is an indicator of potential efficacy and could be particularly useful for dose finding studies. The advantages in the adaptive non-linear methodology is that the actual range of dose response and lowest

non-effective dose levels are more quickly and accurately determined using fewer subjects than typically needed for a conventional early phase clinical trial. Using the nonlinear logistic model, we demonstrate, with simulations, that the DOSEFIND approach has better asymptotic relative efficiency than a fixed-dose approach. Further, we demonstrate that, on average, this method is consistent in reproducing the target dose, that it has very little bias. This is an indicator of reproducibility of the method, showing that the long-run average error is quite small. Additionally, DOSEFIND is more cost effective because the sample size needed to obtain the desired target dose is much smaller than that needed in the fixed dose approach.

CHAPTER 1

1.0 Purpose of Early Clinical Trials

First-in-man (FIM) clinical trials are the first time that a new compound entity (NCE) is dosed in human subjects. Thus, FIM Phase I clinical trials are part of the critical path in the development of an NCE, and the designs used in these trials are geared toward patient safety. Based on Food and Drug Administration (FDA) guidelines (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005), the starting dose of FIM trials are identified from preclinical animal studies. Typically, trials are conducted such that the dose is escalated in some sequential manner until some prespecified dose level is attained or until unacceptable adverse events are observed.

The FIM study is usually conducted with healthy normal volunteers (HNVs) using a fixed set of predetermined dose levels. At each dose level HNVs are randomized to receive either a single dose of the NCE or placebo. Each dose level or cohort starting with the lowest dose and proceeding in an ascending manner is evaluated for safety before the next

cohort is dosed with the NCE. Exceptions to FIM studies that use HNVs are trials that are conducted with cytotoxic compounds or monoclonal antibodies. The primary objectives of FIM trials are: the discovery of the maximum tolerated dose (MTD), the no effect level (NOEL), the no adverse effect level (NOAEL), characterization of the pharmacokinetics (PK) and, secondarily, the pharmacodynamics (PD) of the NCE (Ting, 2006).

An accurate assessment of the MTD is crucial to the safety of patients in later stage clinical trials. Likewise, measurement of the pharmacokinetics is essential to the understanding of the rate and extent of exposure and the NCE half-life. Data from FIM studies will be used to define appropriate dosing intervals so that hazards associated with repeat dosing, such as drug accumulation in the body, are avoided. The NOEL and NOAEL, which may not necessarily occur at the same dose level, provide information regarding the therapeutic and safety dosing window. Thus, a major concern in these types of trials is the safety of the participating subjects (Zhou, 2004). Typical sample sizes of an FIM trial are small, ranging from 20 to 50 subjects. Typically, a fixed range of doses are predefined by the sponsor, where single doses are given in an ascending order where $d_1 < d_2 < \ldots < d_n$.Often one or two subjects at each dose level is given a placebo for control purposes (Zhou, 2004).

1.1 Current State of Early Stage Clinical Trials

Current conventional statistical methods for FIM trials include the '3 + 3' design (Schroeder, 2002), Coin up-and-down methods (Stylianou, et al., 2004) and the continual reassessment method (CRM; O'Quigley, et al., 1990), which will be described in Section 1.3. The 3+3 and Coin up-and-down methods are based on a frequentist approach, while the CRM is generally based on a Bayesian approach.

In the Bayesian model the parameter of interest is believed to follow some known prior distribution. The distribution is not necessarily based on prior data, but can be based on the beliefs of the investigator. Hence, the resulting statistical inference is subjective. In contrast, the frequentist approach assumes no prior information about the parameter of interest beyond information provided by the study (Bickel and Doksum, 2001), but rather the method is based on model assumptions and empirical observations.

The traditional design used in phase I oncology is the 3+3 design where the MTD is identified from the data. The 3+3 design is a dose-escalation design, and the starting dose is typically the human equivalent dose of 1/10th the MTD in the most sensitive animal species. Three subjects, usually healthy normal volunteers (HNV) are dosed, concurrently. The dose escalation procedure is as follows:

- start at the lowest dose d_1 and dose three subjects;

- repeat dose d_i with three additional subjects, if one of the initial three subjects had a DLT;
- stop the study if two or more subjects displayed a DLT or;
- if no DLTs were observed then escalate to dose d_{i+1}.

The algorithm iterates moving the dose up or down depending on the number of toxicities observed, and the MTD is defined as the highest dose studied with less than, say, one-third toxicities. Reiner et al. (1999) showed that the probability of recommending the MTD at the end of the trial never exceeded 44% for the 3+3 design. A recent example of the 3+3 design approach can be found in a study by Ryan, et al. (2004).

Hutmacher et al. (2005) describes another type of FIM trial in which subjects are given single doses of a treatment in a rising fashion. Hutmacher provides an example where HNV's were assigned to receive one of seven ascending dose levels with a multiplier on each succeeding dose level of 1x, 3.3x, 10x, 26.7x, 53.3x, 106.7x and 160x, respectively. In this design, eight subjects per group were assigned to each dose level and then randomized in a cross-over fashion to a sequence of either active treatment/placebo or placebo/active treatment.

Coin up-and-down methods are non-parametric and are used to find the MTD, at which the probability of toxicity is Γ, where Γ (the level of risk) is pre specified by the sponsor. For $\Gamma \leq 0.5$, the Biased Coin up-and-down (BCD) steps down by a dose level if a DLT is

observed at the previous dose, and randomizes with probability $b = \Gamma / (1- \Gamma)$ to the next higher dose and probability 1- b to the same dose if no DLT is observed at the previous dose. For $\Gamma \geq 0.5$, the BCD steps up a dose if no DLT is observed at the previous dose and randomizes with probability $b = (1- \Gamma)/\Gamma$ to the next lower dose and probability 1 - b to the same dose if a DLT is observed at the previous dose. The BCD assigns a dose to the next subject only after evaluation for the last dosing period is completed. If n subjects are required to complete the study, then the study will require at least n evaluation periods. In the BCD, as in conventional designs, subjects are dosed sequentially, and escalation only occurs when no toxicities are observed.

BCD designs have advantages of being nonparametric, having a workable finite distribution theory, and being simple and intuitive to implement. They generate a cluster of doses around the quantile of interest and possess some optimality properties (Durham and Flournoy, 1994). Durham et al. (1997) describes a random walk approach where dose-levels are sequentially allocated. Here, subjects are assigned the next higher or lower dose from a finite set of dose levels. The assignment to a dose level can be based on a probability distribution as well as the patient response. Thus, as Durham et al. point out, the BCD described above is a special case from the set of random walk designs.

1.2 Review of the Continual Reassessment Method

The original Continual Reassessment Method (CRM; O'Quigley, 1990) was suggested as an alternative approach to dose finding trials. While the CRM is based on a fixed set of dose levels, data are evaluated from one dose at a time in a Bayesian approach. Thus, in contrast to the typical dose response trials, the CRM does not have a fixed sample size. Additionally, the CRM application does not include a placebo dose group, and its application is usually in oncology trials where treating terminal patients with placebo is considered unethical.

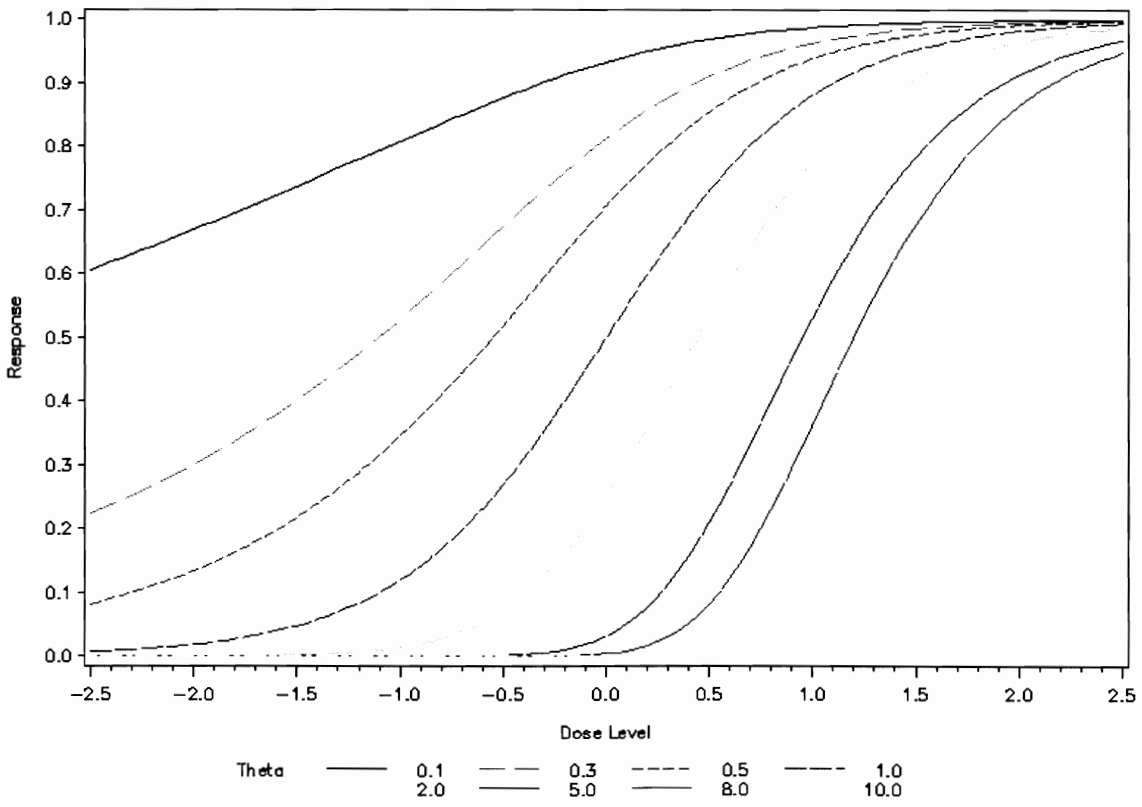
Generally, a goal of dose response trials is to define or describe the shape of the dose response curve. The CRM seeks to estimate a shape parameter on a given dose response function, say $\psi(x_i, \theta)$, where x_i is the dose level and θ is the shape parameter. However, this response curve is based on the observance of adverse events, which do not necessarily coincide with a clinically relevant efficacy response. Therefore, as only toxicity has been observed additional studies are still needed to determine if there is any clinical utility for the NCE under investigation.

The CRM, estimates the MTD as the dose level that yields a particular target proportion of responses for a predefined set of doses and a binary response. The method operates by updating the posterior distribution of the model parameters after observing each response. The dose for the next patient is chosen as the dose with (Bayesian current) probability of

toxicity closest to the target response level. Several modified CRM approaches that mitigate risk of toxicity exposure above acceptable limits have been developed and implemented (O'Quigley, et al. 1990; Faries, 1994; Korn, et al., 1994 Goodman et al., 1995, Piantadosi et al. 1998, Potter 2002). O'Quigley, 1990

uses $\Psi\left(x_i,\theta\right)=\left\{\left[\tanh\left(x_i\right)+1\right]/2\right\}^{\theta}$ because the hyperbolic tangent has a sigmoidal shape which will be sharper and more distinct for increasing values of the shape parameter θ. An example of this is presented in Figure 1.1 below:

Figure 1.1: Dose Response Curves for Values of Theta



To apply the CRM, a prior distribution function, or $g(\theta)$, must be determined. Often in the Bayesian approach, the prior distribution is based on data obtained from previous trial experience. In the absence of any previous data, a non-informative prior can be applied. In the case of the CRM, the prior is defined as:

$$g(\theta) = e^{-\theta}$$

The probability distribution of response Y given θ is:

$$f(Y \mid \theta) = \phi(x(j), y_j, \theta) = \psi^{y} j(x(j), \theta)\{1 - \psi(x(j), \theta)\}^{(1-y_j)},$$

where $x(j)$ denotes the dose used in the jth step.

In order to estimate the shape parameter, the posterior distribution must be obtained. The posterior distribution is the conditional density of θ given $Y_1 = y_1, Y_2 = y_2, \ldots, Y_j = y_j$. Once the posterior distribution is calculated, the CRM estimates the posterior Bayes estimator, θ (the shape parameter). The posterior distribution is defined as:

$$f(\theta \mid \mathbf{Y}_j = \mathbf{y}_j) = \frac{g(\theta) \prod_{l=1}^{j} \phi\{x(l), y_l, \mu\}}{\int_0^{\infty} g(\mu) \prod_{l=1}^{j} \phi\{x(l), y_l, \mu\} \partial\mu},$$

and the posterior Bayes estimator with respect to the prior distribution $g(\theta)$ is defined as:

$$\mu = E[\theta \mid Y_1, Y_2, ..., Y_j] = \int_0^{\infty} \theta f(\theta \mid \mathbf{Y}_j = \mathbf{y}_j) \partial\theta$$

In order to begin estimation, the initial estimates for (θ, x_1) are chosen, which allow the evaluation of the dose response. To illustrate, suppose dose levels associated with the toxicity probabilities for $\theta = 1$ are as given in Table 1.1.

Table 1.1: Example Dose Levels and Associated Toxicity Probabilities for $\theta = 1$

i	1	2	3	4	5	6
x_i	-1.47	-1.1	-0.69	-0.42	0.0	0.42
$[\tanh(x_i)+1]/2$	0.05	0.1	0.2	0.3	0.5	0.7

The data in Table 1.1 are from O'Quigley (1990), and since it is not possible to give a negative dose these data have been scaled in some fashion.

Solving the posterior distribution requires recognizing the following:

1. The numerator is a product of the probability of response that is:

$$\phi(x(j), y_j, \theta) = \begin{Bmatrix} \Psi(x(j), \theta), & for\ y_j = 1 \\ 1 - \Psi(x(j), \theta), & for\ y_j = 0 \end{Bmatrix}$$

2. This product is multiplied by the prior distribution $g(\theta)$.

3. The denominator integrates to:

$$\frac{1}{1 - \log\left((\tanh(x_i) + 1)/2\right)}, when\ y_i = 1\ and$$

$$\frac{\log\left((\tanh(x_i) + 1)/2\right)}{\log\left((\tanh(x_i) + 1)/2\right) - 1}, when\ y_i = 0$$

For the first dose level, no toxicity was observed $(Y_1 = 0)$, the posterior distribution resolves to $1.62e^{-\theta}[1 - (\tanh(x_1) + 1)/2]$, then solving for the Bayes estimator gives μ = 1.38.

Finally, a decision as to which dose to give to the next subject must be determined. This is accomplished by choosing the dose x_i, which is closest to $\psi^{-1}_{\theta=\mu}(\theta)$ for the value of μ obtained from the current iteration of the Bayes estimator. The new recommended dose is –0.39 and the dose closest to this value is chosen for the second dose level, which is –0.42 (dose level 4). At this point, the process iterates again.

For the second dose level, no toxicity was observed $(Y_2 = 0)$ and the posterior distribution resolves to $1.31e^{-\theta}[1-(\tanh(x_1)+1)/2]^2$. The Bayes estimator is found to be $\mu = 1.18$, the new recommend dose is –0.47 and the dose chosen for the third dose level is –0.42 or dose level 4.

The CRM is designed to find the dose that results in observing toxicity at the desired pre-specified level. This is accomplished through estimation of the Bayes estimator, which in this case is the shape parameter of the dose response function. At any point in the study, the next dose must be either the current dose or the dose immediately prior to or succeeding the current dose $\left(x_{i-1}, x_i, or\, x_{i+1}\right)$; small steps can potentially make reaching the desired dose response a slow and tedious process. Further, with fixed dose levels, it may not be possible to obtain a true estimate of the desired result as the optimal dose may be either below or above the specified set of dose choices. Since dose response curves tend to be non-linear (often sigmoidal) in nature, a linear approach is only useful if the choice of dose levels was fortuitous enough to be in a linear portion of the sigmoidal curve If dose response is measured in terms of DLT, and the response curve is well-behaved, and the predetermined set of doses chosen contains the MTD, then the CRM can do a reasonable job of estimating a safety dose response curve. However, there is a need for a method that can handle more complicated cases for the multi-parameter model. In this case, the CRM

is not likely to provide the desired result, and a non-linear approach is needed to handle more complex models.

O'Quigley (1990) gives an example for the case of the TD20 (i.e., the dose at which there is a 20% chance of observing a DLT), in which doses are administered to one patient at a time. The probability of a DLT at a dose d_i, is given by π_i, $i = 1,\ldots,n$. Initial choices or priors for each π_i are generated by the sponsor. The dose-escalation procedure starts with a dose at which the initial chosen probability of a DLT is closest to 0.2. Once "r" responses have been observed, the estimated probability of a DLT (posterior probabilities) at each dose is updated using Bayes theorem. The $(r + 1)^{th}$ patient will be administered the dose at which posterior probability of a DLT is closest to 0.2. This process continues until the maximum sample size has been reached.

In practice, the original format of the CRM has rarely been used due to ethical concerns (e.g., Korn, 1994). For example, the starting dose in the CRM might be a dose in the middle of the dose range. Several authors (Korn, 1994; Faries, 1994; Goodman, 1995, Piantadosi et al., 1998; Potter, 2002) have recommended modifications to the CRM. These modifications avoid exposing the first subject to high doses and minimize the risk of assigning patients to higher, more dangerous doses than the target dose or upper bound identified in pre-clinical studies. The two-stage version of the CRM starts at the dose d_1 and escalates one dose step at a time until the first toxicity is observed. Once the first toxicity appears, the second stage in which the CRM is used begins.

O'Quigley and Shen (1996) incorporated the concept of a two-stage version of the CRM with a likelihood approach, referred to as "The Likelihood CRM" (CRML). In the first stage, one patient is dosed at a time, and in the second stage, three subjects are dosed at the same time. From this point on, the CRML uses a likelihood form to calculate the probability of a DLT. The CRML is thus no longer a Bayesian method. Thus, the updated CRML still has the same limitations of the original method in terms of a pre-specified set of dose levels that contains the MTD. Additionally, there is still a need to estimate cases where multi-parameter models are needed, and the CRML (like the CRM) is not equipped to do this.

Piantadosi et al. (1998) present a modified approach to the CRM. In their modification the true dose-toxicity measured as a dichotomous variable is modeled against dose as a logistic regression model. The dose-toxicity is defined to be present if a grade 3 or 4 is observed and absent otherwise. Then the probability of toxicity is modeled as,

$$\Pr[\text{toxicity}] = \left[1 + e^{-\beta\left(d - d_{50}\right)}\right]^{-1},$$

where d is the dose used and d_{50} is the dose for which the probability of a toxicity is one-half. The parameters $\hat{\beta}$ and $\hat{d}_{50}$ are estimated from preliminary data and for subsequent doses by updating the estimates of the model parameters and estimating d_{30}, the dose at which the probability of toxicity is 30%, as

$$\hat{d}_{30} = \hat{d}_{50} + \log\left(\frac{0.3}{1-0.3}\right)\Big/\hat{\beta}\,.$$

This procedure is repeated until the target dose changes by less than 10 percent. This method does not require a fixed set of doses or a fixed sample size. Also the target dose for each new group of patients is computed from the parameter estimates of the data from previous doses. Since estimating parameters of a logistic regression model heavily depends on the distribution of successes and failures, sparse cells do not often provide reliable estimates. Piantadosi, et al, neither discuss this issue in their article nor provide estimates of variance for the doses in each step. Moreover, when there are no toxicities in some cases they suggest using data from other trials to improve on the estimates. This is often not practical, especially in first-in-man trials. The method developed herein named DOSEFIND will also employ the features of no fixed set of doses or sample size. In addition, the DOSEFIND uses a non-linear model approach and uses a PD marker for examination of efficacy. A more complete discussion of the differences in the two methods is presented in Chapter 4.

Potter (2002) consider the sparseness of toxicity and proposes an improvement to the Piantadosi method. This method, termed adaptive dose finding algorithm, consists of two stages. In the first stage, doses are escalated in a fixed order. The second stage begins when a DLT is observed. According to this method, three patients are used for each dose sampled. The dose response model is $\log(p/1-p) = \mathrm{A} + \mathrm{B}\log(d)$, where p is the DLT

probability and A and B are constants that are updated during stage two. Additionally, two stopping rules have been considered

- At least nine patients treated in stage two; at least three DLTs must have been observed; the estimated variance of $\log(p/1-p)$ at the MTD must be less than 0.4.
- At least nine patients treated in stage two at least four DLTs must have been observed; at least 18 patients must have been treated.

Although this addresses the issue of fitting models to non-existing toxicities, the issue of reliability is not well addressed and the focus remains only on toxicity. Unlike the DOSEFIND, which uses a nonlinear approach, a logistic regression is used by Potter to determine the next dose. Additionally, the DOSEFIND, method in contrast, is specifically designed for determining the dose for a specified efficacy target. The outcome therefore is not necessarily a dichotomous outcome and often is a continuous outcome. This allows the method to implement a confidence interval around the target dose to set criteria for finding the appropriate dose.

1.3 Adaptive Clinical Trials Design

An adaptive design is defined as a multistage study design in which accumulating data is evaluated in order to decide how to modify aspects of the study without undermining the

validity and integrity of the trial (Dragalin, 2006). In adaptive designs, a main objective for examination of accruing data is to allow implementation of an adaptation that will govern some aspect of the conduct of the remainder of the trial (Gallo et al., 2006). A number of adaptations have been suggested (modification of the planned sample size, patient population, primary endpoint, trial hypothesis, treatment regimen, statistical analysis plan and randomization allocation (Gallo, 2006)).

Hence, an adaptive design requires multiple stages with access to the accumulated data with at least one of the following rules applied to each review of the data: allocation rule, (how patients are assigned to different arms of the study), sampling rule (how many patients are to be treated in the next stage), stopping rule (when or how to stop the clinical trial) and decision rule (changes that are made to the study other than the three rules previously mentioned) (Dragalin, 2006). Further, this methodology has been developed to include varying the number and timing of interim analyses and early stopping rules. The newer adaptive designs also allow for even broader design modifications (such as, changing the endpoint, switching between superiority and non-inferiority, discontinuation of treatment arms, etc.) of ongoing clinical trials.

In this Section a description of the salient adaptive designs is presented. In Section 1.3.1, group sequential, optimal two-stage designs and the linkage of these clinical trial designs to the adaptive dose response approach are discussed. In Section 1.3.2, the seamless design, which typically combines objectives from separate trials into one design, is

described. In Section 1.3.3, the application of sample size modifications to adaptive designs is discussed. In Section 1.3.4, adaptive designs where treatment arms are discontinued are described. In Section 1.3.5, adaptive designs that consider computation of confidence intervals are reviewed. Finally, in Section 1.3.6 dose response adaptive designs are discussed.

1.3.1 Adaptive Group Sequential Designs

Based on Dragalin's rules, group sequential designs would be the considered adaptive designs. The European Agency for the Evaluation of Medicinal Products EMEA (2006) subscribes to this definition by acknowledging that group sequential designs have been developed to avoid inflation of type I error associated with repeated testing of treatment effects based on accumulating data.

Thall and Cheng (2001) present optimal two-stage designs based on a multivariate group sequential hypothesis test including both safety and efficacy outcomes. This approach, using both safety and efficacy, requires more patients than approaches designed to evaluate efficacy alone. Hence, this particular method may be more suited to oncology trials where survival is of interest and an example of this type is discussed in the paper. Emerson (2006) provides a link between group-sequential designs and adaptive designs. Emerson points out that sequential methods can be divided into two overlapping categories:

'prespecified' sequential sampling plans and 'adaptive' sampling plans. The in the adaptive approach the sampling plan is redesigned during the clinical trial.

There is sizeable overlap in the characteristics of adaptive clinical trials. For example, updating the sample size may be seen as changing a stopping rule. Modification of the measure for describing treatment effects, likely entails a change in the statistics and inferential methods. One could also argue that increasing the sample size to power a study to detect a different alternative is changing the hypothesis.

Jennison and Turnbull (2006) provide additional linkage between group sequential and adaptive designs. That is, group sequential designs sample the first stage, then evaluate the data, and then make a decision to stop or continue. Adaptive two-stage designs perform the same task, but choose new sample sizes and stopping boundaries based on the data from the first stage. Further, evidence of the relationship between adaptive designs is seen in the small improvement of optimal adaptive designs over group sequential designs.

The goal in all of these designs is to determine a superior dose through hypothesis testing; these designs do not evaluate the non-linear characteristics of dose response.

Each of these designs dose share the common feature of repeat analysis on accumulating data to determine the next step in the trial.

1.3.2 Seamless Adaptive Dose Response Designs

In a seamless design, objectives that are typically addressed in separate trials are coordinated into a single study. In the adaptive seamless case, the final analysis is performed on patients from both before and after any adaptations to the study. In Phase II/III seamless designs, a major advantage is that it allows data from the learning phase (Phase II) and the confirmatory (Phase III) study to be combined. This also helps in long-term safety evaluation as patients in the learning phase continue in the study for a longer period than would otherwise be the case (Maca, et al., 2006).

Bischoff and Miller (2005) demonstrate a two-stage adaptive design with a minimal number of patients in which they control the type I error rate, detect a given clinically relevant difference in the means (if it exists), and controls for the probability of an inferior treatment being chosen after stage one. Bischoff's approach performs standard hypothesis testing and is not non-linear in nature. Bauer and Köhne (1994) proposed an adaptive interim analysis procedure designed to combine the p-values from tests before and after a preplanned adaptation into a single test statistic controlling the overall α-level. This approach assumes a fixed sample size, performs standard hypothesis testing and is not a non-linear approach.

Thall et al. (2001) proposed a sequential Bayesian phase II/III design. This design was based on survival time, discrete early events related to survival and a mixture model. The

decision to stop early, stay in phase II or move to phase III was assessed in the phase II portion of the design. This is a confirmatory rather than dose-response design (survival is the desired outcome) and it is not a non-linear method.

Todd and Stallard (2005) present a frequentist approach to seamless phase II/III studies design. In this design, it is presupposed that a short-term endpoint is available at the phase II stage, but a long-term endpoint is not available. Further, the short-term endpoint must be a reasonable surrogate for determining the selected treatment for phase III, and it is presupposed that the long-term endpoint is only of interest in phase III. This method is not designed to evaluate the dose response curve, but rather to move one of several dose levels from a phase II to a phase III trial based on hypothesis testing results.

Wang (2006) proposes an approach where the best of several treatments from a phase II learning study are selected for a phase III pivotal study. This is essentially a drop-the-loser method, but with the added application of using the conditional error function for determination of the type I error function in pivotal studies based on information from the learning stage.

Seamless designs evaluate the data from the learning stage to continue into the pivotal stage. This includes the evaluation of a fixed set of doses with hypothesis testing to decide which dose levels give the response of interest for study in the pivotal stage of the trial.

Seamless designs are not evaluating dose response curve and are not non-linear in approach.

1.3.3 Adaptive Dose response Designs – Sample Size Modifications

One major consideration of the adaptive design is to allow for sample size modifications, which reduces the risk of an uninformative outcome due to an underpowered trial (Golub H., 2006). Cui et al. (1999) propose a method for a new group sequential test that preserves the type I error rate and allows for increasing the sample size. This is applied to traditional group sequential designs in which hypothesis testing is of interest. Müller and Schäfer (2001) propose blending adaptive and group sequential designs by allowing changes to the sample size, the alpha spending function and the number of future interim analyses. These changes can be made at each occurrence of an interim analysis.

Banerjee and Tsiatis (2006) consider two-stage designs in which the sample size and the rejection rule are dependent upon the results of the first stage. They present a two-stage adaptive design that minimizes the average sample size under the null hypothesis. These are all traditional study designs in the sense that a hypothesis test is used to determine if the treatment is better than placebo and is not a dose-response approach where the dose-response curve is determined. Mehta and Patel (2006) propose an adaptive approach to

sample size re-estimation for group sequential clinical trials that do so without inflating the type I error.

Proschan and Hunsberger (1995) suggest a double sampling method approach that uses information from the significance of treatment differences from the first stage to determine the additional sample needed and the critical value to use at the end of the study. This is done by using an increasing conditional error function that specifies the amount of type I error rate for the second stage of the study. Lehmacher and Wassmer (1999) define a method based on classical stopping boundaries that simultaneously permits sample size re-estimation based on observed data. The method is based on the inverse normal method of combining independent tests to generate an exact solution for the unknown variance and sample size between stages in the trial.

Liu and Chi (2001) provide a sample size re-estimation approach that protects the type I error rate, produces the desired statistical power and limits the total sample size. This is done by extending the conditional error function from Proschan and Hunsberger to the general case.

All of the designs in Section 1.3.3 use hypothesis testing of a clinical endpoint to determine superiority of a treatment and take steps to ensure the maintenance of the α-level, but are not estimating a dose response curve. However, what is common to our

method is the combining of data gathered in previous steps with the current step to evaluate the parameter of interest.

1.3.4 Adaptive Designs - Treatment Discontinuation

Hung et al. (2006) describe methodological issues in adaptive designs. One of their considerations is allowing for elimination of ineffective treatment arms during clinical trials. Treatments may be dropped due to lack of efficacy or poor safety profiles. This class of designs is commonly called the drop-the-losers or play-the-winners rule. The remaining sample size of a dropped dose level is reallocated to those dose levels still under consideration. König et al. (2006) provide a hierarchical testing procedure starting with the highest dose and proceeding down to the lowest dose only if the higher dose was shown to be more effective than placebo.

Morita and Sakamoto (2006) provide simulation examples of treatment selection based on a Bayesian approach. For the usual hypothesis of active equal to control, their results indicate that selection of an active treatment that is actually comparable to placebo is higher than expected. However, with regard to intolerable toxicity or poor efficacy, early termination of a treatment arm could be expected. Hence, patients would be at lower risk to exposure of ineffective treatments.

These designs can reduce the risk of exposure to ineffective treatments, but do not provide an evaluation of the dose response curve.

1.3.5 Adaptive Designs – Confidence Interval Estimation

Another measure of interest is the construction of confidence intervals. Ford and Silvey (1980) demonstrate that the construction of the confidence interval remains reasonable even though a design is sequential in nature. Hartung and Knapp (2006) confirm this method in self-designing clinical trials where repeated confidence intervals are derived for the parameter of interest. The confidence interval can be calculated at each interim analysis and always holds the predefined overall nominal confidence level. Moreover, the confidence intervals calculated during the course of the trial are nested in the sense that a calculated interval is completely contained in the previous intervals.

Mehrotra and Fan (2006) note that the application of repeated confidence intervals can be applied to any type of adaptive trial design including those that include sample size adjustment due to an update in the variance estimate.

1.3.6 Adaptive Designs – Measuring Dose Response

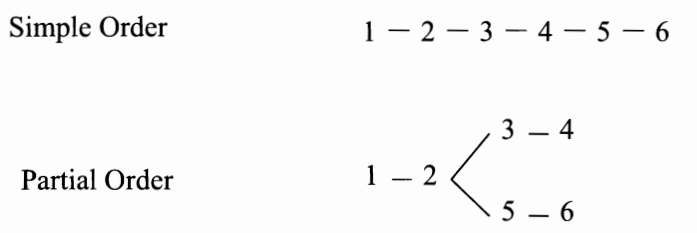
Finally, we consider adaptive designs for measuring dose response. Early phase I trials can all be considered dose response trials in some sense. Typically, these designs look to choose an MTD from a fixed set of predetermined dose levels. Toxicity is measured in a binary fashion as the observance or not of a DLT. Conaway, et al. (2004) present a method for dose escalation when more than one compound is administered simultaneously. A dosing approach for two compounds is presented in Table 1.2:

Table 1.2: Two treatments used in Phase I Trial: paclitaxel and carboplatin in patients with solid tumors from Conaway et al., 2004.

	Treatment (mg)					
Compound	1	2	3	4	5	6
Paclitaxel	54	67.5	81	94.5	67.5	67.5
Carboplatin	6	6	6	6	7.5	9

When more than one treatment is given, the ordering of toxicity between treatments is unknown. In the above case, one can not determine if treatment 3 is more toxic than treatment 5 or if treatment 4 is more toxic than treatment 6. This is because the dose strengths of the two compounds are both different and the synergistic effect on toxicity could be different. However, a partial ordering approach to the probability of observed of toxicity can be applied. An example of partial ordering is presented in Figure 1.2.

Figure 1.2: Example of two partial orders



The next treatment to be dosed in the study is determined by examining the estimated probability of toxicity associated with each treatment $\hat{\pi}_t$. For a set **T** with more than one treatment, then a choice is made based on the following rules:

- If $\hat{\pi}_t > \pi_{\text{target}} \forall t \in T$, then choose the smallest t for the simple order. For the partial order, if there is a tie for the lowest probability of toxicity, then choose randomly from the candidates,
- If $\hat{\pi}_t < \pi_{\text{target}}$ for at least one $t \in T$ then choose the largest dose level in T with $\hat{\pi}_t < \pi_{\text{target}}$ for the simple order. For the partial order, choose randomly among all $t \in T$ that have the largest probability of toxicity.

The Conaway design is novel in its approach, is a Bayesian method with a fixed set of doses, but it is not a non-linear design methodology.

Chang and Chow (2005) propose a hybrid frequentist and Bayesian methodology, is essentially a variation of the CRM. The CRM is modified in that least squares means are

used for estimation of all model parameters, and the Bayesian method is used for re-estimation of the posterior distribution of some parameters. In the simulation, a hyper-geometric model with three parameters and a non-informative prior for parameter a_4 was used:

$$p(x,a) = C(a_1 e^{0.03x} + a_3 e^{-a_4 x})^{-1},$$

where $a_1 \in [0.06, 0.1]$ and $a_3 \in [150, 200]$.

$$a_4 \sim g(a_4) = \begin{cases} \frac{1}{b-a}, & a \le a_4 \le b \\ 0, & otherwise \end{cases}$$

In this example, Bayesian method was used to obtain the posterior distribution for a_4. Also applied was a method of randomization such that when patients were randomized to a treatment, the probability that subsequent patients would be randomized to the same treatment was reduced. This coupled with rules for drop-the-loser also being included make this approach innovative in its design and execution. However, the method is applied to a predetermined set of fixed doses and assumed toxicity probabilities.

Zhou et al. (2006) present a Bayes approach to a bivariate dose escalation design. In this design a logistic regression is used to predict the probability of a DLT and a linear mixed effects model for the desired outcome (DO). This approach allows for the DO to be

continuous, albeit a linear response model, in addition to consideration of the usual binary outcome of observation of a DLT for safety.

Bauer and Röhmel (1995) propose a multistage dose response design methodology. In this hypothesis-testing design, a null hypothesis is tested based at each stage on the product of all previous p-values less than the global critical limit. The global critical limit is based on Fisher's product test statistics. If Ho is rejected at an intermediate step, it is either concluded that a dose-response exists or evaluations continue on to the next stage. The dose levels and number of stages for such a design are a predetermined fixed set.

Adaptive designs in early clinical trials increase the possibility of exposing fewer patients to ineffective treatments (dose levels below the NOEL), provide a better understanding of dose response, and decrease the overall cost of drug development. Adaptive designs can be model based in which patients are assigned to the next dose based on the response of patients dosed at preceding dose levels. Adaptive designs can also provide a better understanding of dose responsiveness, which leads to a better choice of doses going forward into pivotal Phase III trials (Raymond et al., 2006).

Insufficient exploration of the dose-response is often a key shortcoming of clinical drug development. Initial proof-of-concept (PoC) studies often rely on testing just one dose level (e.g., the maximum tolerated dose) without much information on which to base the decision, assuming "more is better" and hoping the "right" dose was selected. Hence,

consideration of adaptive dose-response designs in exploratory development may lead to better choices of dose selection for PoC studies (Gaydos et al., 2006).

None of the above methodologies described provide an approach to estimate the dose response curve by non-linear methods. Our approach is not a hypothesis testing approach, nor does it attempt to generate an α-spending function. The motivation for our approach is described in the next section.

1.4 Motivation for the DOSEFIND

The CRM, 3+3 design, BCD and current adaptive methods are Bayesian and/or frequentist in nature. These design methods are based on a pre-specified set of dose levels to determine an MTD. In current adaptive methods, sequential, group sequential, and seamless confidence interval approaches are used. In current dose response designs, the hypothesis testing of a clinical endpoint to determine superiority of a treatment is used. With the exception of the CRM, none of these methods consider the application of a sigmoidal dose response curve for the evaluation of dose response. For the CRM, the response curve is based on the observance of adverse events, which does not necessarily coincide with a clinically relevant response.

We have generated the DOSEFIND method; a method for obtaining the desired response using an adaptive non-linear approach. This method will be applicable for MTD, NOEL, NOAEL, PK, PD effects or other observed endpoints for which optimization is desired. Using a nonlinear logistic model, a sigmoidal dose response curve will be estimated. Employing an adaptive non-linear approach, the proposed method will allow for an evaluation and elimination of dose levels below the NOEL so that the actual range of dose response will be obtained more quickly, accurately and with fewer subjects than typically needed for a conventional early phase clinical trial. In addition, the DOSEFIND method will be particularly useful for dose finding studies. Toward that end, we will describe the applications of this method in cases where a measurable PD marker is an indicator of potential efficacy.

Due to the logistics of generating PK and some PD results, these methods may extend the time required to complete the study during the early stages of drug development. However, any increases in time at this phase of development have the potential to be more than offset by significant savings in time at later stages. For example, repeating a PoC study due to a poor choice of doses would add significant time and cost to the development of the NCE of interest.

1.5 Safety Considerations

In human clinical trials patient safety is of paramount importance. The DOSEFIND method will work best in compounds that have a fairly clean safety profile in pre-clinical testing. Conversely, compounds with a narrow therapeutic window may not be good candidates for this approach because of the increased chance for adverse events associated with small changes in the dose level.

Safety in clinical trials is measured by serial tracking of clinical laboratory panels, adverse events reported by the patients or those observed by the clinical staff. In the DOSEFIND method, safety is evaluated by considering the probability of adverse events being serious enough that they are considered DLTs. In doing this, a number of trials may have to be stopped prematurely. However, the DOSEFIND method will still provide some measure of efficacy relative to these events. This efficacy data could help reseachers decide whether or not to continue drug development. That is, observing a sufficient efficacy at a lower dose than anticipated could keep an NCE a viable candidate for future work. Alternatively, if little or no efficacy is observed, the viability of the NCE is called into question.

1.6 Prospectus

In Chapter 2, the methodology of the DOSEFIND method is presented in Section 2.1. The algorithm for the DOSEFIND is described in Section 2.2, adjustment of the method for safety considerations is described in Section 2.3 and an example of how the procedure works is presented in Section 2.4. In Chapter 3, a description of various simulations is presented in Section 3.1, and the results and discussion are presented in Section 3.2. Finally, a brief summary and the results of the DOSEFIND method along with considerations for future work are presented in Chapter 4.

CHAPTER 2

2.0 Introduction

The DOSEFIND methodology is presented in Section 2.1. The DOSEFIND method may be used with any non-linear function. Thus, the general form of the non-linear (along with some representative functions) are presented first. Particular attention is given to the logistic function as it is adopted for use in this dissertation. An algorithm detailing the stepwise process of how the DOSEFIND method performs is described in Section 2.2. Modification of the DOSEFIND method adjusting for safety considerations is presented in Section 2.3. Finally, an illustration of the DOSEFIND method is presented in Section 2.4 using simulated data generated with parameter estimates from a clinical trial.

2.1 DOSEFIND Method

Consider a series of continuous responses at various dose levels to some unknown dose (d^k). Each observed response is assumed to be independent as each comes from a different subject or patient. For the DOSEFIND method, each new dose (in the series of

doses) is chosen based on the parameter estimates from the data obtained from previous dose levels. New parameter estimates are generated, which in turn specify the next new dose level. This process continues until the stopping rules are achieved. The number of subjects at the current state of the process is n, and the total sample size at the completion of the process is N_T.

There is a general class of nonlinear functions that can be used to estimate sigmoidal dose response curves from binary, count or continuous data. The general form is:

$$\mu = \alpha + \gamma F\left(\mathbf{D}; \underset{\sim}{\mathbf{B}}\right) \tag{2.1}$$

where

F is a continous and monotonically increasing function with range in the unit interval

$\mathbf{D}$ is the set of doses $\mathbf{D} = \left\{d^{(1)}, \ldots, \quad d^{(k)}\right\}$, where k is the number of dose steps

μ denotes the unknown effect,

$\underset{\sim}{\mathbf{B}}$ denotes the vector of unknown parameters, and

α is the minimum and $\alpha + \gamma$ is the maximum unknown effect parameter.

Examples of these types of models include the Gompertz model

where $F\left(d;\beta_0,\beta_1\right)=e^{-e(-(\beta_0+\beta_1 d))}$ and the Michaelis-Menten model

where $F\left(d;\phi\right)=\frac{d}{\phi+d}$. We illustrate the proposed method with the nonlinear logistic

model, where $F\left(d;\beta_0,\beta_1\right)=\left[1+e^{-\left(\beta_0+\beta_1 d\right)}\right]^{-1}$. Each of these non-linear functions

will produce results that differ only at the tails of the sigmoid. That is, all of these functions will produce similar results in the linear ("middle") portion of the response profile. Simulations for the Gompertz and Michaelis-Menten models are also provided, discussed and compared to the non-linear logistic model. Hence, we have chosen to utilize the nonlinear logistic model as the primary model of choice for illustration of the DOSEFIND method.

The estimate of the target dose $\left(T_D\right)$ for the general nonlinear form is

$$T_D=\frac{F^{-1}\left(\left(\mu_{T_D}-\alpha\right)/\gamma\right)-\beta_0}{\beta_1} \tag{2.2}$$

In an attempt to estimate the $\left(T_D\right)$, we assume the observed response of interest is either the expression or suppression of some pharmacodynamic or biological marker. For example,

suppose that the amount of suppression of a specific biological marker is of interest where the biological marker is endogenous. Therefore, levels of the biological marker are reported as the amount of suppression, relative to baseline for each subject. For our example, baseline is defined as the observed levels of the biological marker before administration of the NCE.

Both expression and suppression of a marker can be constrained such that the marker is bounded below by zero. In this case, the value for α (for the non-linear logistic and the Gompertz models) in (2.1) and (2.2) is zero, and for the nonlinear logistic, Gompertz and Michaelis-Menten the T_D is:

$$\text{Logistic:} \qquad T_D = \frac{\log\left(\mu_{T_D} / \left(\gamma - \mu_{T_D}\right)\right) - \beta_0}{\beta_1}$$

$$\text{Gompertz:} \qquad T_D = \frac{-\log\left(\log\left(\gamma / \mu_{T_D}\right)\right) - \beta_0}{\beta_1} \tag{2.3}$$

$$\text{Michaelis-Menten:} \quad T_D = \phi\left(\frac{\mu_{T_D} - \alpha}{\gamma - \mu_{T_D} + \alpha}\right)$$

The variance of Y is assumed to be a function of the mean. That is,

$$\text{Var}(Y) = \tau V(\mu) \tag{2.4}$$

Based on the premise that the observed variance is larger in the "linear" portion of the dose response curve compared with the tails and μ is in the unit interval, $V(\mu)$ is assumed to follow $\mu(1-\mu)$.

Applying a quasi-likelihood estimation criterion, it is of interest to maximize

$$Q(\mu;Y)=\sum_i Q(\mu_i;y_i)$$

where

$Q\left(\mu_i;y_i\right)=\int_y^{\mu}\frac{y-t}{\tau V(t)}dt$ and in the illustration becomes

$$\int_y^{\mu}\frac{y-t}{\tau t(1-t)}\partial t=\frac{1}{\tau}\left[y_i\log\left(\frac{\mu_i}{1-\mu_i}\right)+\log\left(1-\mu_i\right)\right] \qquad (2.5)$$

Estimation of τ is based on the moment estimator

$$\hat{\tau}=\frac{1}{(n-p)}\sum_i\frac{\left(y_i-\hat{\mu}_i\right)^2}{\hat{\mu}_i}$$

To use the maximum quasi-likelihood criterion in PROC NLIN (SAS® Version 8.02, Cary, NC), loss and weight functions must be generated. The loss function is the negative log quasi-likelihood for the i^{th} observation. For the logistic model the LOSS function is

$$LOSS = -\left(y_i \log\left(\mu_i/(1-\mu_i)\right) + \log(1-\mu_i)\right)/w_i \tag{2.6}$$

and the weight function is

$$w_i = 1/\left(\mu_i(1-\mu_i)\right), \tag{2.7}$$

which is the reciprocal of $V(\mu)$. Application of these loss and weight statements maximizes the quasi-likelihood given in (2.5) using the nonlinear model given in (2.1) and the variance assumption given in (2.4). The weighted mean square error is the moment estimator for τ.

Let $\mathbf{G}_i = \alpha + \gamma \mathbf{F}\left(d^{(i)}, \underset{\sim}{\mathbf{B}}\right)$ and $\theta' = [\alpha \quad \gamma \quad \underset{\sim}{\mathbf{B}}]$, then $\boldsymbol{\Sigma}$ is derived using the quasi-likelihood approach found in Seber and Wild (1989) with the following regularity conditions:

a. $\dfrac{\partial^3 \mathbf{G}_i}{\partial\theta_r \partial\theta_s \partial\theta_t}$ is bounded with $(\mathrm{i} = 1, 2, \ldots, n; \mathrm{r,s,t} = 1, 2, \ldots p)$

b. The third moments of $\mathbf{G}$ exist, and

c. $n^{-1}\mathbf{I}_n(\boldsymbol{\theta})$ has a positive definite limit as $n \to \infty$.

$$\boldsymbol{\Sigma}^{-1} = \mathbf{I}_n(\boldsymbol{\theta}) = -E\left[\frac{\partial^2 Q}{\partial \boldsymbol{\theta}\, \partial \boldsymbol{\theta}'}\right] = \mathbf{G}_*'(\boldsymbol{\theta})\mathbf{V}^{-1}(\boldsymbol{\theta})\mathbf{G}_*(\boldsymbol{\theta})\frac{1}{\tau},$$

where $\mathbf{G}_*(\theta)$ is an n x p first derivative matrix with respect to θ and

$\mathbf{V}(\boldsymbol{\theta}) = diag(v_1, v_2, \ldots, v_n)$, $i = 1, 2, \ldots, n$.

Here $v_i = \mu_i(1-\mu_i)$ from (2.4).

To estimate τ, γ and $\underset{\sim}{\mathbf{B}}$, starting values must be generated. This is accomplished by collecting data from an initial set of doses $\left(d^{(0)}\right)$. At a minimum, $d^{(0)}$ must consist of three dose levels in order to begin non-linear estimation. A simple linear regression using the transformation $\log(\mu/(1-\mu))$ of the response data provides the starting values for β_0 and β_1, where μ is the response. For our purposes, μ is assumed to be a percentage of expression or suppression of the pharmacodynamic or biological marker. The starting value for γ is chosen based on experience with the biomarker under consideration. The estimate of τ is the weighted mean square error from the non-linear model.

The large sample confidence interval on T_D is found using the delta method. That is an approximate estimate for the variance is $\mathrm{Var}(\hat{T}_D) = \mathbf{H}\boldsymbol{\Sigma}\mathbf{H}'$, where $\mathbf{H}$ is the partial derivatives from (2.3). For example, in the nonlinear logistic case the partial derivatives are:

$$\frac{\partial T_D}{\partial \gamma} = \frac{dF^{-1}((\mu_{T_D} - \alpha)/\gamma)/\partial \gamma}{\beta_1} \tag{2.8}$$

$$\frac{\partial T_D}{\partial \beta_0} = -\frac{1}{\beta_1} \tag{2.9}$$

$$\frac{\partial T_D}{\partial \beta_1} = -\frac{F^{-1}((\mu_{T_D} - \alpha)/\gamma)}{\beta_1^2} \tag{2.10}$$

Now define $\mathbf{H} = \left[\frac{\partial T_D}{\partial \beta_0} \quad \frac{\partial T_D}{\partial \beta_1} \quad \frac{\partial T_D}{\partial \gamma} \right]$ (2.11)

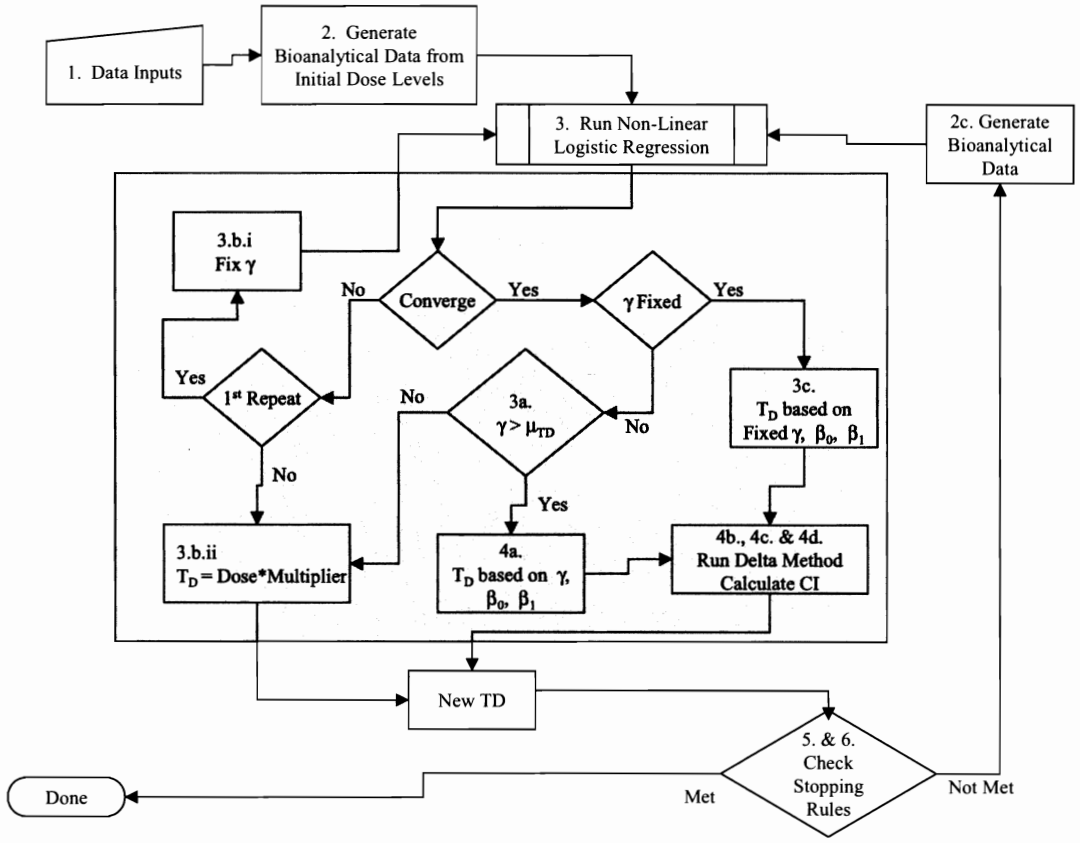
Then a large sample 100(1-α)% confidence interval is given by

$$\hat{T}_D \pm t_{1-\alpha/2;n-p} \sqrt{Var(\hat{T}_D)} \tag{2.12}$$

2.2 DOSEFIND Algorithm

As shown in flow diagram Figure 2.1, the algorithm begins with the required data inputs. Once sufficient data are obtained (e.g., bioanalytical data from $d^{(0)}$), the non-linear regression is executed and evaluated. Once model convergence occurs, the 100(1-α) % confidence interval for T_D is estimated. If conditions that govern the stopping rules are satisfied, the procedure stops. If not, bioanalytical data based on the new T_D are generated for the next iteration. The DOSEFIND method is completed after successful estimation of T_D. Failure to estimate T_D can happen for a variety of reasons, and discussion of this is included in the explanatory text that follows Figure 2.1.

Figure 2.1: Flow Diagram of Method



The steps in Figure 2.1 are described as follows:

1) Obtain the following data inputs from the clinicians, statisticians, pharmacokineticists and other professionals on the development team:

    a) The target effect (desired response) of interest;

    b) The dose multiplier or the amount to increase the dose level if the nonlinear regression fails (e.g., convergence failure or singularity of the Hessian);

c) Minimum dosing unit referred to as the bin size (e.g., tablets, milligrams, mg/kg);

d) Number of subjects per dose level (active treatment and placebo);

e) Define the following stopping rules:

i) The number of times the dose multiplier may be used;

ii) The alpha level for the 100(1-α)% confidence interval; and

iii) The desired width of the confidence interval.

Stopping rules are discussed below and subjects per dose level will be varied in the simulation experiment presented in Chapter 3.

2) Determine the initial dose levels ($d^{(0)}$)

a) The initial starting dose is based either on information from non-clinical data or previous experience in humans. For a FIM study the starting dose is usually calculated as $1/10^{th}$ the no adverse effect level (NOAEL) of the most sensitive animal species and is converted to a human equivalent dose (FDA Guidance Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005). For trials that are not FIM the initial dose should be based on previous human experience;

b) The additional doses may be the amount of the initial dose multiplied by the dose multiplier. Generally three dose levels with placebo controls are used in the initial set of dose levels;

c) Generate bioanalytical data from the initial dose levels; and

d) Begin non-linear estimation. once data are obtained from the first three dose levels;

3) Execute the nonlinear regression analysis using a specific form of (2.1), (in our case the nonlinear logistic, the loss (2.6) and weight (2.7) functions) to obtain parameter estimates of $\gamma, \underset{\sim}{\mathbf{B}}$ (in our example α=0) and their covariance matrix (Σ). There are four possible outcomes of the regression:

a) Given that the procedure converges, the Hessian is nonsingular and the estimate of γ is greater than μ_{T_D} (the target response of interest), then both the target dose T_D and its variance as computed by the delta method described above can be obtained

b) If convergence and/or singularity issues exist after attempting to estimate γ and $\underset{\sim}{\mathbf{B}}$, then fix γ at its defined maximum and rerun the estimation:

i) The procedure fails to converge after fixing γ and no parameter estimates are obtained;

ii) The Hessian is singular after fixing γ and no covariance matrix is estimated; and

c) If the estimate of γ is less than μ_{T_D} then the next T_D is estimated based on $\gamma = 1$. The new T_D is the larger of the calculated T_D or the current T_D multiplied by the dose multiplier.

In each of the above cases (3b[i], 3b[ii], and possibly 3c) the subsequent dose is chosen based on the multiplication of the current dose with the specified dose multiplier.

4) Assuming that both the target dose T_D and its variance in (2.4) can be obtained (as described in 3a above), the algorithm may be continued with the following steps:

   a) Estimate the dose using (2.3); the result is assigned to the closest bin and becomes the new T_D for the next iteration. The bin is based on the bin size specified in the Data Input step; the first bin is the bin size then and ith bin is i*bin size, where $i = 1, 2, \ldots$;

   b) Calculate the $\mathrm{Var}(\hat{T}_D)$ by application of the delta method;

   c) Calculate a 100(1-α)% confidence interval about T_D (using a t-critical value $t_{\alpha/2, n-p}$, where n is the number of observations and p is the number of parameters estimated);

   d) The possible causes of inability to compute a confidence interval are:

      i) Failure of the non linear regression to converge; or

      ii) The Hessian is singular.

5) There are two possible ways to stop the study from a pharmacodynamic perspective.

a) Once the confidence interval is calculable the algorithm is designed to stop if:

   i) The length of the confidence interval is less than ½ the bin size; or

   ii) The length of the confidence interval is less than the bin size and the same dose was chosen three consecutive times.

b) If the number of dose multiplications defined in the Data Input step occurs then the study stops; and

c) If the maximum number of iterations or dose levels occur (as defined in the Data Input step) then the study stops

6) All stopping rules sre checked and if none are met, return to step 2c and repeat the process.

The stopping rules in this section are not based on safety considerations. This will be addressed in the next section.

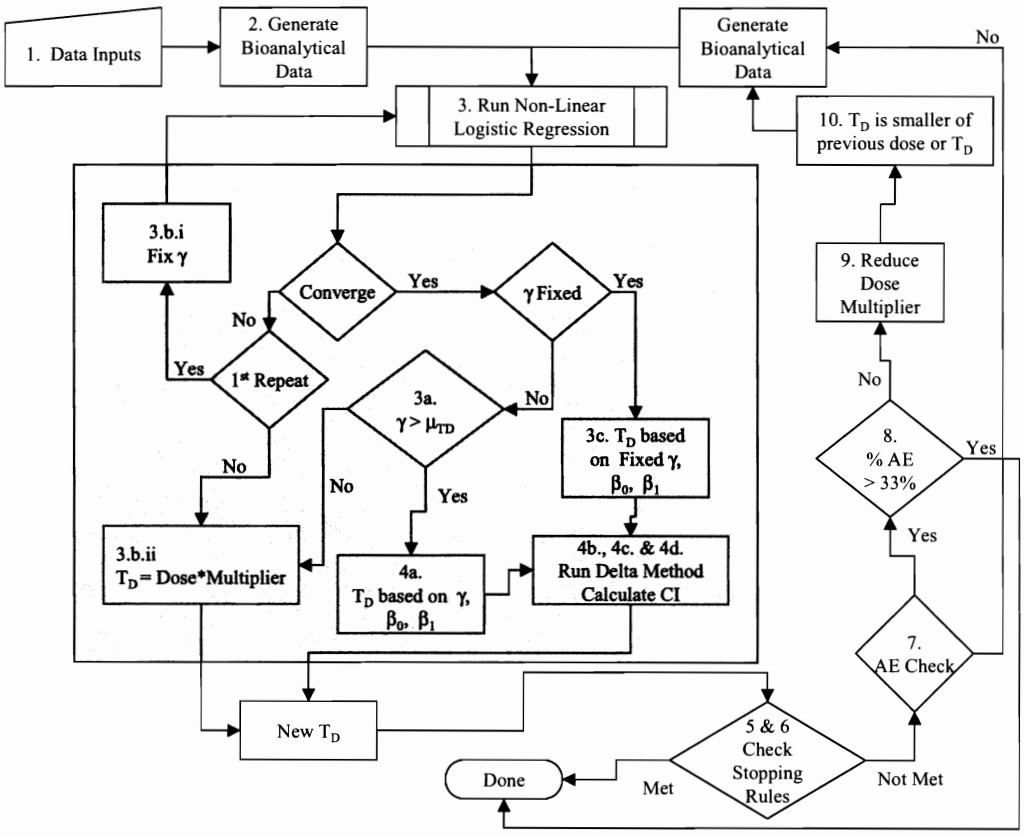
2.3 DOSEFIND Algorithm Adjusted for Safety Considerations

Depending on non-clinical toxicology information, the application of the dose multiplier and/or dosage increase can be altered for safety considerations. Also, alternative rules can be defined for either stopping the study or changing the next dose due to safety concerns. Safety of the subjects is paramount and, therefore, stopping rules for safety concerns must be independent of and supersede stopping rules based on PD effects. In general, it is

reasonable to expect that the chance of observing a DLT increases with dose level. Under this assumption, studies are typically stopped when two or more DLTs occur at one dose level. Without supporting dose-response information, additional trials may be planned and conducted based on the observed MTD. However, if it were known that the desired dose response was not obtainable due to an MTD having been determined at a low dose, testing of the compound would stop. Alternatively, having knowledge of the dose response earlier rather than later in the drug development process allows for more efficient dose response designs and better choices of dose selection for PoC studies, resulting in substantial reductions in the number of clinical trials that need to be executed.

The flow diagram in Figure 2.2 is an update of Figure 2.1 to include accounting for the occurrence of adverse events Three additional steps (7-10) are added to the procedure, and this explanatory text follows the diagram.

Figure 2.2: Flow Diagram Adjusted for Safety Effects



Steps 7-10 are described as follows:

7) Check for the occurrence of adverse events. If an adverse event is observed then

8) Check to see if the frequency of adverse events exceeds 33% for an observed dose level or for the study population. If so, then the study stops;

9) If not, permanently reduce the dose multiplier by a pre-specified amount; and

10) Assign the next dose to be the smaller of the previous dose or the current updated dose.

Assuming that, the probability of observing an adverse event increases with increasing dose levels, the dose multiplier is permanently reduced once an adverse event is observed. This rule results in a more conservative method due to the need for patient safety.

2.4 Illustration of the DOSEFIND Approach

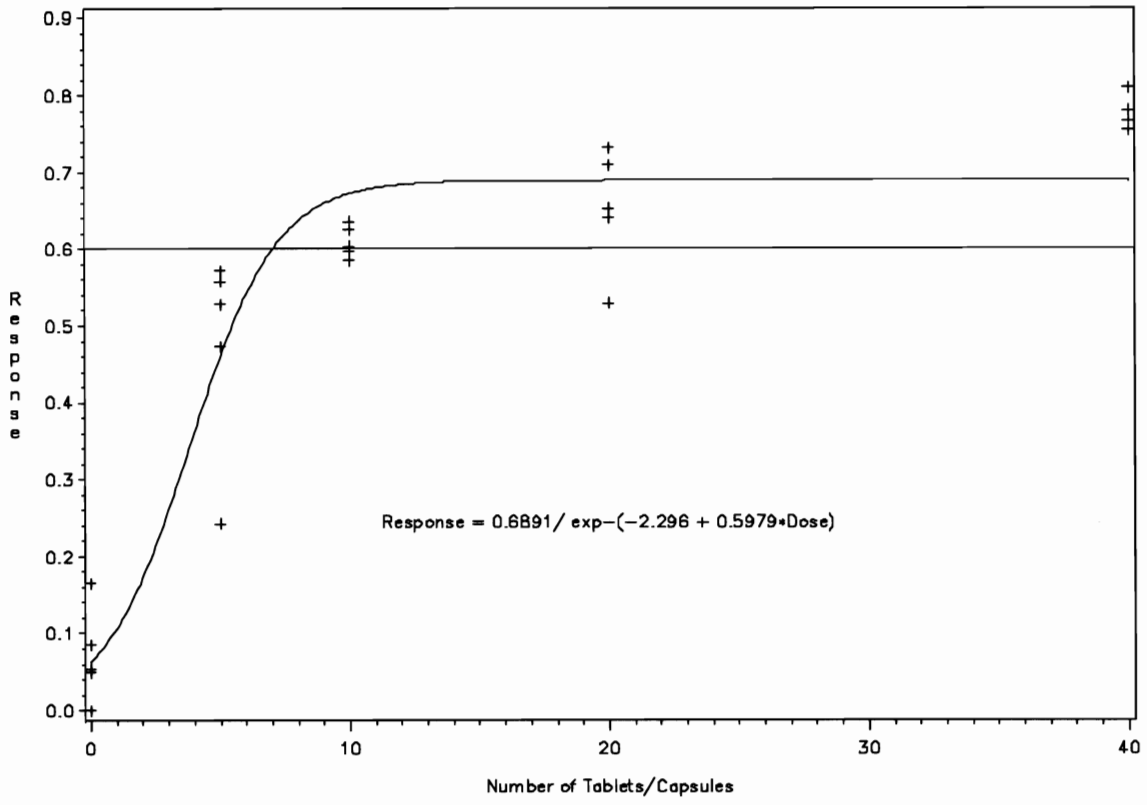
An example is presented to illustrate the DOSEFIND method. First, pharmacodynamic data observed from a clinical trial was fit using a nonlinear logistic model to estimate values for τ, γ and $\underset{\sim}{\mathbf{B}}$ and since we are interested in suppression of the PD marker, α is set to zero. The variance used in the illustration and the simulations were based on assuming a quasi-likelihood approach and with $Var(Y) = \tau\mu(1-\mu)$. The choice of $V(\mu)$ is based on the assumption that the response variable takes on values between 0 and 1. Thus, the maximum variance would be expected when the average response is estimated as 0.50.

Using the biomarker suppression results, the predicted sigmoidal curve from the nonlinear logistic fit is presented in Figure 2.3. The non-linear logistic fit of the PD data from a clinical trial using Drug X resulted in estimates for τ, γ, β_0 and β_1 of 0.0461, 0.6891, -2.296 and 0.5979, respectively. The T_D associated with the target threshold level displayed in Table 2.1 is based on these parameter estimates. It is important to note that the data used in this example was simulated assuming these parameter estimates.

Table 2.1: Expected Values of T_D for the Given Level of Desired Response

Desired Response or Target Threshold $\left(\mu_{T_D}\right)$	Target Dose
0.55	6.14

Figure 2.3: Clinical Trial Non-Linear Sigmoidal Curve Fit



Before proceeding with this example, values for the input criteria (target threshold effect, dose multiplier, bin size and initial dose levels) must be assigned. For the purpose of this example, the target threshold effect is defined to be 0.55, the dose multiplier is defined to be 2, the bin size is defined to be one unit and the initial dose levels $d^{(0)}$ are defined to be 1.25, 2.5 and 5 units.

With regard to the number of subjects at each dose, one subject is assigned to active treatment and one is assigned to placebo at the first three dose levels. At each subsequent dose level, three subjects are assigned to active treatment and one is assigned to placebo.

The stopping rules are defined as:

a) If the dose increase is doubled six times the study stops or;

b) If the desired width of the 95% confidence interval is ½ the bin size or if the dose level remains constant for three consecutive iterations and the confidence interval width is less than the bin size, the study stops.

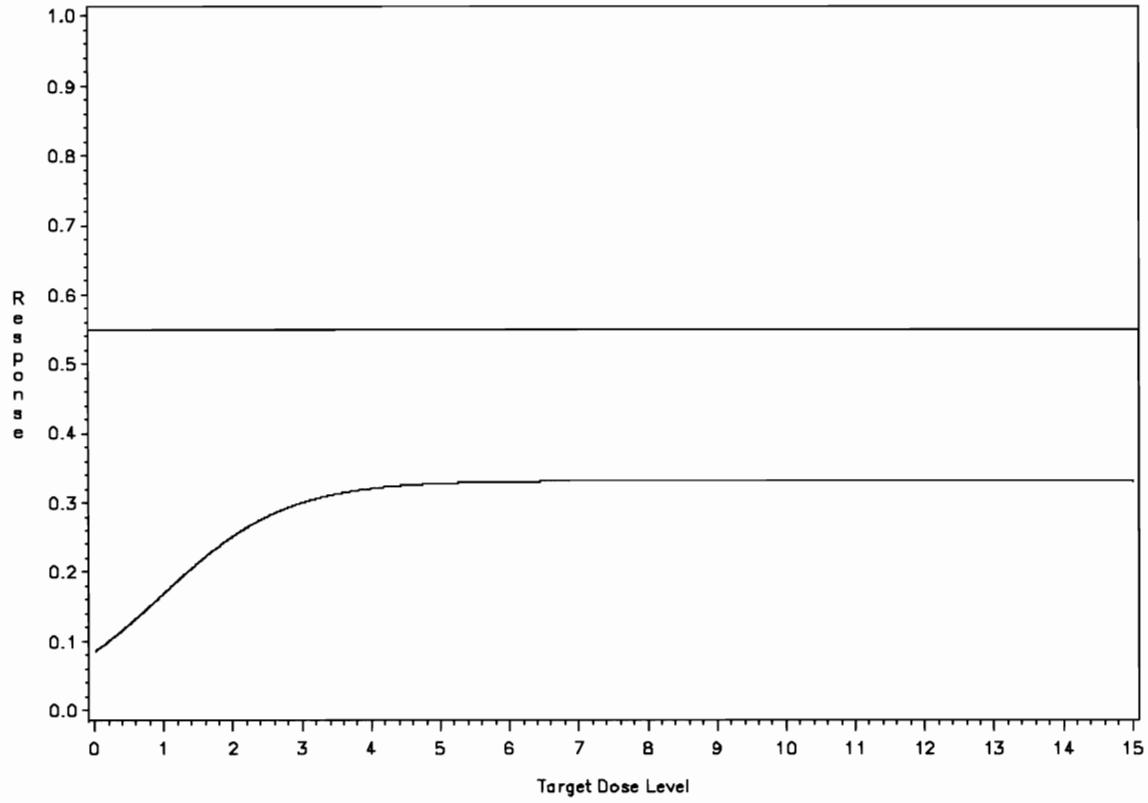
The input criteria, sampling schema and stopping rules defined above were applied to the simulated responses for the first three doses resulting in the data displayed in Table 2.2.

Table 2.2: Simulated PD Responses for the Initial Three Dose Levels and the Associated Placebo Subjects

Response	Dose Units
0.202	1.25
0.114	0.00
0.266	2.50
0.048	0.00
0.334	5.00
0.088	0.00

Using these data, a non-linear logistic model was fit with the starting values for γ, β_0, and β_1 of 1.00, -2.102 and 0.2830, respectively. While this is a sufficient amount of data to fit a curve the result is well below the desired threshold effect. The results of the initial non-linear regression resulted in estimated values for $\hat{\beta}_0 = -1.0698, \hat{\beta}_1 = 1.1054$ and $\hat{\gamma} = 0.33145$. The non-linear logistic curve for these parameter estimates is presented in Figure 2.4.

Figure 2.4: Initial Iteration Illustrating the Sequential Approach



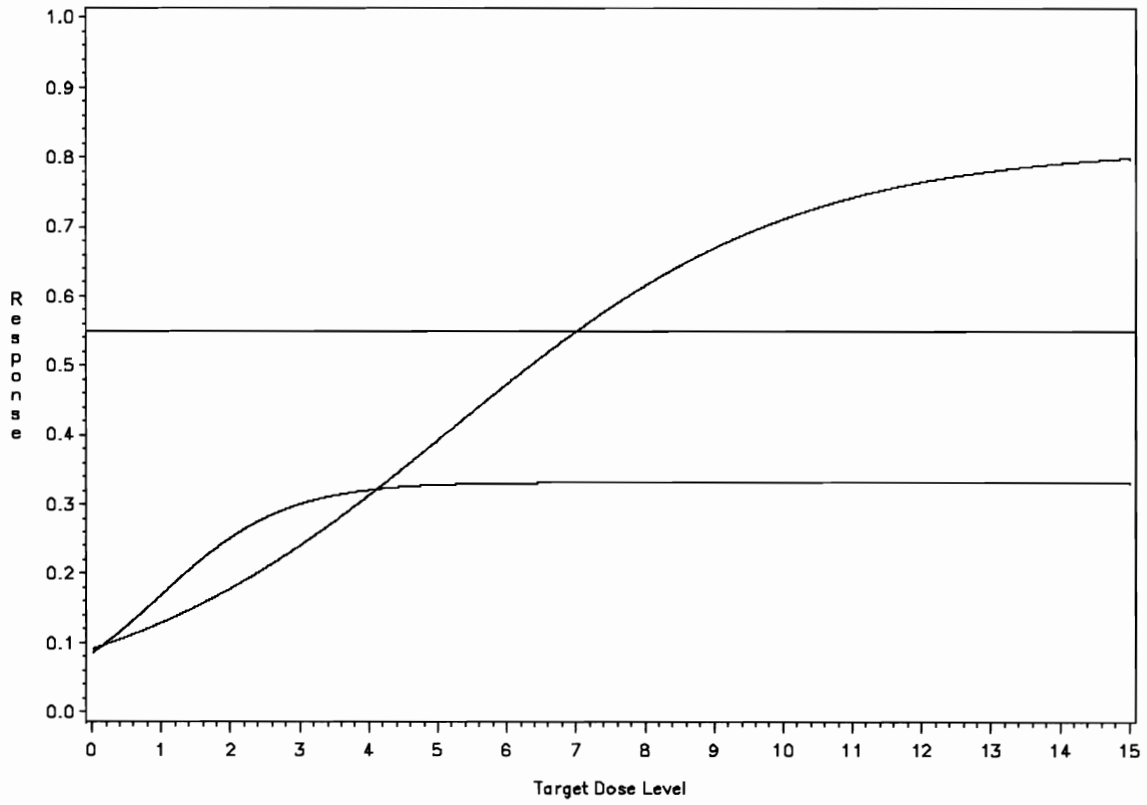
Since $\hat{\gamma}$ is less than the target threshold effect (0.55), the estimate for the target dose is calculated as the maximum of T_D or the dose multiplier is applied to the previous dose resulting in a dose of 10 units. Next, three active subjects and one-placebo subject were simulated at the new dose level and the results are shown in Table 2.3.

Table 2.3: Simulated PD Responses for the Fourth Dose Level and the Associated Placebo Subject

Response	Dose Units
0.722	10.0
0.749	10.0
0.668	10.0
0.042	0.00

Adding these data to the previous data and executing the non-linear regression, results in values for $\hat{\beta}_0$, $\hat{\beta}_1$ and $\hat{\gamma}$ of -2.07356, 0.40014 and 0.81388, respectively. In this iteration, the value of $\hat{\gamma}$ is greater than 0.55, which results in calculated dose of 7.01759 and a target dose of 7 units. Since the number of iterations is greater than 1 and $\hat{\gamma}$ is greater than 0.55, the delta method is executed to estimate the variance of the dose and its confidence interval. With the t-critical value of 2.364, the ½ width of the 95% confidence interval was 1.800. Since the value of the ½ width of the 95% confidence interval is greater than 0.50 (½ bin size), the next iteration will be performed. The results of this iteration are displayed in Figure 2.5.

Figure 2.5: Second Iteration Illustrating the DOSEFIND Method



Continuing the process and applying the above criteria, a total of five iterations of the simulation were required to obtain the stopping criteria. The complete list of the simulated doses and responses are shown in Table 2.5 and Figure 2.6.

Table 2.4: Simulated PD Responses and Dose Units for Iterations Three through Five

Response	Dose Units	Iteration #
0.861, 0.473, 0.616	7.00	3
0.103	0.00	
0.725, 0.528, 0.581	6.00	4
0.056	0.00	
0.686, 0.712, 0.610	6.00	5
0.076	0.00	

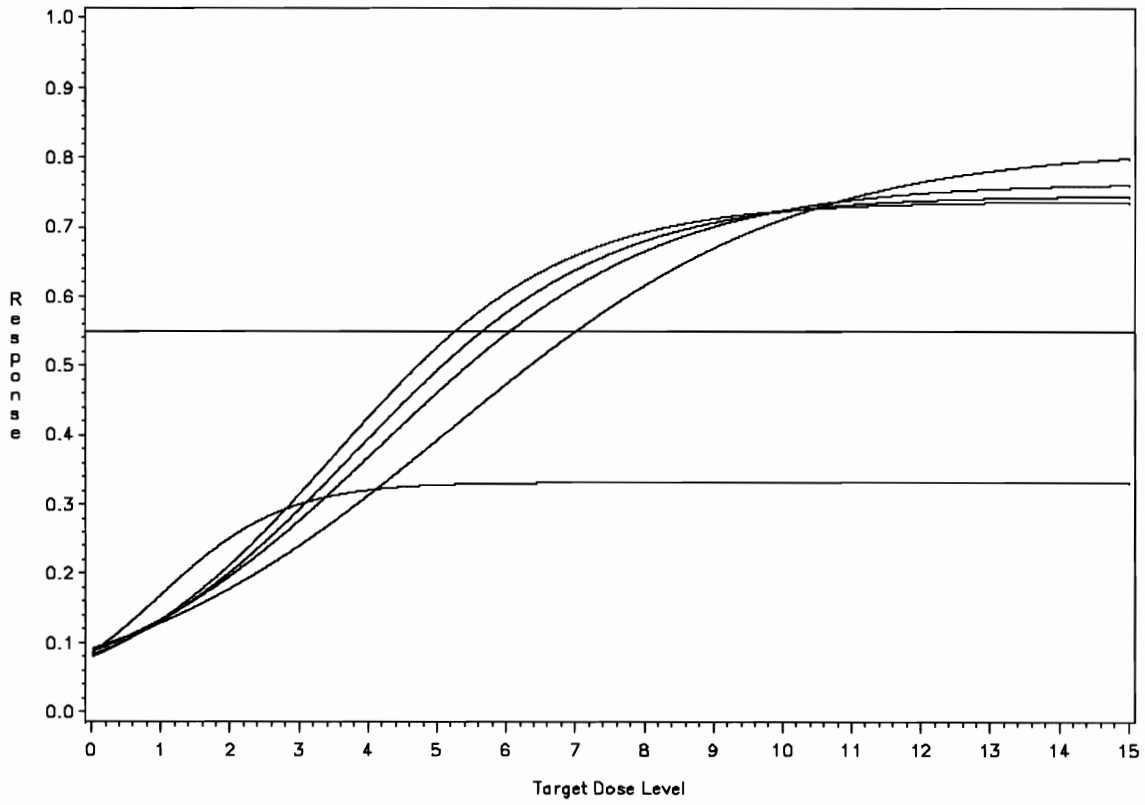
These simulations produced estimates for β_0, β_1, γ, actual dose, target dose, $Var\left(\hat{T}_D\right)$ and ½ width of the 95% confidence interval. Complete results of all iterations are displayed in the Table 2.5.

Table 2.5: Illustration Results for Sequential Approach to Dose Finding

Iteration	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\gamma}$	Actual Dose $\left(\hat{T}_D\right)$	Target Dose	$Var\left(\hat{T}_D\right)$	½ 95% CI
1	-1.0698	1.1054	0.33145	-	10.0	-	-
2	-2.07356	0.40014	0.81388	7.0176	7.0	0.7612	1.800
3	-2.05163	0.49431	0.76334	6.0664	6.0	0.5695	1.254
4	-2.10020	0.55409	0.74503	5.6615	6.0	0.2968	0.633
5	-2.1183	0.60724	0.73635	5.2707	5.0	0.2121	0.444

The stopping rule of ½ the width of the 95% confidence interval being less than 0.500 is met at the fifth iteration. Graphical representations of all five iterations are represented Figure 2.6.

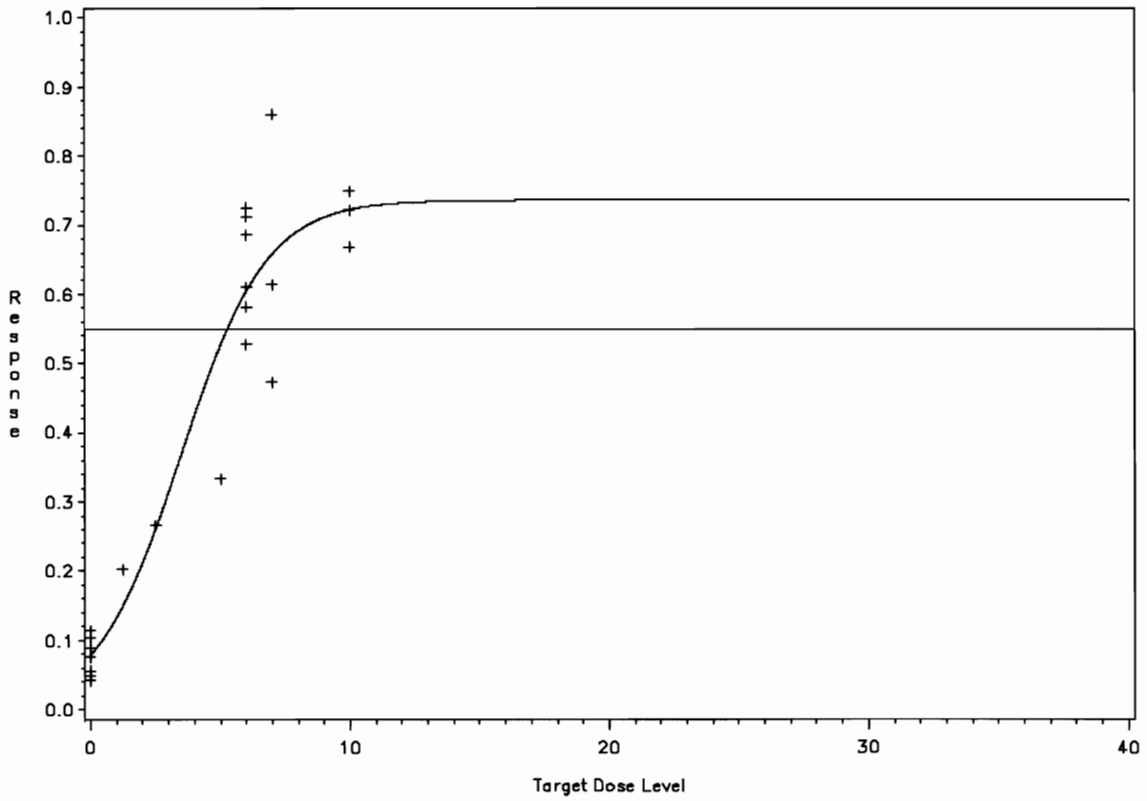
Figure 2.6: Graphical Display Results of All Five Iterations



Using only 15 subjects (on active drug) the DOSEFIND method versus 20 (on active drug) from the clinical trial data (see Figure 2.3). The DOSEFIND method was able to produce a dose response curve in the simulated example with similar parameter estimates to the "truth" in the simulated study. The DOSEFIND method estimated the target to be either 5 or 6 units (5.27 ± 0.44) and yielded a dose response curve that is presented in Figure 2.7. In the clinical trial, data from 40% (n=10) of the subjects provided no dose response information (i.e., not in the linear portion of the curve). In contrast, data from all of the subjects in the DOSEFIND approach were in the linear portion of the dose response curve

and subsequently provided information that describes the dose response shape. In the DOSEFIND method, data from all of the subjects were in the linear range, and 13 of the 15 subjects were between 5 and 10 dose units. In the clinical trial, data there were data from 5 subjects, each at 5 and 10 dose units, respectively, but none of these subjects were at dose levels between 5 and 10 units. In fact from the DOSEFIND estimated curve, other target doses ($\hat{T}_D$) can be subsequently estimated. That is, the DOSEFIND method can be used to provide dose estimates that represent the ED10, ED50 and ED90, for example.

Figure 2.7: Example Study Final Dose Response Curve with Simulated Response Data



In the next chapter we will demonstrate, via simulations, that the DOSEFIND method can find the expected target dose from the clinical trial on average.

CHAPTER 3

3.0 Introduction

The simulation study was designed to demonstrate the ability of the DOSEFIND method to effectively generate an accurate target dose, demonstrate where the method is robust, evaluate alternative non-linear functions (the Gompertz and Michaelis-Menten) and examine the effects of subject adverse events on the method. A target threshold of 0.55 was chosen for convenience only. Ten simulations each of size (n=100) were generated using various values of the slope (β_1), intercept (β_0) and various numbers of patients assigned to either active treatment or placebo and various non-linear models. Parameter estimates, the predicted target dose, associated confidence interval, sample sizes and failure rates from each simulation run will be presented. The simulation failure rate was defined as the percentage of simulations that have either had the occurrence of six dose doublings, three consecutive replicates of the same dose and a ½ width 95% confidence interval length less than the bin size, or 27-dose levels achieved without attaining a confidence level of length less than bin size. In addition, for the adverse events simulation, the failure rate will represent the number of trials stopped due to occurrence of adverse events.

In Section 3.1 the simulation plan and design is described. The results and a discussion are presented in Section 3.2.

3.1 Simulation Plan and Design

One thousand studies were simulated with the following characteristics:

$E(Y)=\mu$, $\mathrm{Var}(Y)=\tau\mu(1-\mu)$ and using a normal random number generator such that $y_i=\mu_i+z\sqrt{\tau\mu_i(1-\mu_i)}$, where z is a standard normal random variable.

Next, the form of the non-linear function is described. A logistic model to estimate a sigmoidal dose response curve will be defined using (2.1), or:

$$G(\boldsymbol{\theta})=\gamma F(d;\mathbf{B})=\frac{\gamma}{1+e^{-\left(\beta_0+\beta_1 d\right)}} \tag{3.1}$$

The estimate of the target dose T_D using (2.2) is

$$T_D=F^{-1}\left((\mu-\alpha)/\gamma;\mathbf{B}\right)=\frac{\log\left(\mu_{T_D}/\left(\gamma-\mu_{T_D}\right)\right)-\beta_0}{\beta_1}$$

For the logistic model, the partial derivatives with respect to estimated parameters γ, β_0 and β_1, and the covariance matrix of γ, β_0 and β_1 are shown as:

$$\frac{\partial T_D}{\partial \beta_0} = -\frac{1}{\beta_1} \tag{3.2}$$

$$\frac{\partial T_D}{\partial \beta_1} = -\frac{1}{\beta_1^2}\left[\log\left(\frac{\mu_{T_D}}{\gamma - \mu_{T_D}}\right) - \beta_0\right] \tag{3.3}$$

$$\frac{\partial T_D}{\partial \gamma} = -\left(\frac{1}{\gamma - \mu_{T_D}}\right)\left(\frac{1}{\beta_1}\right) \tag{3.4}$$

and $\mathbf{H}$ is defined as $\mathbf{H} = \left[\frac{\partial T_D}{\partial \beta_0} \quad \frac{\partial T_D}{\partial \beta_1} \quad \frac{\partial T_D}{\partial \gamma}\right]$.

Then $\mathrm{Var}(\hat{T}_D) = \mathbf{H}\boldsymbol{\Sigma}\mathbf{H}'$ (for large samples) and $\boldsymbol{\Sigma}$ is derived as described in Chapter 2.

The partial derivatives for $\mathbf{G}(\boldsymbol{\theta})$ are

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \beta_0{}^{(i)}} = \frac{-\gamma^{(i)}\left(e^{-\left(\beta_0{}^{(i)} + \beta_1{}^{(i)} d^{(i)}\right)}\right)}{\left(1 + e^{-\left(\beta_0{}^{(i)} + \beta_1{}^{(i)} d^{(i)}\right)}\right)^2} = -\gamma^{(i)} F^{(i)}\left(1 - F^{(i)}\right)$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \beta_1^{(i)}} = \frac{-\gamma^{(i)} T_D^{(i)} \left(e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} T_D^{(i)} \right)} \right)}{\left(1+e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} T_D^{(i)} \right)} \right)^2} = -\gamma^{(i)} T_D^{(i)} F^{(i)} \left(1-F^{(i)} \right)$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \gamma^{(i)}} = \frac{1}{1+e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} T_D^{(i)} \right)}} = F^{(i)}$$

Two additional non linear models the Gompertz and Michaelis-Menten that will be used in simulations are described using (2.1).

Gompertz: $G(\boldsymbol{\theta}) = \gamma \mathrm{F}(d;\mathbf{B}) = \gamma e^{-e(-(\beta_0 + \beta_1 d))}$

Michaelis-Menten: $G(\boldsymbol{\theta}) = \alpha + \gamma \mathrm{F}(d;\mathbf{B}) = \alpha + \frac{\gamma d}{\phi + d}$

The estimate of the target dose T_D using (2.2) for the Gompertz and the Michaelis-Menten are:

Gompertz $T_D = \dfrac{-\log\left(\log\left(\gamma/\mu\right)\right)-\beta_0}{\beta_1}$

and

Michaelis-Menten $T_D = \dfrac{\phi(\mu-\alpha)}{(\gamma-\mu+\alpha)}$

The partial derivatives for the Gompertz and Michaelis-Menten models are also provided. The Gompertz partial derivatives from (2.3) are:

$$\frac{\partial T_D}{\partial \beta_0} = -\frac{1}{\beta_1} \tag{3.2}$$

$$\frac{\partial T_D}{\partial \beta_1} = \frac{1}{\beta_1^2}\left[\log\left[\log\left(\frac{\gamma}{\mu}\right)\right]+\beta_0\right] \tag{3.3}$$

$$\frac{\partial T_D}{\partial \gamma} = -\left(\frac{1}{\gamma\beta_1\left(\log\gamma/\mu\right)}\right) \tag{3.4}$$

and $\mathbf{H}$ is defined as $\mathbf{H} = \left[\dfrac{\partial T_D}{\partial \beta_0} \quad \dfrac{\partial T_D}{\partial \beta_1} \quad \dfrac{\partial T_D}{\partial \gamma}\right]$.

Then $\mathrm{Var}(\hat{T}_D) = \mathbf{H}\boldsymbol{\Sigma}\mathbf{H}'$ and $\boldsymbol{\Sigma}$ are derived as described previously and the partials derivatives for $\mathbf{G}(\boldsymbol{\theta})$ are

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \beta_0^{(i)}} = \gamma^{(i)} e^{-e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} d^{(i)}\right)}} e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} d^{(i)}\right)}$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \beta_1^{(i)}} = \gamma^{(i)} d^{(i)} e^{-e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} d^{(i)}\right)}} e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} d^{(i)}\right)}$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \gamma^{(i)}} = e^{-e^{-\left(\beta_0^{(i)} + \beta_1^{(i)} d^{(i)}\right)}}$$

The Michaelis-Menten partial derivatives from (2.3) are:

$$\frac{\partial T_D}{\partial \phi} = -\frac{\mu - \alpha}{\gamma - \mu + \alpha} \tag{3.2}$$

$$\frac{\partial T_D}{\partial \gamma} = \frac{-\phi(\mu-\alpha)}{(\gamma-\mu+\alpha)^2} \tag{3.3}$$

$$\frac{\partial T_D}{\partial \alpha} = \frac{-\phi\gamma}{(\gamma-\mu+\alpha)^2} \tag{3.4}$$

and $\mathbf{H}$ is defined as $\mathbf{H} = \left[\frac{\partial T_D}{\partial \phi} \quad \frac{\partial T_D}{\partial \gamma} \quad \frac{\partial T_D}{\partial \alpha} \right]$.

Again $\mathrm{Var}(\hat{T}_D) = \mathbf{H}\boldsymbol{\Sigma}\mathbf{H}'$ and $\boldsymbol{\Sigma}$ are derived as described previously and the partials derivatives for $\mathbf{G}(\boldsymbol{\theta})$ are

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \phi^{(i)}} = \frac{-\gamma^{(i)} d^{(i)}}{\left(\phi^{(i)} + d^{(i)} \right)^2}$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \gamma^{(i)}} = \frac{d^{(i)}}{\phi^{(i)} + d^{(i)}}$$

$$\frac{\partial \mathbf{G}^{(i)}}{\partial \alpha^{(i)}} = \frac{\gamma^{(i)} d^{(i)}}{\phi^{(i)} + d^{(i)}}$$

The numbers of patients assigned to active and placebo dose groups are varied across the runs of the simulations. The four different assignment schemas are:

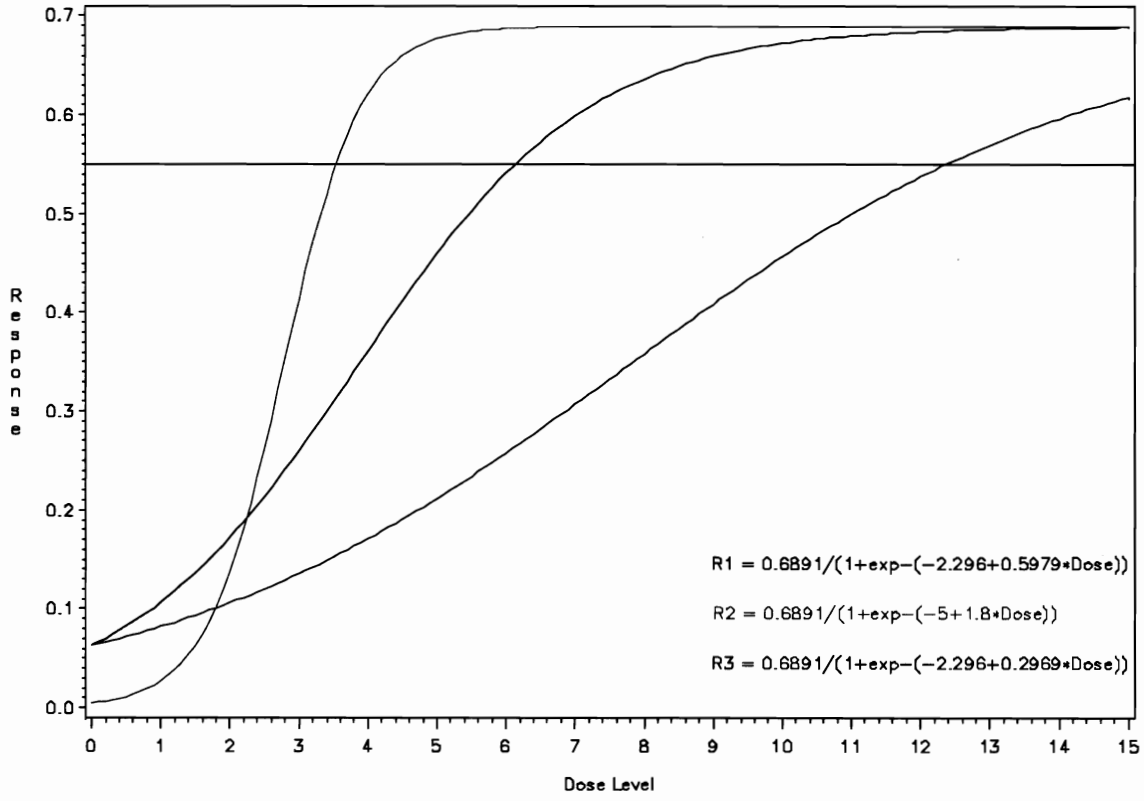
1) One subject on active treatment and one subject on placebo at each dose level (1-1, 1-1)
2) One active and one placebo subject at the initial three dose levels and then three active and one placebo subject at each additional dose level (1-1, 3-1)
3) Three active and one placebo subject at each dose level (3-1, 3-1)
4) Three active and one placebo at the initial three dose levels and then one active and one placebo subject at each additional dose level (3-1, 1-1)

Various shapes of the logistic model will be simulated. The shape of the logistic model is modified by choosing different slopes (β_1) and intercepts (β_0). The various parameters used are detailed below. In all three cases the values for τ and γ are 0.0461 and 0.6891, respectively, for simulation of data.

1) $\beta_0 = -2.296$ and $\beta_1 = 0.5979$, Base Model (SIM 1)
2) $\beta_0 = -5$ and $\beta_1 = 1.8$, Steep slope (SIM 2)
3) $\beta_0 = -2.296$ and $\beta_1 = 0.2969$, Shallow slope (SIM 3)

A graphical representation of the various parameter estimates is presented in Figure 3.1. These three curves will allow dose estimation for both steep $(\beta_1 = 1.8)$ and shallow $(\beta_1 = 0.2969)$ slopes, in comparison to the base model, which uses the example data set slope ($\beta_1 = 0.5979$) estimate.

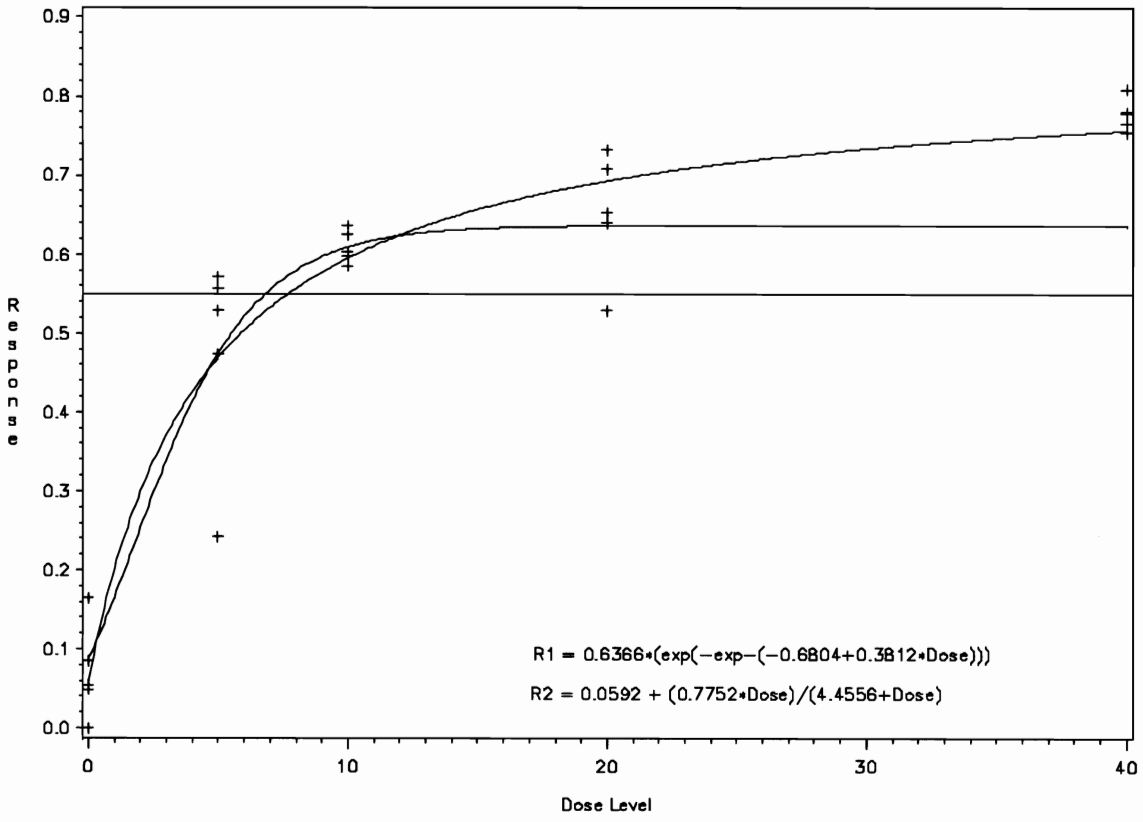
Figure 3.1: Non-Linear Logistic Using Various Estimates for β_0 and β_1, Base Model (R1), Steep Slope (R2) and Shallow Slope (R3)



Two alternative non-linear models, the Gompertz (SIM 4) and the Michaelis-Menten SIM 5) will also be evaluated. The parameter values for simulation for the Gompertz model are $\gamma = 0.6891$ and $\tau = 0.0461$, $\beta_0 = -2.296$ and $\beta_1 = 0.5979$. The parameter values for

simulation for the Michaelis-Menten are $\gamma = 0.7752$ and, $\tau = 0.0358$, $\alpha = 0.0592$, and $\phi = 4.4556$. The graphical displays of these two functions are presented in Figure 3.2. For the Gompertz and Michaelis-Menten, the simulations were run with one active and one placebo subject at the initial three dose levels and then three active and one placebo subject at each additional dose level (1-1, 3-1).

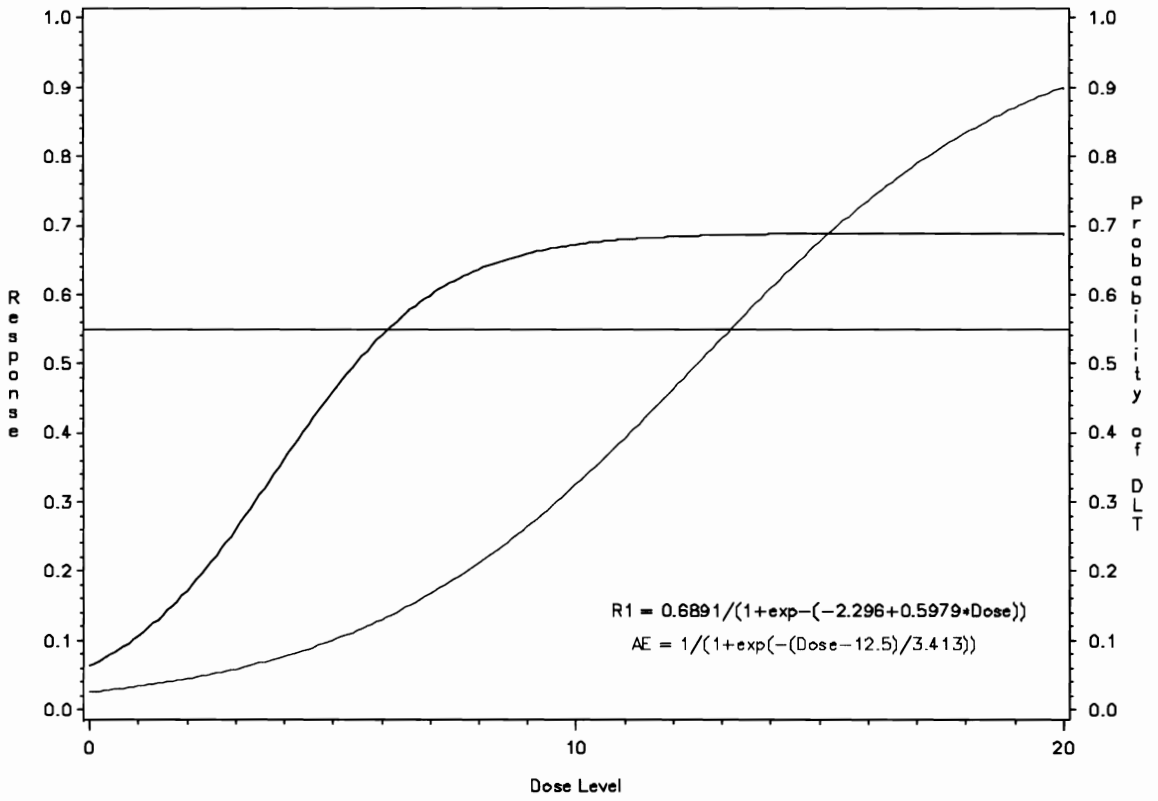
Figure 3.2: Gompertz (R1) and Michaelis-Menten (R2) Non-Linear Functions



The base nonlinear logistic model with a curve estimating the probability of an adverse event (SIM 6) is presented in Figure 3.3. This simulation was executed to evaluate the

ability of the DOSEFIND method to adjust to adverse effects and safety considerations. For this particular simulation, the (1-1, 3-1) sampling schema was chosen because all 1000 runs of the (1-1, 3-1) simulation successfully converged for the base model. Therefore, when applying the additional criteria that allow occurrences of adverse events the run failures were assumed to be due to the occurrence of an adverse event.

Figure 3.3: Non-Linear Logistic (R1) with Adverse Event (AE) Probability Curve



Finally, many early trials in man (FIM or early dose finding trials) use a fixed set of doses. Hence, simulations using a fixed set of doses 0.5, 1, 2, 4, 8 and 16 tablets (SIM 7) will be

presented. This set of dose levels was chosen because it represents six consecutive doublings of the initial dose. This is a common approach in early trials in humans for evaluation of MTD and dose response.

Multiple models from the class of $\mu = \alpha + \gamma F(\mathbf{D};\underline{\boldsymbol{\theta}})$ were chosen to show the utility of the DOSEFIND method. SIM 7 is used to evaluate asymptotic relative efficiency (ARE) which is the ratio of the $Var(\hat{T}_D)$ of the DOSEFIND method (σ^2_{Sim}) and the usual fixed dose approach ($\sigma^2_{FixDose}$). The ARE of the DOSFIND method is shown to be superior to the fixed dose approach. The squared bias and mean square error (MSE) for SIM 1 – SIM 3 is calculated to demonstrate the long term average error. Finally, a summary of the relative cost is examined. The cost is based on the number of subjects needed on average for SIM 1 – SIM 3 versus the fixed dose design.

3.2 Simulation Results of the DOSEFIND Approach to Finding a Target Dose

The expected value of the T_D was computed from (2.3), with a target threshold effect of 0.55, for SIM 1 – SIM 5 using the example clinical trial data to estimate the parameters for each respective simulation. The expected T_D for the target threshold effect of 0.55 is listed in Table 3.1. When the DOSEFIND method results in estimates close to the expected T_D, the DOSEFIND method will be evidence that the method can reproduce the dose response curve.

Table 3.1: Expected Values of T_D for the Target Threshold Effect

	Dose Levels				
Target Threshold Effect	SIM 1 Non-Linear Logistic	SIM 2 Larger β_1	SIM 3 Smaller β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten
0.55	6.14	3.54	12.36	6.33	7.69

The results of the base nonlinear logistic model (SIM 1), using the parameter estimates from the example data set, are presented in Table 3.2. For this case, the expected T_D result is 6.14, and the 95% confidence interval contains this result for all four sampling scenarios. Further, for sampling scenarios (1-1, 3-1) and (3-1, 3-1), the width of the 95% confidence interval is less than the bin size of one unit. The four sampling scenarios averaged between 6 and 9 dose levels and 18 to 26 subjects (see Table 3.8). Thus, under various sampling conditions the results of the base nonlinear logistic model (SIM 1) were consistently reproducible, and the sample sizes were smaller than the fixed dose design (n=36). Finally, the asymptotic relative efficiency to a fixed dose design is clearly superior in all four cases, ranging from 35%-50%.

Table 3.2: Results from SIM 1 (10 simulations of size n=100 each) for Four Sampling Scenarios

Desired Response: 0.55 and Desired Target Dose: 6.14				
Run*	Mean Parameter Estimates (Standard Error)			
	T_D	D_N	½-width 95% CI	ARE
1-1, 1-1	6.18 (0.060)	9.00 (0.306)	0.639 (0.017)	50%
3-1, 1-1	6.09 (0.047)	7.98 (0.2001	0.583 (0.004)	47%
1-1, 3-1	6.21 (0.035)	6.99 (0.108)	0.466 (0.017)	37%
3-1, 3-1	6.15 (0.036)	6.40 (0.082)	0.435 (0.015)	35%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_{0=}$ -2.296, $\beta_{1=}$ 0.5979 and $\tau = 0.0461$.
D_N is the average number of dose levels for each simulation scenario
Initial starting doses: 1.25, 2.5 and 5 tablets.
Asymptotic Relative Efficiency (ARE): $\sigma^2_{Sim}/\sigma^2_{FixDose}$.

* 1-1, 1-1: One subject on active drug and one subject on placebo at each dose level.
3-1,1-1: Three subjects on active drug and one on placebo at the first three dose levels, then one subject on active drug and one on placebo at each subsequent dose level.
1-1,3-1: One subject on active drug and one on placebo at the first three dose levels then three subjects on active drug and one on placebo at each subsequent dose level.
3-1, 3-1: Three subjects on active drug and one on placebo at the each dose level.

To evaluate the effect of a steep slope (SIM 2) values for β_0 and β_1 were set to –5 and 1.8, respectively, for data simulation. Under these conditions, the desired target dose was 3.54 tablets at a target threshold effect of 0.55. The 95% confidence intervals for SIM 2 contained the desired target dose (3.54 tablets) for all four sampling schemas (1-1, 1-1), (3-1, 1-1), (1-1, 3-1) and (3-1, 3-1). The average number of dose levels was 5 for each sampling schema and the sample size ranged from 10 to 20 patients (see Table 3.8). Again the results are consistently reproducible and considerably fewer subjects are needed than the fixed dose approach (n=36). The asymptotic relative efficiency with respect to the

fixed dose design was clearly superior (18%-35%). This result was not unexpected because the upper plateau of the sigmoid shape is reached between 4 and 5 tablets, with the steep slope. In contrast the fixed dose design dose levels of 8 and 16 tablets do not contribute to the evaluation of the dose response curve. The resultsof SIM 2 are presented in Table 3.3.

Table 3.3: Results from SIM 2 (10 simulations of size n=100 each) for Four Sampling Scenarios

Desired Response: 0.55 and Desired Target Dose: 3.54				
Run*	Mean Parameter Estimates (Standard Error)			
	T_D	D_N	½-width 95% CI	ARE
1-1, 1-1	3.72 (0.052)	5.19 (0.031)	0.192 (0.0061)	35%
3-1, 1-1	3.67 (0.023)	5.02 (0.014)	0.150 (0.0041)	29%
1-1, 3-1	3.69 (0.038)	5.09 (0.040)	0.126 (0.0056)	24%
3-1, 3-1	3.71 (0.037)	5.01 (0.008)	0.089 (0.0031)	18%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_0 = -5$, $\beta_1 = 1.8$ and $\tau = 0.0461$.
D_N is the average number of dose levels for each simulation scenario
Asymptotic Relative Efficiency (ARE): $\sigma^2_{Lgr\,\beta 1}/\sigma^2_{FixDose}$.

* 1-1, 1-1: One subject on active drug and one subject on placebo at each dose level.
3-1,1-1: Three subjects on active drug and one on placebo at the first three dose levels, then one subject on active drug and one on placebo at each subsequent dose level.
1-1,3-1: One subject on active drug and one on placebo at the first three dose levels, then three subjects on active drug and one on placebo at each subsequent dose level.
3-1, 3-1: Three subjects on active drug and one on placebo at the each dose level.

To evaluate the effect of a shallow slope in SIM 3, values for β_0 and β_1 were set to -2.296 and 0.2969, respectively, for data simulation. For SIM 3 the desired target dose was 12.36 tablets at a target threshold effect of 0.55. Under this scenario, the desired target dose

(12.36 tablets) for all four sampling schemas (1-1, 1-1), (3-1, 1-1), (1-1, 3-1) and (3-1, 3-1) was within the 95% confidence interval. The sample sizes ranged from 34 to 46 patients (see Table 3.8), which is greater than the fixed dose sample size of 36. Additionally, for simulations (1-1, 1-1) and (3-1, 1-1) a failure rate of 24% was observed (see Table 3.7). While disappointing, this result is not surprising considering that maximum variability occurs near the mid-point, and sparseness of the data in this area where the largest variability is expected. This is further demonstrated in the SIM 3 sample schemas (1-1, 3-1) and (3-1, 3-1) in which failure rates of 1.5% and 1.4%, respectively (see Table 3.7) were observed. This suggests that the DOSEFIND method may not be the best choice if a very shallow slope is anticipated, despite the fact that the relative efficiency with respect to the fixed dose design is better. Hence, under these conditions a fixed dose approach may be more appropriate. Table 3.4 displays the results from SIM 3.

Table 3.4: Results from SIM 3 (10 simulations of size n=100 each) for Four Different Sampling Scenarios

Desired Response: 0.55 and Desired Target Dose: 12.36				
Run*	Mean Parameter Estimates (Standard Error)			
	T_D	D_N	½-width 95% CI	ARE
1-1,1-1	12.34 (0.088)	16.87 (0.456)	0.8467 (0.013)	25%
3-1,1-1	12.23 (0.100)	16.09 (0.448)	0.8326 (0.007)	25%
1-1,3-1	12.38 (0.064)	11.90 (0.403)	0.7284 (0.019)	22%
3-1,3-1	12.31 (0.051)	11.51 (0.423)	0.7038 (0.017)	21%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_0 = -5$, $\beta_1 = 1.8$ and $\tau = 0.0461$.
D_N is the average number of dose levels for each simulation scenario
Asymptotic Relative Efficiency (ARE): $\sigma^2_{Lgr\,\beta 1}/\sigma^2_{FixDose}$.

* 1-1, 1-1: One subject on active drug and one subject on placebo at each dose level.
3-1,1-1: Three subjects on active drug and one on placebo at the first three dose levels, then one subject on active drug and one on placebo at each subsequent dose level.
1-1,3-1: One subject on active drug and one on placebo at the first three dose levels, then three subjects on active drug and one on placebo at each subsequent dose level.
3-1, 3-1: Three subjects on active drug and one on placebo at the each dose level.

Three additional simulations using two alternative nonlinear sigmoidal models (Gompertz and Michaelis-Menten) and the non-linear logistic with the safety adjustment as described previously were run for comparison.

For a target threshold effect of 0.55, the target dose levels for the nonlinear logistic, the Gompertz and the Michaelis-Menten were 6.14, 6.83 and 7.69 tablets, respectively. All three simulations were run with the (1-1, 3-1) sampling schema, only. The 95% confidence intervals for each case included the target dose level for each respective model. The Gompertz performed similarly to the Michaelis-Menten with a relative efficiency of

91%. The nonlinear logistic with safety adjustment applied produced similar results as the base nonlinear logistic model. However, for the given AE probability curve, 19.8% of the runs would be halted for occurrence of a DLT. Table 3.5 displays the results of SIM 4, SIM 5 and SIM 6.

Table 3.5: Results from simulation (10 simulations of size n=100 each) for the Gompertz (SIM 4), the Michaelis-Menten Nonlinear (SIM 5) and the Non-Linear Logistic with Safety Adjustment (SIM 6) Models

Desired Response: 0.55			
Run*	Mean Parameter Estimates (Standard Error)		
	T_D	½-width 95% CI	$Var\left(\hat{T}_D\right)$
Gompertz	6.83 (0.031)	0.6777 (0.0189)	0.3304 (0.009)
Michaelis-Menten	7.44 (0.058)	0.7378 (0.020)	0.3618 (0.010)
Non-linear Logistic + Safety	6.22 (0.055)	0.4731 (0.020)	0.2233 (0.010)

Values of Parameters for simulation of data:
Gompertz: $\gamma = 0.6891$ and $\tau = 0.0461$, $\beta_0 = -0.6804$ and $\beta_1 = 0.3812$
Michaelis-Menten $\gamma = 0.7752$ and $\tau = 0.0358$, $\alpha = 0.0592$, and $\phi = 4.4556$

* 1-1,3-1: One subject on active drug and one on placebo at the first three dose levels, then three subjects on active drug and one on placebo at each subsequent dose level.

In order to evaluate the efficiency of the DOSEFIND method for the three non-linear logistic simulations (SIM 1 – SIM 3), a simulation using a fixed set of dose levels (SIM 7) was performed. The fixed dose design was a natural choice as many clinical and non-clinical trials are based on this sampling scheme. The fixed dose design was run for

SIM1, SIM2 and SIM 3. The expected target dose for the three non-linear logistic simulations was 6.14, 3.54 and 12.36, respectively. The results of SIM 7 are presented in Table 3.6.

Table 3.6: Results from SIM 7 (10 simulations of size n=100 each) for Fixed Dose Levels

Desired Response: 0.55			
Run	Mean Parameter Estimates (Standard Error)		
	T_D	½-width 95% CI	$Var\left(\hat{T}_D\right)$
Logistic	6.21 (0.032)	1.212 (0.011)	0.596 (0.005)
Steep β_1	3.62 (0.010)	0.481 (0.004)	0.236 (0.002)
Shallow β_1	12.62 (0.059)	3.335 (0.937)	1.639 (0.460)

Values of Parameters for simulation of data:
Constant across all simulations $\gamma = 0.6891$ and $\tau = 0.0461$.
Non-Linear Logistic: $\beta_{0=}$ -2.296 and $\beta_{1=}$ 0.5979
Steeper β_1: $\beta_{0=}$ -5 and $\beta_{1=}$ 1.8
Shallow β_1: $\beta_{0=}$ -2.296 and β_1 =0.2969
Dose levels 0.5, 1, 2, 4, 8 and 16 tablets

For each of the six simulations (SIM 1- SIM 6), the observed rates of stopping before the convergence of the confidence interval, the sample sizes and the number of dose levels for each respective run are presented in Tables 3.7 and 3.8 below. Both SIM 1 and SIM 2 provided good response with respect to the target dose and few or no observed failures. As previously discussed, SIM 3 did not perform well for runs (1-1, 1-1) and (3-1, 1-1), but failures dropped below 2% for runs (1-1, 3-1) and (3-1, 3-1). SIM 4 (Gompertz) and SIM 5 (Michaelis-Menten) had observed failure rates of 4.5% and 3.3%, respectively. Finally, SIM 6, which uses the same parameter estimates as SIM 1, with the addition of safety considerations, had 19.8% of the runs stop due to adverse events.

Table 3.7: Observed Simulations that Stopped Before Convergence of the Confidence Interval

Stopping Rates for Each Simulation						
Run	SIM 1 Non-Linear Logistic	SIM 2 Larger β_1	SIM 3 Smaller β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten	SIM 6 Non-Linear Logistic + Safety
1-1, 1-1	1.6%	0%	24%	-	-	-
3-1, 1-1	0.4%	0%	24%	-	-	-
1-1, 3-1	0%	0%	1.5%	4.5%	3.3%	19.8%*
3-1, 3-1	0%	0%	1.4%	-	-	-

* Percentage of runs that stopped due to an adverse event.

For reference, recall that the fixed dose design used 6 dose levels and 36 patients. SIM 1 and SIM 2 had sample sizes less than the fixed dose design at the various sampling schemas evaluated. In general, the (1-1, 3-1) run provides the optimal choice for SIM 1 and SIM 2 in terms of the failure rate, predicted sample size and number of dose levels. SIM 3 requires a larger sample size than the fixed dose except for the (1-1, 1-1) run. However, run (1-1,1-1) for SIM 3 has a 24% failure rate which is not desirable, and thus, it is recommend that the fixed dose design be applied when SIM 3 conditions are anticipated. The Gompertz (SIM 4) required the same sample size as the fixed dose design, while the Michaelis-Menten (SIM 5) requires a larger sample size compared with the fixed dose design.

Table 3.8: Estimation of Number of Dose Levels and Associated Sample Size for each Simulation

Sample Size and (Relative* Cost) for Each Simulation and Run						
Run	SIM 1 Non-Linear Logistic	SIM 2 Larger β_1	SIM 3 Smaller β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten	SIM 6 Non-linear Logistic + Safety
1-1, 1-1	18.0 (50.0%)	10.4 (28.9%)	33.7 (93.6%)	-	-	-
3-1, 1-1	16.0 (44.4%)	16.0 (44.4%)	38.2 (106%)	-	-	-
1-1, 3-1	20.0 (55.6%)	14.4 (40.0%)	41.6 (116%)	36.0 (100%)	41.2 (114%)	20.8 (57.8%)
3-1, 3-1	25.6 (71.1%)	20.0 (55.6%)	46.1 (128%)	-	-	-

* - Relative to the fixed dose design

An examination of the distribution of the target doses for each simulation set indicates that the DOSFIND method captures the expected target dose. The mean estimated T_D, the associated 95% confidence interval and the expected T_D for the distribution of each simulation are displayed in Table 3.9. These results show that the mean T_D of the distribution of each simulation was contained within the distribution 95% confidence interval. Across a range of different curves (SIM 1-SIM 3 and SIM 6) and different nonlinear models (SIM 4-SIM 5), DOSEFIND was consistent in reproducing the expected T_D. However, the confidence interval coverage with the DOSEFIND is not nominal. That is, on the average the T_D will not be contained in the confidence interval 95% of the time. This is because the DOSEFIND method uses the width of the confidence interval as the key stopping rule and the 95% confidence intervals computed are uniformly small with

little variability in the range of the confidence intervals, by design. So, even though we are using the usual approach to calculate the 95% confidence interval, it is a stopping rule criterion. Thus, it should not be used in an interpretive sense to examine coverage probability.

Table 3.9: Target Dose 95% confidence intervals of the distribution for each simulation

Target Dose 95% Confidence Intervals						
Run	SIM 1 Non-Linear Logistic $T_D = 6.14$	SIM 2 Larger β_1 $T_D = 3.54$	SIM 3 Smaller β_1 $T_D = 12.36$	SIM 4 Gompertz $T_D = 6.83$	SIM 5 Michaelis-Menten $T_D = 7.69$	SIM 6 Non-linear Logistic + Safety $T_D = 6.14$
1-1,1-1	6.17 (4.71, 7.68)	3.69 (3.06, 4.68)	12.34 (9.45, 14.01)	-	-	-
1-1,3-1	6.20 (5.03, 7.60)	3.66 (3.18, 4.48)	12.40 (10.40, 14.12)	6.82 (4.86, 8.77)	7.42 (5.32, 9.07)	6.19 (5.07, 7.69)
3-1,1-1	6.09 (5.50, 7.23)	3.66 (3.20, 4.32)	12.24 (9.59, 13.94)	-	-	-
3-1,3-1	6.15 (5.17, 7.33)	3.63 (3.23,4.14)	12.32 (10.32, 14.12)	-	-	-

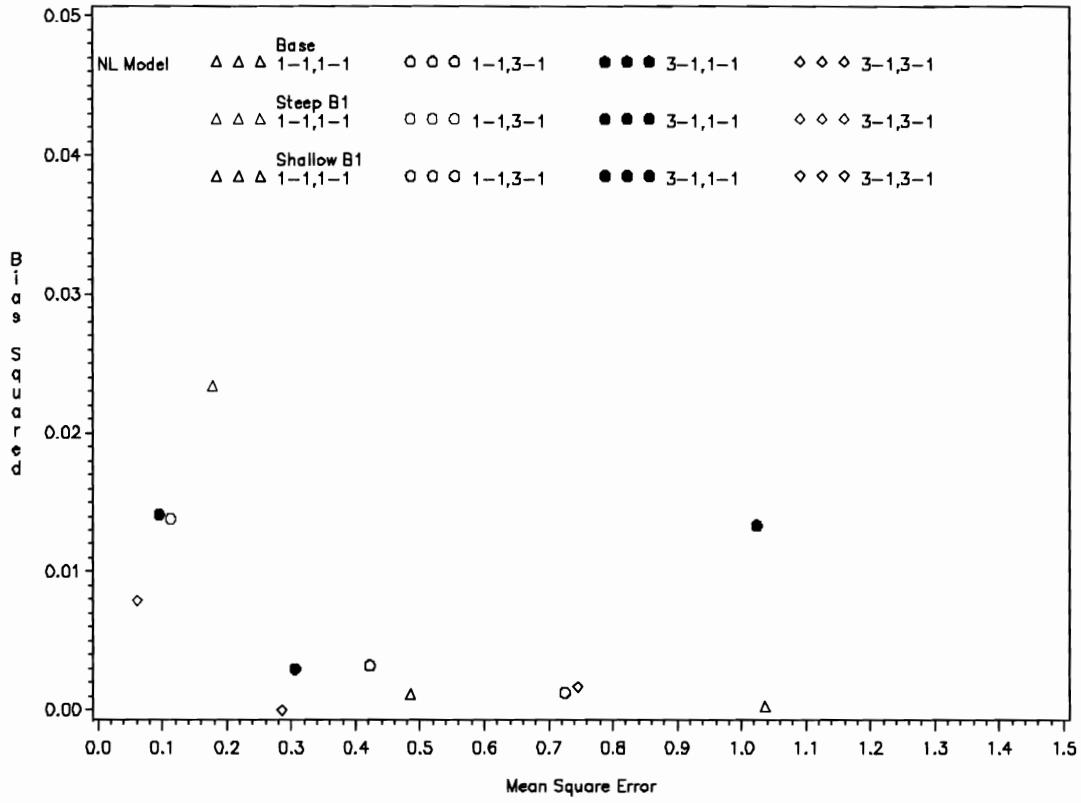
An examination of the results of the confidence intervals based on the actual dose (rather than the bin dose) and the delta method indicates that the 95% confidence interval contains the expected T_D, for each simulation. The distributions for each simulation can be is presented in Appendix B. The results of the confidence intervals from the delta method computations are presented in Table 3.10.

Table 3.10: Actual Dose 95% confidence intervals of simulation results (delta method)

Target Dose 95% Confidence Intervals						
Run	SIM 1 Non-Linear Logistic $T_D = 6.14$	SIM 2 Larger β_1 $T_D = 3.54$	SIM 3 Smaller β_1 $T_D = 12.36$	SIM 4 Gompertz $T_D = 6.83$	SIM 5 Michaelis-Menten $T_D = 7.69$	SIM 6 Non-linear Logistic + Safety $T_D = 6.14$
1-1,1-1	6.17 (5.53, 6.81)	3.69 (3.50, 3.88)	12.34 (11.49, 13.19)	-	-	-
1-1,3-1	6.20 (5.73, 6.67)	3.66 (3.53, 3.79)	12.40 (11.67, 13.13)	6.82 (6.14, 7.50)	7.42 (6.68, 8.16)	6.19 (5.71, 6.66)
3-1,1-1	6.09 (5.51, 6.67)	3.66 (3.51, 3.81)	12.24 (11.41, 13.07)	-	-	-
3-1,3-1	6.15 (5.71, 6.59)	3.63 (3.54, 3.72)	12.32 (11.62, 13.02)	-	-	-

A graphical display of the comparison of bias-squared (i.e., $\left(\hat{T}_D - E\left(T_D\right)\right)^2$) to the MSE (i.e., $Var\left(\hat{T}_D\right) + bias^2$) is presented in Figure 3.4. As shown the bias-squared is quite small relative to the MSE for all simulations. The base nonlinear logistic has the smallest amount of bias and the worst case is from SIM 2 run (1-1, 1-1) with the bias being 13% of the MSE. This is another indicator of reproducibility of the method in the long-run average error of the T_D being quite small.

Figure 3.4: Comparison of Bias-Squared versus Mean Square Error, for Nonlinear Logistic Models



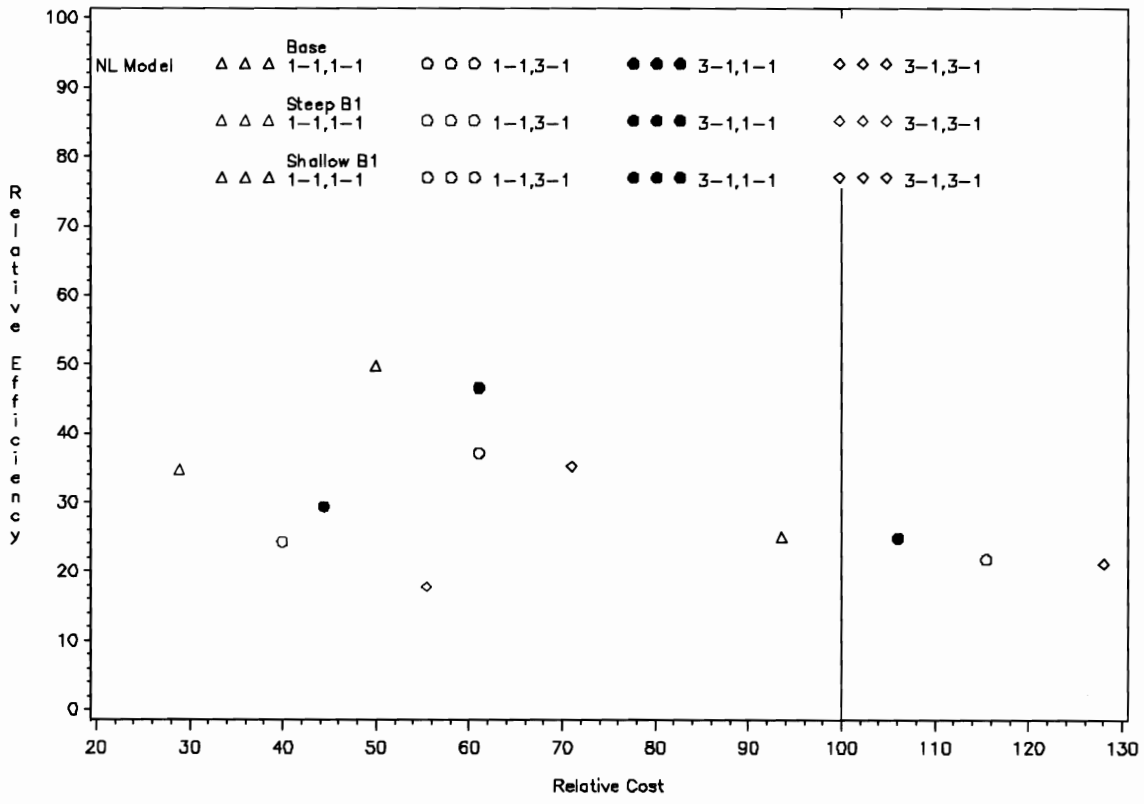
An important consideration in clinical trial research is both the efficiency and cost of the trials. For a new approach, it is necessary to demonstrate that the method will either be cost effective, more efficient than alternative approaches or lead to a reduction in the time to get an NCE to the market place. The standard approach in dose response trials is to predetermine a fixed set of doses and then perform the clinical trial. Based on the simulations presented here, the standard approach to clinical trials is inferior to the DOSEFIND method in both cost (measured by the number of patients required) and the efficiency (measured by the variance of the target dose). The relative efficiency is the ratio

of the variance of the T_D from the respective nonlinear logistic model simulation to the variance of the T_D from the fixed dose model simulation. Results of this comparison are presented in Figure 3.5. Values less than 100 are indicative that the DOSEFIND approach is superior to the fixed dose approach. In all cases the DOSEFIND had better efficiency than the fixed dose clinical trial. The models with the best efficiency results were those that had three active patients in the dose levels following the initial three dose levels. This result is intuitively reasonable as these models would have more data in the area of the curve where the dose of interest would be expected. In terms of relative cost, the DOSEFIND was superior with the exception of runs (1-1, 3-1), (3-1, 1-1) and (3-1, 3-1) from the nonlinear logistic with a shallow slope (β_1).

In conclusion, the DOSEFIND method is shown to be reproducible with good distributional coverage. Relative cost is the ratio of the given sample size to the fixed dose sample size of 36. Therefore, SIM3 and SIM5 on average require more subjects than the fixed dose design and have a relative cost greater than 100%. More importantly however, the DOSEFIND method has better relative efficiency and is more cost effective than fixed dose approaches under most conditions. While other issues in addition to sample size are used to determine the cost of a clinical trial, most of these costs are fixed and would be incurred regardless of the approach taken. As shown in Figure 3.5 both SIM 1 and SIM 2 show impressive improvements in both efficiency and cost relative to the fixed dose design. Additionally, the ability to limit the exposure of an NCE to the patient population

during early stages of clinical trials, while simultaneously gaining gaining valuable relevant data regarding dose response can not be overstated.

Figure 3.5: Comparison of Relative Efficiency versus Relative Cost, for Base (SIM 1), Steep (SIM 2) and Shallow (SIM 3) Nonlinear Logistic Models



The DOSEFIND method may take more time to complete than conventional trials when specialized testing for PD markers or other measurements is required. However, the DOSEFIND methods ability to obtain an accurate and effective estimate of the target dose (see Table 3.10) and determination of an optimal dose response more than compensates for this. Finally, by obtaining a good estimate of the dose response, the chances for

successful choice of the proper dose for pivotal Phase III clinical trials is increased. Since the costs of Phase III clinical trials are substantial, the choice of the dose levels for these trials is critical.

In the next chapter we will provide a brief synopsis of the original work contained in this dissertation and present considerations for future work on this topic.

CHAPTER 4

4.0 Introduction

The proposed method, DOSEFIND, is an adaptive design that uses accumulated data to define the dose response model until a valid target is obtained. The DOSEFIND method has been shown to have advantages over the fixed dose design with a sample size of 36. The CRM (O'Quigley, 1990) , a Bayesian method, attempts to describe a dose response curve relative to the MTD but lacks efficacy information. Piantadosi et al. (1998) and Potter (2002) make important improvements to the CRM, but also lack efficacy information. While it is important and useful to understand the MTD, the clinical picture is incomplete without corresponding efficacy information. Other adaptive dose response designs are less than optimal in that they use a fixed set of doses and thus the design may fail to adequately sample within the linear region of the sigmoidal dose response. Insufficient exploration of the dose-response is often a key shortcoming of clinical drug development. Initial proof-of-concept (PoC) studies often rely on testing just one dose level (e.g., the maximum tolerated dose) largely because there is not much additional information on which to base the decision. With these types of PoC studies it is typically assumed that "more is better" and the hope is that the "right" dose was selected. Hence,

consideration of adaptive dose-response designs in exploratory development may lead to better choices of dose selection for PoC studies (Gaydos et al., 2006).

In Section 4.1, a summary and concluding remarks are presented for the work presented in this dissertation. In Section 4.2, future work regarding the DOSEIND methodology will be presented.

4.1 Discussion and Concluding Remarks

The DOSEFIND method generalizes and extends Piantadosi et al. (1998) and Potter (2002) by doing the following:

1. Addition of "dosing bins" to accommodate differences in drug potency.
2. Application of general non-linear 3 and 4 parameter models.
3. Simulations on non-linear logistic, Gompertz and Michaelis-Menten models.
4. Provides a general structure for variance which allows for precision in estimation of the target dose.
5. Proposes the use in early trials in humans to assess efficacy as well as toxicity.

The DOSEFIND method has demonstrated several positive qualities.

1. Using an extensive simulation study, the DOSEFIND has been shown through simulations to be flexible in regards to the number of patients or subjects assigned to active treatment. The method demonstrated an ability to estimate credible

average target dose levels and confidence intervals that contained the expected target dose.

2. The sigmoidal models used in the simulations are more representative of the dose response behavior in humans, than fixed dose approaches. For each different sigmoid model the DOSEFIND method was able to reproduce the expected T_D and;
3. DOSEFIND was also efficient, in that all of the sampling approaches were, on average, able to produce the desired target dose.
4. DOSEFIND was, on average, consistently more efficient relative to a fixed dose design using 6 dose levels. This was true for all the non-linear logistic designs and sampling strategies. That is, the $Var(\hat{T}_D)$ was higher for the fixed dose design in all cases.
5. Exposure to ineffective dose levels was minimized and more dose levels that produced a desired response were maximized.
6. In general, the number of subjects used in the DOSEFIND was consistently less than the fixed dose design, the exception being a nonlinear logistic with a shallow slope and the Michaelis-Menten models.
7. DOSEFIND provides an inproved understanding of dose response over the fixed dose design or a design that looks only at safety effects. This will likely result in better choices for the dose levels going forward into PoC trials and subsequently Phase III pivotal trials.
8. DOSEFIND allows the investigator to start looking at efficacy potential earlier than is typically the case in current design methodology.

9. The time spent on the DOSEFIND approach may be longer than the standard early dose response trials. However, the potential gain in a look at early efficacy and an ability to understand the full dose response curve could provide for substantial savings in later phase clinical trials.

An important consideration for the DOSEFIND method is the establishment of a meaningful dose response. Our objective is to estimate a dose for evaluation of PoC in later trials, rather than an α spending function or an hypothesis testing approach, that is, $H_0 : \mu = \mu_0$.

4.2 Future Work

The DOSEFIND method is just the beginning of the exploration of adaptive dose response trial design. There are several important follow-on projects that deserve consideration.

1. The DOSEFIND method currently allows only a single marker to evaluate dose response. A modification of the DOSEFIND method allowing the use of multiple markers would essentially allow linking one or more PD markers so that the interrelationship of the PD markers on the T_D could be evaluated. Therefore, instead of observing a single response, multiple responses on each subject could be observed, and this could be multivariate or composite in nature. The generalized method would then reflect multiple body processes. For example, one approach to

lowering glucose is to cause glucagon-like–peptide 1 (GLP-1) levels to increase by inhibiting dipeptidylpeptidase IV (DPP-4) levels. So, in addition to inhibiting DPP-4 one must also consider the effect of sustained increase in GLP-1 levels, which will lower blood glucose levels. Then reduction in blood glucose levels will result in the desired effect of sustained reduction of HbA1c, which are glycosylated hemoglobin levels.

2. The current DOSEFIND method does not include covariates. Consideration of covariates could provide additional explanation of the dose response curve and the variance estimate of the T_D, which could lead to improvements in the estimation of the confidence interval.
3. The DOSEFIND method does not assume any prior knowledge of the NOEL or NOAEL. The application of threshold models to the DOSEFIND method would provide for a maximum no effect level. An example for an exponential threshold model is of the form $\mu = \alpha + \gamma e^{\beta(x-\delta)I(x>\delta)}$. This particular approach assumes some understanding of the dose such that some amount greater than some δ is required to see any effect.
4. The DOSEFIND method applies a quasi likelihood framework allowing the $Var(Y)$ to be of the form of $\tau V(\mu)$. Since the PD marker scale was on a [0, 1] scale and the maximum variation is expected at 0.5 then the choice of $\mu(1-\mu)$ was clear for our case. However, if we allow the range of PD marker to be extended beyond the [0, 1] scale for expression or suppression of the marker of interest, then

the parameters α and γ are not bounded by [0, 1]. Therefore, consideration of different variance forms for the quasi likelihood may be more appropriate. As data are collected reevaluation of the variance form could be conducted to determine if an improved form exists for the quasi likelihood variance.

5. The DOSEFIND method only considers response in terms of a dose. Applications using a marker versus viral or bacterial load, or some other measure rather than a dose could be evaluated. For example, the level of the marker needed to generate and sustain a reduction in the viral or bacterial load could be considered. This is a simple extension of the method that would require substitution of the marker for dose level and rescaling the change in viral or bacterial load so that its described as suppression on a [0, 1] scale. The choice of the quasi likelihood variance also must be evaluated.
6. Currently the DOSEFIND method only measures the response of one PD marker against dose. A modification to the method would be to combine efficacy, PD and safety together. This is essentially a variation of (1) where clinical outcomes and safety effects are substituted or added to the evaluation of one or more PD markers. Again the idea is to combine the various measures through a link or composite score to be able to evaluate an overall effect on patient outcome.
7. Repeated measures extension with collection of multiple data points on each subject could be considered. This approach would necessitate repeat dosing be performed on each subject. An evaluation of both safety and the ability to sustain

a target threshold could be considered under this proposition. This would lead to n independent T_D's, which could then be summarized with summary statistics.

8. Evaluation of sub populations (e.g., age, sex and race) is a logical extension to the DOSEFIND method in which individualized dose response curves are considered. That is, sub populations may behave differently and require varied dosing schemas. This could be accomplished through stratification. However, consider applying a function such that all the subpopulations of interest are all estimated at the same time. This would allow simultaneous estimation of dose response curves for each subpopulation.
9. Consider a study design that is based on minimum variance of T_D, but not at T_D necessarily. Employ an optimum criterion like minimum variance. Collect initial dose levels and evaluate the dose response curve. Based on the evaluation, determine where to put the next dose or doses, to minimize the variance and optimize the slope, which would provide a T_D. Note, there are potential safety issues because of the need to put doses much higher than the TD. Use a search algorithm, such as, Nelder-Mede to evaluate the minimum variance as a function of where the next dose or doses are located and how many subjects at each dose. This could be considered in conjunction with work by Shih, et al. 2003 in examination of dosing strategies that have multiple compounds being given at the same time.
10. An interesting extension to the DOSEFIND method would be to find the minimum variance associated with the testing of complex non linear hypotheses. Suppose there is something besides target dose, for example ED50 and ED90 and it is

desirable to minimize both. Separate subjects into subpopulations and determine if the dose response curves are different between the populations.

Literature Cited

Literature Cited

Banerjee A, Tsiatis A. Adaptive two-stage designs in phase II clinical trials. Statistics in Medicine (2006) 25:3382-3395

Bauer P., Köhne K. Evaluation of Experiments with Adaptive Interim Analyses. Biometrics (1994) 50:1029-1041

Bauer P, Röhmel J. An Adaptive Method for Establishing a Dose-Response Relationship Statistics in Medicine (1995) 14: 1595-1607

Bickel P., Doksum K. Mathematical Statistics. Basic Ideas and Selected Topics Prentice Hall Vol.1 2nd Edition, 2001:12-13.

Bischoff W, Miller F. Adaptive two-stage test procedures to find the best treatment in clinical trials. Biometrika, 2005; 92:197-212.

Conaway, M. Dunbar, S., Peddada S. Designs for Single- or Multiple-Agent Phase I Trials. Biometrics (2004) 60: 661-669

Chang M., Chow S.C. A Hybrid Bayesian Adaptive Design for Dose Response Trials. Journal of Biopharmaceutical Statistics (2005) 15: 677-691

Cui L., Hung J., Wang, S. Modification of Sample Sixe in Group Sequential Clinical Trials. Biometrics (1999) 55:853-857

Dragalin V. Adaptive Designs: Terminology and Classification. Drug Information Journal, Vol. 40, pp. 425–435, 2006

Durham SD, Flournoy N. Random walks for quantile estimation. Gupta SS, Berger JO, ed. Statistical Decision Theory and Related Topics New York: Springer; 1994:467–476.

Durham SD, Flournoy N., Rosenberger W A Random Walk Rule for Phase I Clinical Trials. Biometrics (1997) 53:745-760

European Medicines Agency (EMEA). Reflection Paper on Methodological Issues in Confirmatory Clinical T4rials with Flexible Design and Analysis Plan March 2006.

Emerson S. Issues in the use of adaptive clinical trial designs. Statistics in Medicine (2006) 25: 3270-3296

Faries D. Practical Modifications of the Continual Reassessment Method for Phase I Cancer Clinical Trials. Journal of Biopharmaceutical Stat. (1994) 4 147–164.

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005

Ford I., Silvey S.D A Sequentially Constructed Design for Estimating A Nonlinear Parametric Function. Biometrika (1980), 67, 2, pp. 381-8

Gallo P. Operational challenges in adaptive design implementation. Pharmaceutical Statistics, 2006: 5: 119-124

Gallo P., Chuang-Stein C, Dragalin V., Gaydos B., Krams M., Pinheiro J. Adaptive Designs in Clinical Drug Development – An Executive Summary of the PhRMA Working Group. Journal of Biopharmaceutical Statistics (2006) 16 (3), 275-283

Gaydos B, Krams M., Perevezskaya I., Bretz F., Liu Q., Gallo P., Berry D., Chuang-Stein C., Pinheiro J., Bedding A. Adaptive Dose Response Studies. Drug Information Journal, Vol. 40, pp. 451–461, 2006

Golub H., The need for more efficient trial designs. Statistics in Medicine (2006) 25: 3231-3235

Goodman S.N., Zahurak M.L., Piantadosi S. Some Practical Improvements in the Continual Reassessment Method for Phase I Studies. Statistics in Medicine (1995) 14: 1149-1161

Graybill F., Mood A., Boes D. Introduction to the Theory of Statistics, 3rd Edition McGraw-Hill Inc. 1974.

Hartung J., Knapp G. Repeated Confidence Intervals in Self-Designing Clinical Trials and Switching between Noninferiority and Superiority. Biometrical Journal 48 (2006) 4, 697–709

Hung H., Wang S., O'Neill R. Methodological issues with adaptation of clinical trial design. Pharmaceutical Statistics (2006) 5: 99-107

Hutmacher M., Mukherjee D., Kowalski K., Jordan D. Collapsing Mechanistic Models: An Application to Dose Selection for Proof of Concept of a Selective Irreversible Antagonist. Journal of Pharmaockinetics and Pharmacodynamics (2005)

Jennison C., Turnbull B.W. Efficient group sequential designs when there are several effect sizes under consideration. Statistics in Medicine (2006) 25:917-932

König F., Bauer P, Brannath W. An Adaptive Hierarchical Test Procedure for Selecting Safeand Efficient Treatments Biometrics (2006) 48: 663-678

Korn E.L., Midthune D., Chen T.T., Rubinstein L.V., Christian M.C., Simon R.M. A Comparison of Two Phase I Designs. Statistics in Medicine (1994) 13: 1799–1806

Lehmacher W., Wassmer, G. Adaptive Sample Size Calculations in Group Sequential Designs. Biometrics (1999) 55: 1268-1290

Liu Q., Chui G. On Sample Size and Inference for Two-Stage Adaptive Designs Biometrics (2001) 57: 172-177

Maca J, Bhattacharya S., Dragalin V., Gallo P., Krams M. Adaptive Seamless Phase II/III Designs Background, Operational Aspects and Examples. Drug Information Journal, Vol. 40: 463-473, 2006.

Mehta C., and Patel N. Adaptive, group sequential and decision theoretic approaches to sample size estimation. Statistics in Medicine (2006) 25: 3250-3269

Mehrotra D., Fan X. Adaptive vs. Group Self-designing Trials. Biometrical Journal 48 (2006) 4, 710-712.

Morita S., Sakamoto J. Application of an adaptive design to a randomized phase II selection trial in gastric cancer: a report on the study design. Pharmaceutical Statistics (2006) 5: 109-118

Müller H, Schäfer, H. Adaptive Group Sequential Designs for Clinical Trials: Combining the Advantages of Adaptive and of Classical Group Sequential Approaches. Biometrics (2001) 57: 886-891

O'Quigley J., Pepe M., Fisher L. Continual reassessment Method: A Practical Design for Phase I Clinical Trials in Cancer. Biometrics (1990) 46: 33–48

O'Quigley J., Shen L.Z. Continual Reassessment Method: a Likelihood Approach. Biometrics (1996) 52: 673–684

O'Quigley J., Reiner E. A Stopping Rule for the Continual Reassessment Method. Biometrika Vol. 85, No. 3 (Sep., 1998), 741-748

Piantadosi S., Fisher J., Grossman S. Practical implementation of a modifed continual reassessment method for dose-finding trials. Cancer Chemother Pharmacol (1998) 41: 429-436

Potter D. Adaptive dose finding for phase I clinical trials of drugs used for chemotherapy of cancer. Statist. Med. 2002; 21:1805–1823

Proschan M, Hunsberger S. Designed Extension of Studies Based on Conditional Power. Biometrics (1995) 51: 1315-1324

Raymond R., Balch A., Shen F. Model Based Adaptive Dose Ranging Designs. BASS XII, 2006.

Reiner E, Paoletti X, O'Quigley J. Operating characteristics of the standard phase I clinical trial design. Comp Stat Data Anal. 1999; 30:303–315.

Ryan C., Vogelzang N., Vokes E., Kindler H., Undevia S., Humerickhouse R., Andre´ A, Wang Q. , Carr R., Ratain, R. Dose-Ranging Study of the Safety and Pharmacokinetics of Atrasentan in Patients with Refractory Malignancies. Clinical Cancer Research Vol. 10, 4406–4411, July 1, 2004.

Seber G., Wild C. Nonlinear Regression. John Wiley & Sons 1989:42-44.

Schroeder, G. Phase 1 Oncology Clinical Trials for Related Subpopulations: The Power Walk Design. Drug Information Journal Jul-Sep 2002.

Shih M., Gennings C., Chinchili V., Carter W. Titrating and evaluating multi-drug regimens within subjects. Statistics in Medicine (2003) 22: 2257-2279

Stylianou, M. and Follmann D. The Accelerated Biased Coin Up-and-Down Design in Phase I Trials. Journal of Biopharmaceutical Statistics Vol. 14, No.1, pp. 249–260, 2004

Thrall P., Cheng, S. Optimal two-stage designs for clinical trials based on safety and efficacy. Statistics in Medicine (2001) 20: 1023-1032

Thall P., Inoue L., Berry D. Seamlessly Expanding a Randomized Phase II Trial to a Phase III. Technical Report #006-1 MD Anderson Cancer Center, University of Texas April,

2001

Ting N. Dose Finding in Drug Development: Statistics for Biology and Health. Springer 1st Edition 2006 32-33.

Todd S., Stallard N. A New Clinical Trial Design Combining Phase 2 and 3: Sequential Designs with Treatment Selection and a Change of Endpoint. Drug Information Journal Vol. 59 pp 109-118, 2005

Wang J. An Adaptive Two-stage Design with Treatment Selection Using the Conditional Error Function Approach. Biometrical Journal 48 (2006) 4, 679-689

Zhou Y. Choice of Designs and Doses for Early Phase Trials. Fundamental & Clinical Pharmacology 18 (2004) 373–378

Zhou Y., Whitehead J., Bonvini E., Stevens J. Bayesian decision procedures for binary and continuous bivariate dose-escalation studies. Pharmaceutical Statistics (2006) 5: 123-133

APPENDIX A

For Tables A.1-A.5 the Run values are defied as follows:

1-1,1-1: One subject on active drug and one subject on placebo at each dose level
3-1,1-1: Three subjects on active drug and one on placebo at the first three dose levels, then one subject on active drug and one on placebo at each subsequent dose level.
1-1,1-3: One subject on active drug and one on placebo at the first three dose levels, then three subjects on active drug and one on placebo at each subsequent dose level.
3-1,3-1: Three subjects on active drug and one on placebo at the each dose level.

Table A.1: Results from SIM 1 (10 simulations of size n=100 each) for four different sampling schemas

Desired Response: 0.55 and Desired Target Dose: 6.14							
Run*	Mean Parameter Estimates and Standard Error						
	γ	β_0	β_1	T_D	D_N	½-95% CI	EFF
1-1,1-1	0.8589 (0.7876)	-2.44 (0.0179)	0.5654 (0.0120)	6.18 (0.0604)	9.00 (0.3055)	0.639 (0.0173)	50%
3-1,1-1	0.8407 (0.0479)	-2.42 (0.0234)	0.5694 (0.0074)	6.09 (0.0266)	7.98 (0.2008)	0.583 (0.0041)	47%
1-1,3-1	0.7840 (0.0500)	-2.39 (0.0249)	0.5789 (0.0033)	6.21 (0.0350)	6.99 (0.1082)	0.466 (0.0168)	37%
3-1,3-1	0.9959 (0.2785)	-2.41 (0.0295)	0.5765 (0.0071)	6.14 (0.0363)	6.40 (0.0815)	0.435 (0.0145)	35%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_{0=}$ -2.296, $\beta_{1=}$ 0.5979 and $\tau = 0.0461$.
Initial starting doses: 1.25, 2.5 and 5 tablets
Efficiency (EFF): $\sigma^2_{Sim}/\sigma^2_{FixDose}$

Table A.2: Results from SIM 2 (10 simulations of size n=100 each) for four different sampling schemas

Desired Response: 0.55 and Desired Target Dose: 3.54							
Run*	Mean Parameter Estimates and Standard Error						
	γ	β_0	β_1	T_D	D_N	½-95% CI	EFF
1-1,1-1	0.7441 (0.0094)	-4.76 (0.0395)	1.6451 (0.0217)	3.73 (0.0523)	5.19 (0.0313)	0.1923 (0.0061)	17%
3-1,1-1	0.7094 (0.0012)	-4.77 (0.0082)	1.6892 (0.0051)	3.67 (0.0226)	5.02 (0.0141)	0.1502 (0.0041)	15%
1-1,3-1	0.7350 (0.0038)	-4.79 (0.0422)	1.6544 (0.0235)	3.69 (0.0378)	5.09 (0.0403)	0.1259 (0.0056)	12%
3-1,3-1	0.7127 (0.0015)	-4.79 (0.0200)	1.6850 (0.0109)	3.71 (0.0369)	5.01 (0.0079)	0.0889 (0.0031)	9%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_0 = -5$, $\beta_1 = 1.8$ and $\tau = 0.0461$.
Efficiency (EFF): $\sigma^2_{Lgr\,\beta 1}/\sigma^2_{FixDose}$

Table A.3: Results from SIM 3 (10 simulations of size n=100 each) for four different sampling schemas

Desired Response: 0.55 and Desired Target Dose: 12.36							
Run*	Mean Parameter Estimates and Standard Error						
	γ	β_0	β_1	T_D	D_N	½-95% CI	EFF
1-1,1-1	1.0721 (0.2736)	-2.53 (0.0496)	0.2638 (0.0034)	12.34 (0.0878)	16.87 (0.4558)	0.8467 (0.0130)	25%
3-1,1-1	1.1317 (0.2307)	-2.56 (0.0416)	0.2602 (0.0032)	12.23 (0.1000)	16.09 (0.4480)	0.8326 (0.0071)	25%
1-1,3-1	0.8432 (0.0688)	-2.41 (0.0214)	0.2789 (0.0028)	12.38 (0.0644)	11.90 (0.4026)	0.7284 (0.0189)	28%
3-1,3-1	0.9656 (0.1157)	-2.46 (0.0478)	0.2744 (0.0047)	12.31 (0.0506)	11.51 (0.4277)	0.7038 (0.0171)	29%

Values of Parameters for simulation of data $\gamma = 0.6891$, $\beta_0 = -2.296$, $\beta_1 = 0.2969$ and $\tau = 0.0461$.
Initial starting dose levels 0.25, 0.5 and 1 tablet
Efficiency (EFF): $\sigma^2_{Sm\beta 1}/\sigma^2_{FixDose}$

Table A.4: Results from simulation (10 simulations of size n=100 each) for fixed dose levels

Desired Response: 0.55						
Run	Mean Parameter Estimates and Standard Error					
	γ	β_0	β_1	T_D	½-95% CI	σ^2
Logistic	0.6910 (0.0012)	-2.29 (0.0010)	0.6014 (0.0033)	6.21 (0.0319)	1.212 (0.0108)	0.596 (0.0053)
LgB1	0.6929 (0.0008)	-4.77 (0.0072)	1.7050 (0.0053)	3.62 (0.0101)	0.481 (0.0035)	0.236 (0.0017)
SmB1	0.7218 (0.0091)	-2.13 (0.0088)	0.2942 (0.0017)	12.62 (0.0588)	3.335 (0.9366)	1.639 (0.4603)

Values of Parameters for simulation of data:
Constant across all simulations $\gamma = 0.6891$ and $\tau = 0.0461$.
Non-Linear Logistic: $\beta_{0=}$ -2.296 and $\beta_{1=}$ 0.5979
Larger B1: $\beta_{0=}$ -5 and $\beta_{1=}$ 1.8; Smaller B1: $\beta_{0=}$ -2.296 and β_1 =0.2969
Dose levels 0.5, 1, 2, 4, 8 and 16 tablets

Table A.5: Results from simulation (10 simulations of size n=100 each) for the Gompertz, the Non-Linear Logistic with Safety Adjustment and the Michaelis-Menten Nonlinear Models

Desired Response: 0.55						
Run*	Mean Parameter Estimates and Standard Error					
	γ	β_0	β_1	T_D	½-95% CI	$Var\left(\hat{T}_D\right)$
Gompertz	1.286 (0.7796)	-0.7647 (0.0125)	0.3142 (0.0092)	6.33 (0.0314)	0.6777 (0.0188)	0.3304 (0.0094)
Non-linear Logistic + Safety	0.7855 (0.0548)	-2.389 (0.0240)	0.5795 (0.0033)	6.22 (0.0434)	0.4648 (0.1612)	0.2210 (0.0079)
	γ	α	θ	T_D	½-95% CI	σ^2
Michaelis-Menten	1.3167 (0.1669)	0.0618 (0.0006)	12.0152 (2.4646)	7.43 (0.0579)	0.7378 (0.0199)	0.3618 (0.0102)

Values of Parameters for simulation of data:
Gompertz: $\gamma = 0.6366$ and $\tau = 0.0461$, $\beta_0 = -0.6804$and $\beta_1 = 0.3812$
Michaelis-Menten $\gamma = 0.7752$ and $\tau = 0.0358$, $\alpha = 0.0592$, and $\theta = 4.4556$

* 1-1,1-3: One subject on active drug and one on placebo at the first three dose levels, then three subjects on active drug and one on placebo at each subsequent dose level.

APPENDIX B

Figure B.1: Distribution of Simulation 1 Base Model Actual Dose Values, Sampling Schema (1-1, 1-1)

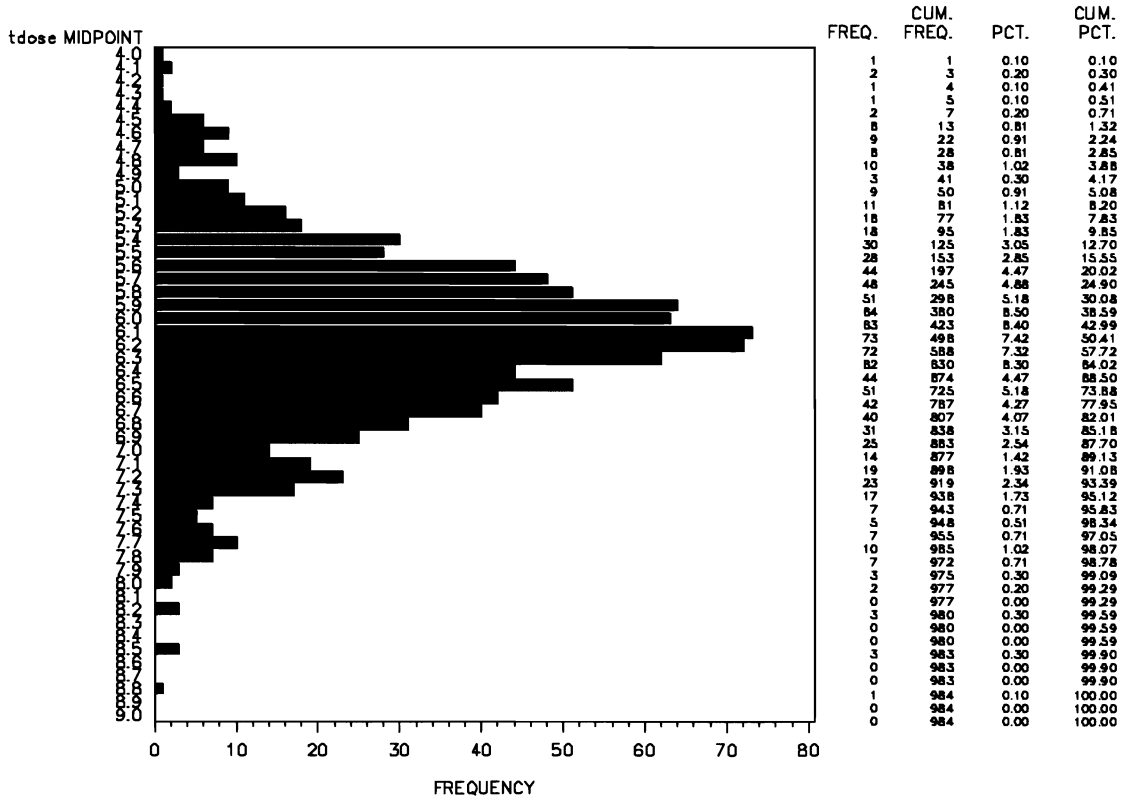
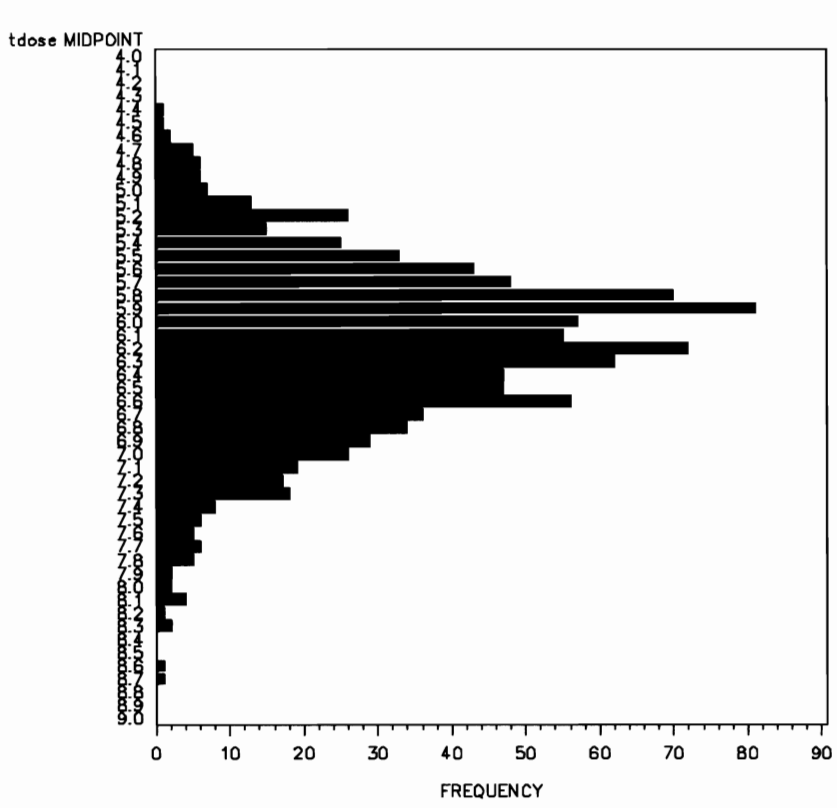
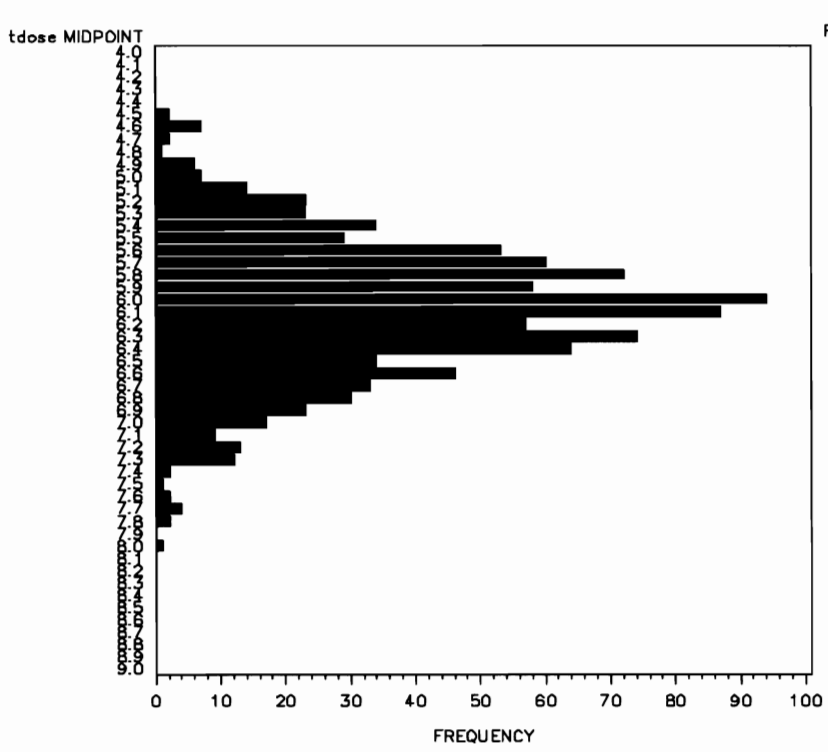


Figure B.2: Distribution of Simulation 1 Base Model, Actual Dose Values, Sampling Schema (1-1, 3-1)



FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
0	0	0.0	0.0
0	0	0.0	0.0
0	0	0.0	0.0
0	0	0.0	0.0
1	1	0.1	0.1
1	2	0.1	0.2
2	4	0.2	0.4
5	9	0.5	0.9
6	15	0.6	1.5
6	21	0.6	2.1
7	28	0.7	2.8
13	41	1.3	4.1
28	69	2.8	6.9
15	84	1.5	8.4
25	109	2.5	10.9
33	142	3.3	14.2
43	185	4.3	18.5
48	233	4.8	23.3
70	303	7.0	30.3
81	384	8.1	38.4
57	441	5.7	44.1
55	496	5.5	49.6
72	568	7.2	56.8
82	650	8.2	64.8
47	697	4.7	69.5
47	744	4.7	74.2
58	802	5.8	80.0
38	840	3.8	83.8
34	874	3.4	87.2
29	903	2.9	90.1
28	931	2.8	92.9
19	950	1.9	94.8
17	967	1.7	96.5
18	985	1.8	98.3
8	993	0.8	99.1
8	1001	0.8	99.9
5	1006	0.5	100.4
8	1014	0.8	101.2
5	1019	0.5	101.7
2	1021	0.2	101.9
2	1023	0.2	102.1
4	1027	0.4	102.5
1	1028	0.1	102.6
2	1030	0.2	102.8
0	1030	0.0	102.8
0	1030	0.0	102.8
1	1031	0.1	102.9
1	1032	0.1	103.0
0	1032	0.0	103.0
0	1032	0.0	103.0
0	1032	0.0	103.0

Figure B.3: Distribution of Simulation 1 Base Model, Actual Dose Values, Sampling Schema (3-1, 1-1)



tdose MIDPOINT	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
4.0	0	0	0.00	0.00
4.1	0	0	0.00	0.00
4.2	0	0	0.00	0.00
4.3	0	0	0.00	0.00
4.4	0	0	0.00	0.00
4.5	2	2	0.20	0.20
4.6	7	9	0.70	0.90
4.7	2	11	0.20	1.10
4.8	1	12	0.10	1.20
4.9	6	18	0.60	1.81
5.0	7	25	0.70	2.51
5.1	14	39	1.41	3.92
5.2	23	62	2.31	6.22
5.3	23	85	2.31	8.53
5.4	34	119	3.41	11.95
5.5	29	148	2.91	14.88
5.6	53	201	5.32	20.18
5.7	80	281	8.02	28.20
5.8	72	333	7.23	33.43
5.9	58	391	5.82	39.28
6.0	94	485	9.44	48.69
6.1	87	572	8.73	57.43
6.2	57	629	5.72	63.15
6.3	74	703	7.43	70.58
6.4	84	787	8.43	77.01
6.5	34	801	3.41	80.42
6.6	48	847	4.82	85.04
6.7	33	880	3.31	88.35
6.8	30	910	3.01	91.37
6.9	23	933	2.31	93.67
7.0	17	950	1.71	95.38
7.1	9	959	0.90	96.29
7.2	13	972	1.31	97.59
7.3	12	984	1.20	98.80
7.4	2	986	0.20	99.00
7.5	1	987	0.10	99.10
7.6	2	989	0.20	99.30
7.7	4	993	0.40	99.70
7.8	2	995	0.20	99.90
7.9	0	995	0.00	99.90
8.0	1	996	0.10	100.00
8.1	0	996	0.00	100.00
8.2	0	996	0.00	100.00
8.3	0	996	0.00	100.00
8.4	0	996	0.00	100.00
8.5	0	996	0.00	100.00
8.6	0	996	0.00	100.00
8.7	0	996	0.00	100.00
8.8	0	996	0.00	100.00
8.9	0	996	0.00	100.00
9.0	0	996	0.00	100.00

Figure B.4: Distribution of Simulation 1 Base Model, Actual Dose Values, Sampling Schema (3-1, 3-1)

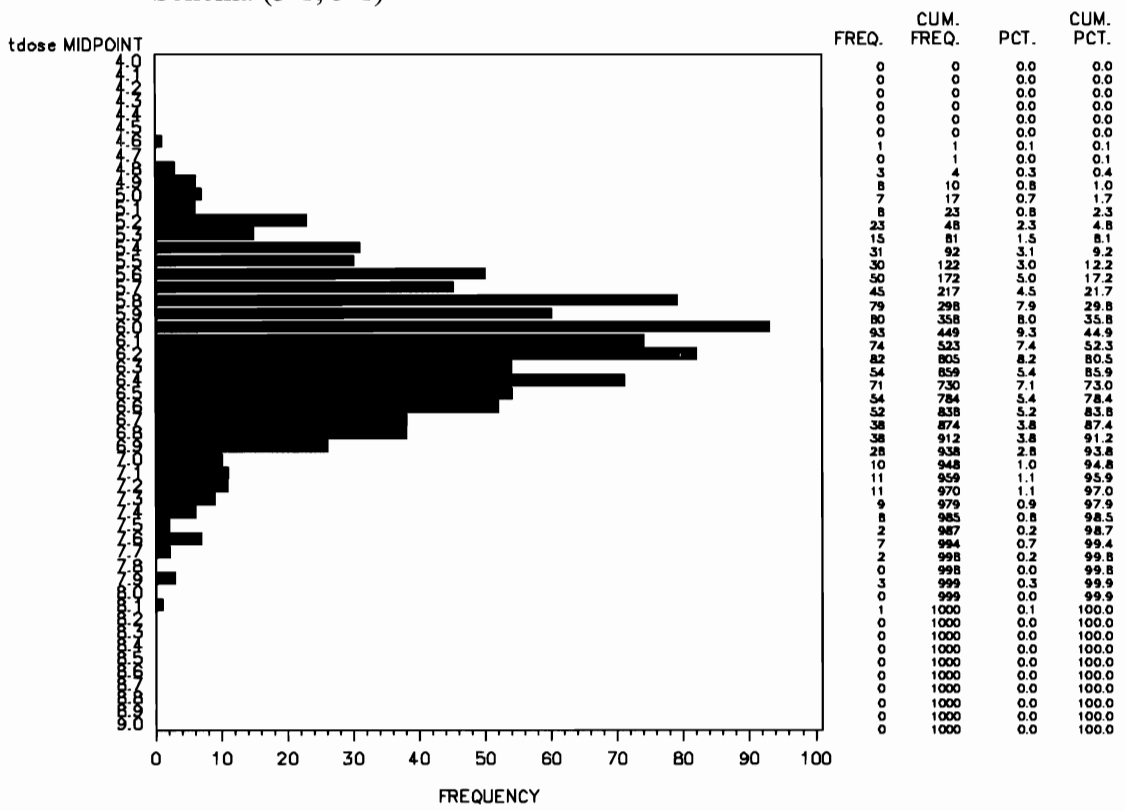
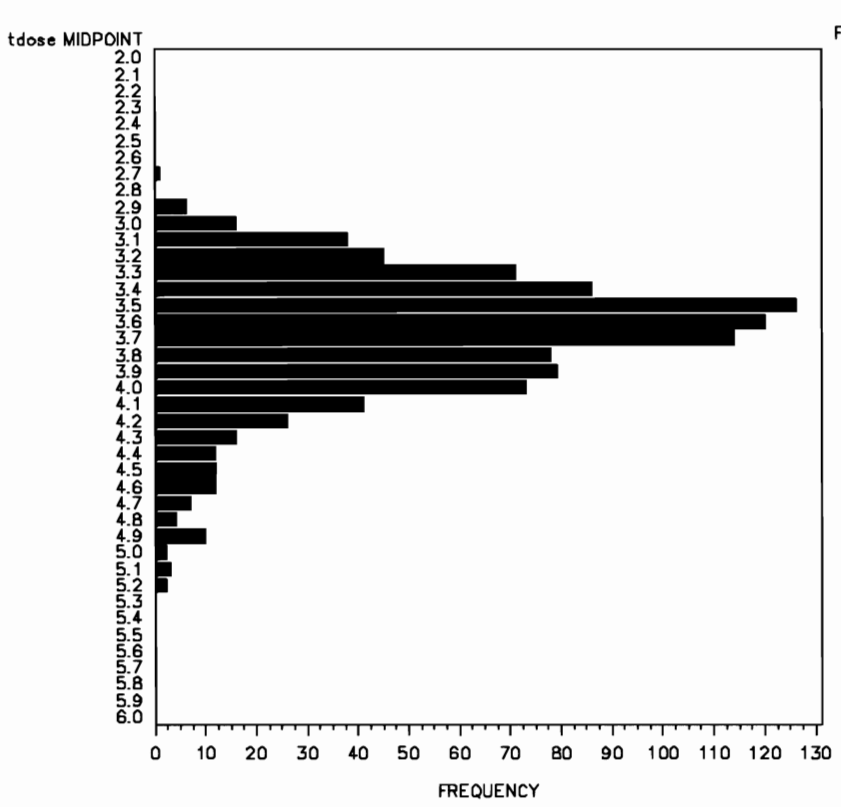
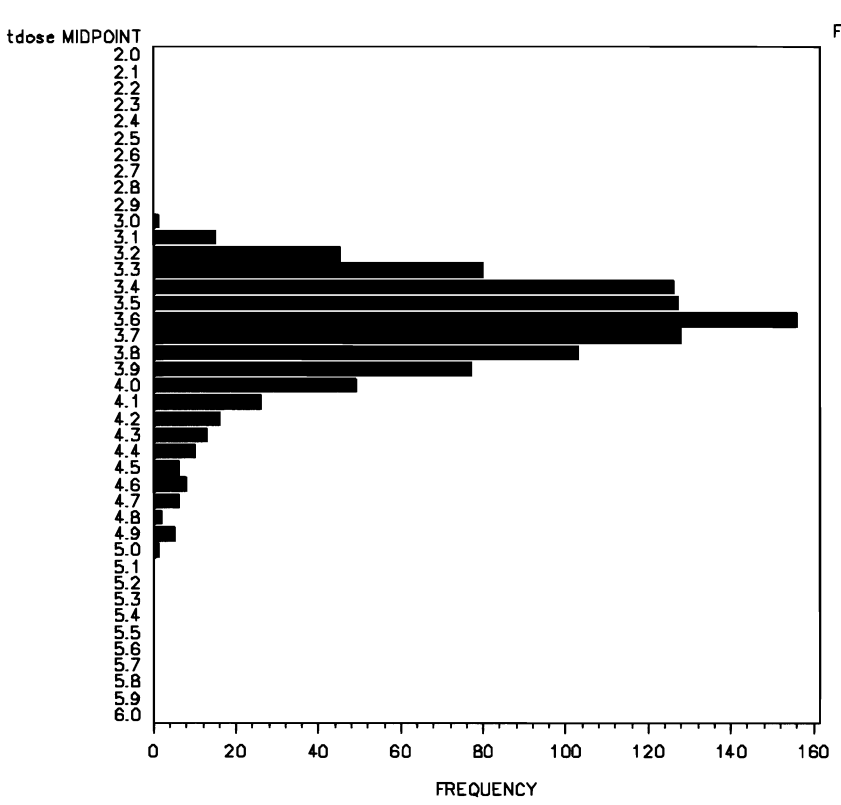


Figure B.5: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (1-1, 1-1)



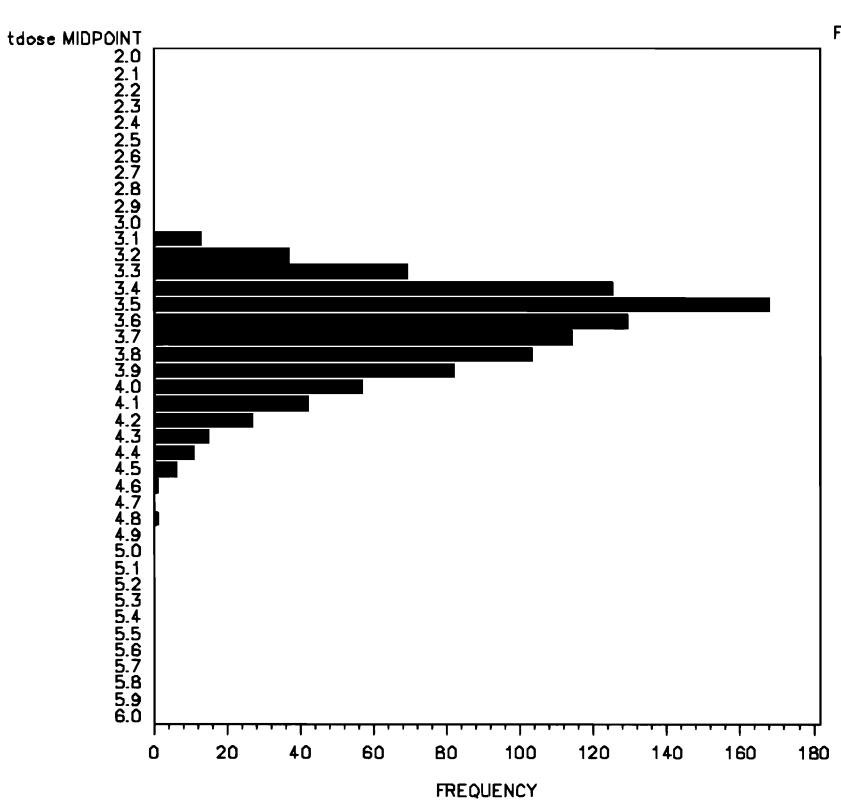
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
2.0	0	0	0.0	0.0
2.1	0	0	0.0	0.0
2.2	0	0	0.0	0.0
2.3	0	0	0.0	0.0
2.4	0	0	0.0	0.0
2.5	0	0	0.0	0.0
2.6	0	0	0.0	0.0
2.7	1	1	0.1	0.1
2.8	0	1	0.0	0.1
2.9	6	7	0.6	0.7
3.0	16	23	1.6	2.3
3.1	38	61	3.8	6.1
3.2	45	106	4.5	10.6
3.3	71	177	7.1	17.7
3.4	86	263	8.6	26.3
3.5	126	389	12.6	38.9
3.6	120	509	12.0	50.9
3.7	114	623	11.4	62.3
3.8	78	701	7.8	70.1
3.9	79	780	7.9	78.0
4.0	73	853	7.3	85.3
4.1	41	894	4.1	89.4
4.2	26	920	2.6	92.0
4.3	16	936	1.6	93.6
4.4	12	948	1.2	94.8
4.5	12	960	1.2	96.0
4.6	12	972	1.2	97.2
4.7	7	979	0.7	97.9
4.8	4	983	0.4	98.3
4.9	10	993	1.0	99.3
5.0	2	995	0.2	99.5
5.1	3	998	0.3	99.8
5.2	2	1000	0.2	100.0
5.3	0	1000	0.0	100.0
5.4	0	1000	0.0	100.0
5.5	0	1000	0.0	100.0
5.6	0	1000	0.0	100.0
5.7	0	1000	0.0	100.0
5.8	0	1000	0.0	100.0
5.9	0	1000	0.0	100.0
6.0	0	1000	0.0	100.0

Figure B.6: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (1-1, 3-1)



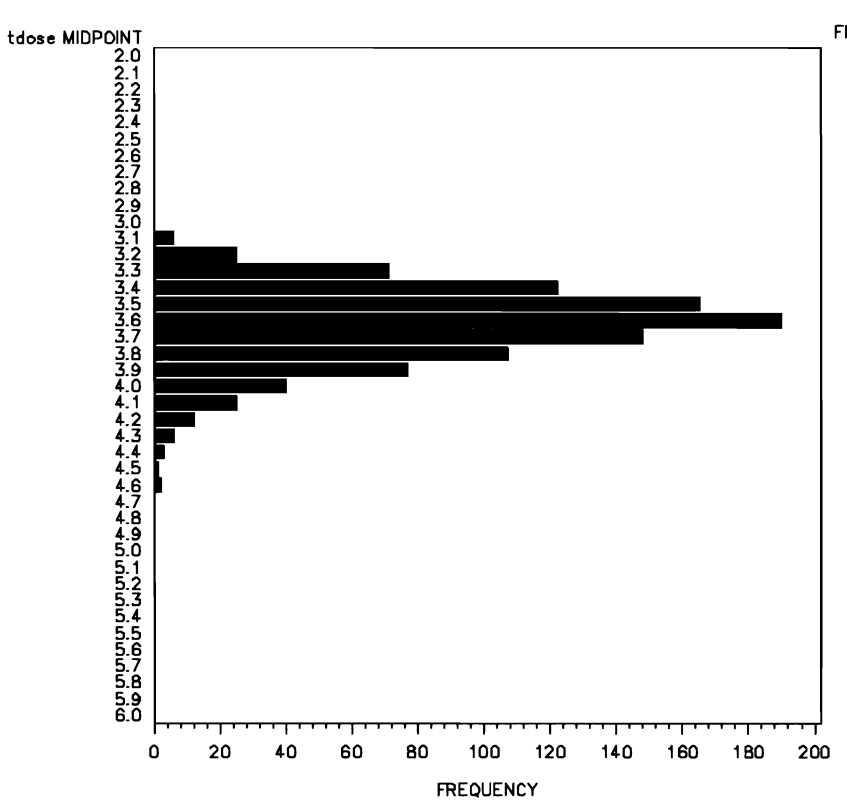
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
2.0	0	0	0.0	0.0
2.1	0	0	0.0	0.0
2.2	0	0	0.0	0.0
2.3	0	0	0.0	0.0
2.4	0	0	0.0	0.0
2.5	0	0	0.0	0.0
2.6	0	0	0.0	0.0
2.7	0	0	0.0	0.0
2.8	0	0	0.0	0.0
2.9	0	0	0.0	0.0
3.0	1	1	0.1	0.1
3.1	15	16	1.5	1.6
3.2	45	61	4.5	6.1
3.3	80	141	8.0	14.1
3.4	126	267	12.6	26.7
3.5	127	394	12.7	39.4
3.6	156	550	15.6	55.0
3.7	128	678	12.8	67.8
3.8	103	781	10.3	78.1
3.9	77	858	7.7	85.8
4.0	49	907	4.9	90.7
4.1	26	933	2.6	93.3
4.2	16	949	1.6	94.9
4.3	13	962	1.3	96.2
4.4	10	972	1.0	97.2
4.5	6	978	0.6	97.8
4.6	8	986	0.8	98.6
4.7	6	992	0.6	99.2
4.8	2	994	0.2	99.4
4.9	5	999	0.5	99.9
5.0	1	1000	0.1	100.0
5.1	0	1000	0.0	100.0
5.2	0	1000	0.0	100.0
5.3	0	1000	0.0	100.0
5.4	0	1000	0.0	100.0
5.5	0	1000	0.0	100.0
5.6	0	1000	0.0	100.0
5.7	0	1000	0.0	100.0
5.8	0	1000	0.0	100.0
5.9	0	1000	0.0	100.0
6.0	0	1000	0.0	100.0

Figure B.7: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (3-1, 1-1)



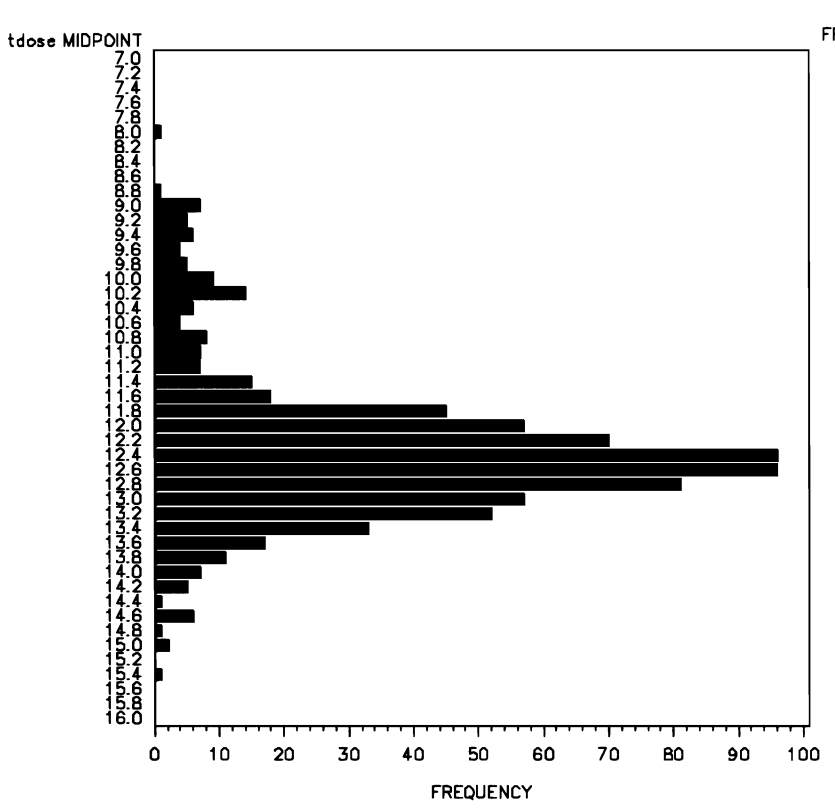
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
2.0	0	0	0.0	0.0
2.1	0	0	0.0	0.0
2.2	0	0	0.0	0.0
2.3	0	0	0.0	0.0
2.4	0	0	0.0	0.0
2.5	0	0	0.0	0.0
2.6	0	0	0.0	0.0
2.7	0	0	0.0	0.0
2.8	0	0	0.0	0.0
2.9	0	0	0.0	0.0
3.0	0	0	0.0	0.0
3.1	13	13	1.3	1.3
3.2	37	50	3.7	5.0
3.3	69	119	6.9	11.9
3.4	125	244	12.5	24.4
3.5	168	412	16.8	41.2
3.6	129	541	12.9	54.1
3.7	114	655	11.4	65.5
3.8	103	758	10.3	75.8
3.9	82	840	8.2	84.0
4.0	57	897	5.7	89.7
4.1	42	939	4.2	93.9
4.2	27	966	2.7	96.6
4.3	15	981	1.5	98.1
4.4	11	992	1.1	99.2
4.5	6	998	0.6	99.8
4.6	1	999	0.1	99.9
4.7	0	999	0.0	99.9
4.8	1	1000	0.1	100.0
4.9	0	1000	0.0	100.0
5.0	0	1000	0.0	100.0
5.1	0	1000	0.0	100.0
5.2	0	1000	0.0	100.0
5.3	0	1000	0.0	100.0
5.4	0	1000	0.0	100.0
5.5	0	1000	0.0	100.0
5.6	0	1000	0.0	100.0
5.7	0	1000	0.0	100.0
5.8	0	1000	0.0	100.0
5.9	0	1000	0.0	100.0
6.0	0	1000	0.0	100.0

Figure B.8: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (3-1, 3-1)



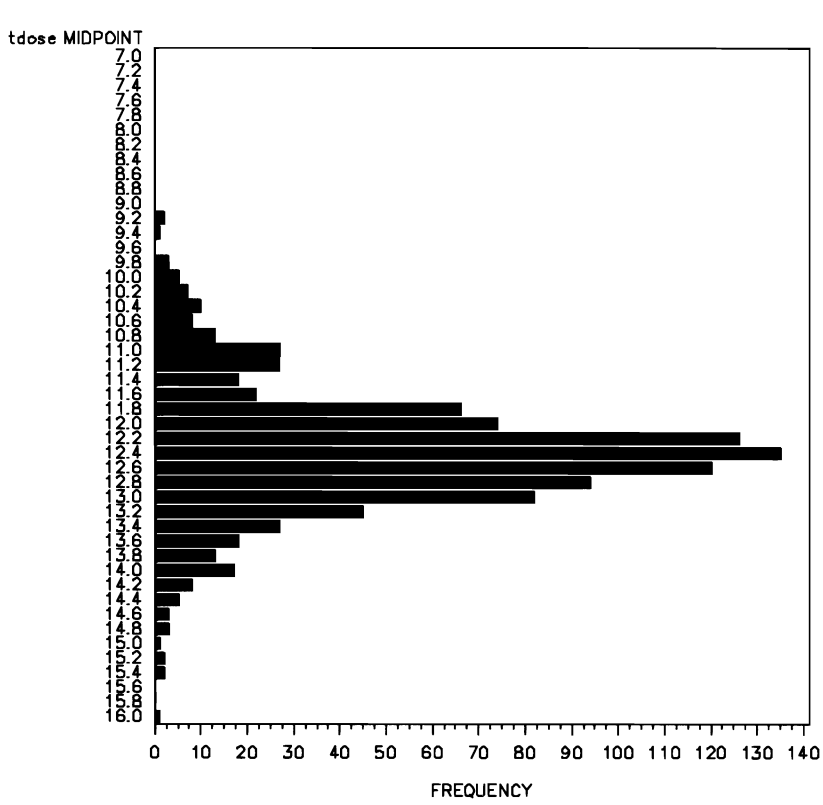
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
2.0	0	0	0.0	0.0
2.1	0	0	0.0	0.0
2.2	0	0	0.0	0.0
2.3	0	0	0.0	0.0
2.4	0	0	0.0	0.0
2.5	0	0	0.0	0.0
2.6	0	0	0.0	0.0
2.7	0	0	0.0	0.0
2.8	0	0	0.0	0.0
2.9	0	0	0.0	0.0
3.0	0	0	0.0	0.0
3.1	6	6	0.6	0.6
3.2	25	31	2.5	3.1
3.3	71	102	7.1	10.2
3.4	122	224	12.2	22.4
3.5	165	389	16.5	38.9
3.6	190	579	19.0	57.9
3.7	148	727	14.8	72.7
3.8	107	834	10.7	83.4
3.9	77	911	7.7	91.1
4.0	40	951	4.0	95.1
4.1	25	976	2.5	97.6
4.2	12	988	1.2	98.8
4.3	6	994	0.6	99.4
4.4	3	997	0.3	99.7
4.5	1	998	0.1	99.8
4.6	2	1000	0.2	100.0
4.7	0	1000	0.0	100.0
4.8	0	1000	0.0	100.0
4.9	0	1000	0.0	100.0
5.0	0	1000	0.0	100.0
5.1	0	1000	0.0	100.0
5.2	0	1000	0.0	100.0
5.3	0	1000	0.0	100.0
5.4	0	1000	0.0	100.0
5.5	0	1000	0.0	100.0
5.6	0	1000	0.0	100.0
5.7	0	1000	0.0	100.0
5.8	0	1000	0.0	100.0
5.9	0	1000	0.0	100.0
6.0	0	1000	0.0	100.0

Figure B.9: Distribution of Simulation 3-Shallow β_1, Actual Dose Values, Sample Schema (1-1, 1-1)



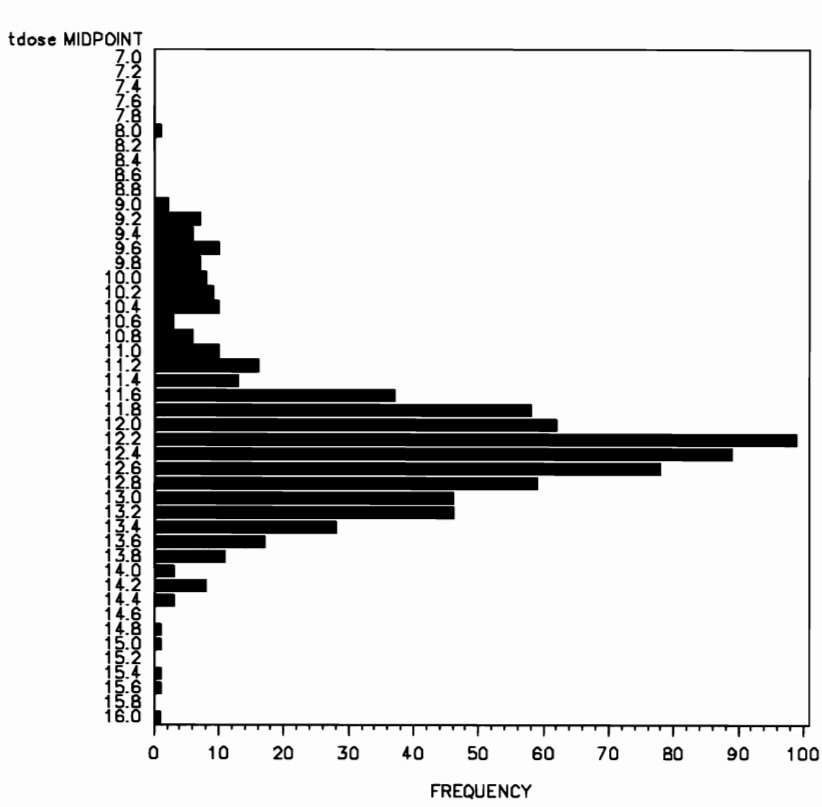
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
7.0	0	0	0.00	0.00
7.2	0	0	0.00	0.00
7.4	0	0	0.00	0.00
7.6	0	0	0.00	0.00
7.8	0	0	0.00	0.00
8.0	1	1	0.13	0.13
8.2	0	1	0.00	0.13
8.4	0	1	0.00	0.13
8.6	0	1	0.00	0.13
8.8	1	2	0.13	0.26
9.0	7	9	0.93	1.19
9.2	5	14	0.66	1.85
9.4	6	20	0.79	2.65
9.6	4	24	0.53	3.18
9.8	5	29	0.66	3.84
10.0	9	38	1.19	5.03
10.2	14	52	1.85	6.89
10.4	6	58	0.79	7.68
10.6	4	62	0.53	8.21
10.8	8	70	1.06	9.27
11.0	7	77	0.93	10.20
11.2	7	84	0.93	11.13
11.4	15	99	1.99	13.11
11.6	18	117	2.38	15.50
11.8	45	162	5.96	21.46
12.0	57	219	7.55	29.01
12.2	70	289	9.27	38.28
12.4	96	385	12.72	50.99
12.6	96	481	12.72	63.71
12.8	81	562	10.73	74.44
13.0	57	619	7.55	81.99
13.2	52	671	6.89	88.87
13.4	33	704	4.37	93.25
13.6	17	721	2.25	95.50
13.8	11	732	1.46	96.95
14.0	7	739	0.93	97.88
14.2	5	744	0.66	98.54
14.4	1	745	0.13	98.68
14.6	6	751	0.79	99.47
14.8	1	752	0.13	99.60
15.0	2	754	0.26	99.87
15.2	0	754	0.00	99.87
15.4	1	755	0.13	100.00
15.6	0	755	0.00	100.00
15.8	0	755	0.00	100.00
16.0	0	755	0.00	100.00

Figure B.10: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (1-1, 3-1)



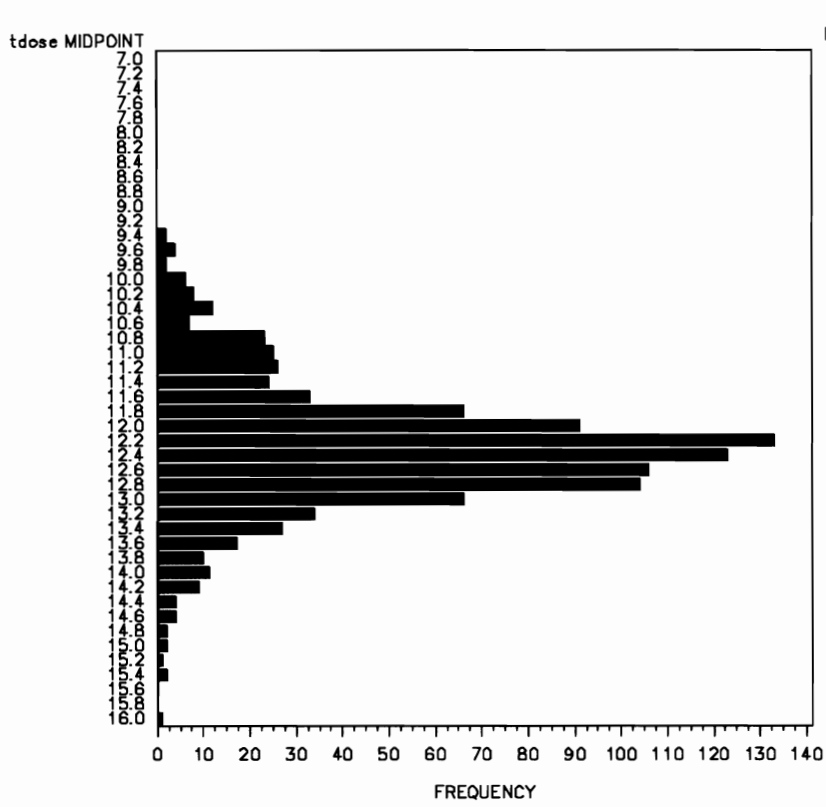
	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
7.0	0	0	0.00	0.00
7.2	0	0	0.00	0.00
7.4	0	0	0.00	0.00
7.6	0	0	0.00	0.00
7.8	0	0	0.00	0.00
8.0	0	0	0.00	0.00
8.2	0	0	0.00	0.00
8.4	0	0	0.00	0.00
8.6	0	0	0.00	0.00
8.8	0	0	0.00	0.00
9.0	0	0	0.00	0.00
9.2	2	2	0.20	0.20
9.4	1	3	0.10	0.30
9.6	0	3	0.00	0.30
9.8	3	6	0.30	0.61
10.0	5	11	0.51	1.12
10.2	7	18	0.71	1.83
10.4	10	28	1.02	2.84
10.6	8	36	0.81	3.65
10.8	13	49	1.32	4.97
11.0	27	76	2.74	7.72
11.2	27	103	2.74	10.46
11.4	18	121	1.83	12.28
11.6	22	143	2.23	14.52
11.8	66	209	6.70	21.22
12.0	74	283	7.51	28.73
12.2	126	409	12.79	41.52
12.4	135	544	13.71	55.23
12.6	120	664	12.18	67.41
12.8	94	758	9.54	76.95
13.0	82	840	8.32	85.28
13.2	45	885	4.57	89.85
13.4	27	912	2.74	92.59
13.6	18	930	1.83	94.42
13.8	13	943	1.32	95.74
14.0	17	960	1.73	97.46
14.2	8	968	0.81	98.27
14.4	5	973	0.51	98.78
14.6	3	976	0.30	99.09
14.8	3	979	0.30	99.39
15.0	1	980	0.10	99.49
15.2	2	982	0.20	99.70
15.4	2	984	0.20	99.90
15.6	0	984	0.00	99.90
15.8	0	984	0.00	99.90
16.0	1	985	0.10	100.00

Figure B.11: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (3-1, 1-1)



	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
7.0	0	0	0.00	0.00
7.2	0	0	0.00	0.00
7.4	0	0	0.00	0.00
7.6	0	0	0.00	0.00
7.8	0	0	0.00	0.00
8.0	1	1	0.13	0.13
8.2	0	1	0.00	0.13
8.4	0	1	0.00	0.13
8.6	0	1	0.00	0.13
8.8	0	1	0.00	0.13
9.0	2	3	0.26	0.40
9.2	7	10	0.92	1.32
9.4	6	16	0.79	2.11
9.6	10	26	1.32	3.43
9.8	7	33	0.92	4.36
10.0	8	41	1.06	5.42
10.2	9	50	1.19	6.61
10.4	10	60	1.32	7.93
10.6	3	63	0.40	8.32
10.8	6	69	0.79	9.11
11.0	10	79	1.32	10.44
11.2	16	95	2.11	12.55
11.4	13	108	1.72	14.27
11.6	37	145	4.89	19.15
11.8	58	203	7.66	26.82
12.0	62	265	8.19	35.01
12.2	99	364	13.08	48.08
12.4	89	453	11.76	59.84
12.6	78	531	10.30	70.15
12.8	59	590	7.79	77.94
13.0	46	636	6.08	84.02
13.2	46	682	6.08	90.09
13.4	28	710	3.70	93.79
13.6	17	727	2.25	96.04
13.8	11	738	1.45	97.49
14.0	3	741	0.40	97.89
14.2	8	749	1.06	98.94
14.4	3	752	0.40	99.34
14.6	0	752	0.00	99.34
14.8	1	753	0.13	99.47
15.0	1	754	0.13	99.60
15.2	0	754	0.00	99.60
15.4	1	755	0.13	99.74
15.6	1	756	0.13	99.87
15.8	0	756	0.00	99.87
16.0	1	757	0.13	100.00

Figure B.12: Distribution of Simulation 2-Steeper β_1, Actual Dose Values, Sample Schema (3-1, 3-1)



	FREQ.	CUM. FREQ.	PCT.	CUM. PCT.
7.0	0	0	0.00	0.00
7.2	0	0	0.00	0.00
7.4	0	0	0.00	0.00
7.6	0	0	0.00	0.00
7.8	0	0	0.00	0.00
8.0	0	0	0.00	0.00
8.2	0	0	0.00	0.00
8.4	0	0	0.00	0.00
8.6	0	0	0.00	0.00
8.8	0	0	0.00	0.00
9.0	0	0	0.00	0.00
9.2	0	0	0.00	0.00
9.4	2	2	0.20	0.20
9.6	4	6	0.41	0.61
9.8	2	8	0.20	0.81
10.0	6	14	0.61	1.42
10.2	8	22	0.81	2.23
10.4	12	34	1.22	3.45
10.6	7	41	0.71	4.16
10.8	23	64	2.34	6.50
11.0	25	89	2.54	9.04
11.2	26	115	2.64	11.68
11.4	24	139	2.44	14.11
11.6	33	172	3.35	17.46
11.8	66	238	6.70	24.16
12.0	91	329	9.24	33.40
12.2	133	462	13.50	46.90
12.4	123	585	12.49	59.39
12.6	106	691	10.76	70.15
12.8	104	795	10.56	80.71
13.0	66	861	6.70	87.41
13.2	34	895	3.45	90.86
13.4	27	922	2.74	93.60
13.6	17	939	1.73	95.33
13.8	10	949	1.02	96.35
14.0	11	960	1.12	97.46
14.2	9	969	0.91	98.38
14.4	4	973	0.41	98.78
14.6	4	977	0.41	99.19
14.8	2	979	0.20	99.39
15.0	2	981	0.20	99.59
15.2	1	982	0.10	99.70
15.4	2	984	0.20	99.90
15.6	0	984	0.00	99.90
15.8	0	984	0.00	99.90
16.0	1	985	0.10	100.00

APPENDIX C

Non-linear logistic base model is shown here. For all other models update the following:

1. The calculation of mu in the simulation macros to reflect the model and parameter values for each respective model.
2. The models in the three PROC NLIN procedures must match the models in the simulation macros
3. Target dose must be based on the model under investigation

```
**** Define path were programs reside and output is to be written ****;
%let path = f:\Disertation;
%let path=
C:\Documents and Settings\davenpmj.LABS\My Documents\School\Disertation;
libname ltest "&path";

**** Write log to file prevents PC SAS from stopping because the buffer
     is full ****;
proc printto log="&path\sim.log" new;run;
options symbolgen macrogen mprint;

*********************************************************************;

**** Data Inputs ****;
%let sdose= 1.25, 2.5, 5; * Initial starting dose levels;
%let fdose=5;             * High starting dose level;
%let thres=0.55;          * Target threshold effect;
%let mstrt=9;             * Start for outer loop counter;
%let mruns=10;            * Outer loop counter for se calc;
%let p=3;                 * Number of parameters to estimate;
%let g1=1;                * Initial starting point for gamma;
%let eint=25;             * Number of times to run the simulation for
                            each NLIN run(Inner Loop);
%let kount=100;           * Number of iterations of the simulation (Outer
                            Loop);
%let numi=3;              * Number of active patients at each initial
                            dose level;
```

```
%let numip=1;              * Number of placebo patients at each initial
                             dose level;
%let num=1;                * Number of patients at each dose level;
%let nump=1;               * Number of placebo patients at each dose
                             level;
%let done=0;               * Used for stopping rule;
%let binsize=1;            * Smallest dose increase/decrease allowed after
                             initial 3 doses;
*********************************************************************;


**** Clean out the work space before beginning run ****;
proc datasets library=work kill; quit;


**** Delta Method if gamma is not estimable. Only use B0 and B1 ***;

%macro delta2p(n);

  * Input data from PROC NLIN run;
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then ouput cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;

  proc iml;
    use cvb; read all var{b0 b1} into covb;
    use prms; read all var {b0 b1} into parms;

    * Compute values of partials for b0, and b1 for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(1-&thres))-parms[1])*(-1/(parms[2]#parms[2]));

    *Build parameter vector;
     beta=j(2,1,0);
     beta[1,1]=parms[1];
     beta[2,1]=parms[2];

       *Generate variance covariance matrix;
    delta=j(1,2,0);
    delta[1]=d_b0;
    delta[2]=d_b1;

    * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;

  * Generate macro variable to hold new variance calculation;
  %if &n=1 %then %do;
```

```
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;

* Delta Method when gamma, B0 and B1 are estimable;

%macro delta(n);

  * Input data from PROC NLIN run;
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;

  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use prms; read all var {b0 b1 gamma} into parms;

    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(parms[3]-&thres))-parms[1])*
         (-1/(parms[2]#parms[2]));
    d_g=(-1/(parms[3]-&thres))*(1/parms[2]);

      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];

    *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
    delta[3]=d_g;

    * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    create devchk from var_ed [colname='vars'];
```

```
    append from var_ed;
  quit;
  run;

  * Generate macro variable to hold new variance calculation;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
        call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;

/************************************************
  Macros for generation of simulations the variance component (tau) is
  the variance observed from the given data using a non-linear logistic
  with a quasi-likelihood assumption of variance showing a binomial
  distribution.

  tau= 0.0461 gamma=0.6891, B0= -2.296, B1 = 0.5979 are the estimates
  from the BASE Logistic

  Resulting suppression values can not be less than zero.
************************************************/

* Simulate initial dose levels and subjects;
%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;

   * Generates active dose levels;
   do d=&sdose;

    *** Estimate mu for current target dose;
    mu = 0.6891/(1+exp(2.296-0.5979*d));

    do i=1 to &numi;

      * Use tau, binomial distribution and randome variable from a normal
        distribution to simulate a data value;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
```

```
      * If result is less than zero then force to zero;
      if result <0 then result=0;
      tabs=d;
      output;
    end;

    *** Estimate mu for placebo subjects;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &numip;

      * Use tau, binomial distribution and randome variable from a normal
        distribution to simulate a data value;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);

      * If result is less than zero then force to zero;
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;

  * Send seed value to a macro variable;
   call symput('sd',&seed);
  run;

  * Generate simulated data set;
  proc append base=b2 data=siminit force;
%mend;

* Simulate additional dose levels;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;

   *** Estimate mu for current target dose;
   mu = 0.6891/(1+exp(2.296-0.5979*&dnew));
   do i=1 to &num;

      * Use tau, binomial distribution and randome variable from a normal
        distribution to simulate a data value;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);

      * If result is less than zero then force to zero;
     if result <0 then result=0;
     tabs=&dnew;
     output;
   end;

    *** Estimate mu for placebo subjects;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &nump;
```

```
      * Use tau, binomial distribution and randome variable from a normal
        distribution to simulate a data value;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);

      * If result is less than zero then force to zero;
      if result <0 then result=0;
      tabs=0;
      output;
    end;

  * Send seed value to a macro variable;
   call symput('sd',&seed);
  run;

  * Generate simulated data set;
  proc append base=b2 data=sim force;
%mend;

/*************************************
 Compute logistic values for input
 into reg to calculate starting values
 use example clinical trials data to obtain
 initial parameter estimates for NLIN run
*************************************/

data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;

data _null_;
 set initial;

 * Push initial parameter estimates to macro variables;
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
*******************;


* Core procedure to calculate new target dose and confidence interval;

%macro testum(n);
   data begin;set b2;run;
   ods listing close;
```

```
* Non-Linear logistic model execution;
proc nlin data=begin outest=beta noitprint;
  parms b0=&b0 b1=&b1 gamma=&g1;
  mu=gamma/(1+exp(-1*(b0+b1*tabs)));

* quasi-likelihood distribution applicaton;
  _weight_=1/(mu*(1-mu));
  _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
  model result = mu;
  output out=pred p=pred&n;
  ods output ConvergenceStatus=conv;
 run;

 * Push convergence status to macro variable;
 data _null_;
   set conv;
     call symput('cvstat',status);
   run;

 * Determine if all parameters are estimable and push result into a
   macro variable;
   data _null_;
     set beta;
   hess=0;
     if trim(left(_name_)) in ("b0","b1","gamma") then do;
       if b0=. | b1=. | gamma=. then do;hess=1;end;
     end;
     call symput('hesstat',hess);
 run;

 %if &cvstat ^=0 %then %do;
    /****************************************
      If unable to estimate gamma then force
      gamma to be a value of 1.00 and re-execute
    ****************************************/
    proc nlin data=begin outest=beta noitprint;
       parms b0=&b0 b1=&b1;
           mu=1/(1+exp(-1*(b0+b1*tabs)));
           _weight_=1/(mu*(1-mu));
           _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
       model result = mu;
       output out=pred p=pred&n;
       ods output ConvergenceStatus=conv2;
    run;


   * Push convergence status to macro variable;
   data _null_;
     set conv2;
     call symput('cvstat2',status);
    run;
 %end;
 %else %if &hesstat=1 %then %do;
```

```
    /*************************************
      If Hessian is singular then force
      gamma to be a value of 1.00 and re-execute
    *************************************/
    proc nlin data=begin outest=beta noitprint;
       parms b0=&b0 b1=&b1;
           mu=1/(1+exp(-1*(b0+b1*tabs)));
           _weight_=1/(mu*(1-mu));
           _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
       model result = mu;
       output out=pred p=pred&n;
       ods output ConvergenceStatus=conv2;
    run;

   * Push convergence status to macro variable;
   data _null_;
    set conv2;
      call symput('cvstat2',status);
     run;
   %end;

   * Combine convergence status and parameter estimates into macro
     variable;
   data _null_;
      call symput('combo',%eval(&cvstat+&hesstat));
   run;
   ods listing;

/*************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";

  * Calculate new target dose for next simulation if method converged
    and all parameters estimable;
  %if &combo=0 %then %do;

       * Target dose calculation if gamma is estimable and greater
         than the target threshold effect;

       if gamma > &thres then do;
```

```
      tdose=(log(&thres/(gamma-&thres))-b0)/b1;
      TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
    end;

    * Target dose calculation if gamma is estimable and less than
      the target threshold effect;
    if gamma <= &thres then do;
      tdose=(log(&thres/(1-&thres))-b0)/b1;
      DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;

      * Get additional possibilities for new target dose if gamma
        less than target threshold effect;
      if &n=1 then do;
        DoseC2=2*&fdose;
      end;
      else do;
       DoseC2=2*&dnew;
       end;

       * Final choice for target dose if gamma less than target
         threshold effect;
       TargetDose=max(of DoseC1,DoseC2);
      if TargetDose=DoseC2 then do;

        * Add one to counter that monitors number of times the dose
          multiplier is used;
        call symput('count',%eval(&count+1));
       end;
    end;
  %end;

* Calculate new target dose for next simulation if method converged
  on second iteration with gamma fixed;
%else %if &cvstat2=0 %then %do;

  *Calculate new target dose;
  tdose=(log(&thres/(1-&thres))-b0)/b1;
    DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;

  * Get additional possibilities for new target dose since gamma
    inestimable;
  if &n=1 then do;
    DoseC2=2*&fdose;
  end;
  else do;
    DoseC2=2*&dnew;
   end;

   * Final choice for target dose if gamma less than target
     threshold effect;
   TargetDose=max(of DoseC1,DoseC2);

  if TargrtDose=DoseC2 then do;
```

```
      * Add one to counter that monitors number of times the dose
        multiplier is used;
      call symput('count',%eval(&count+1));end;
    %end;

    * If NLIN fails to converge twice then apply dose multipler;
    %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
    if &n=1 then do;
        TargetDose=2*&fdose;
     end;
     else do;
        TargetDose=2*&dnew;

      * Add one to counter that monitors number of times the dose
        multiplier is used;
       call symput('count',%eval(&count+1));
     end;
  %end;

    if iter > 1 & TargetDose=&dnew then do;
      * If new target dose is the same as old target dose then add one
        to counter tracking this occurrence;
      call symput('dcnt',%eval(&dcnt+1));
    end;

    * Otherwise reset counter monitor repeats of target dose to one;
    else do; call symput('dcnt',1);end;
 run;

data c;
  set c;
    * Write macro variable to the data set and initialize confidence
      interval and epsilon;
    kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;

  * Update initial parameter estimates for next iteration of NLIN run;
  call symput('b0',b0);
  call symput('b1',b1);
  %if &combo=0 %then %do;
      call symput('g1',gamma);
    %end;
  %else %do; %let g1=1;%end;
  call symput('dnew',TargetDose);
 run;

 * Push data points and degrees of freedom to macro variables;
 data _null;
   set begin nobs=nobs;
   call symput('DF',nobs-&p);
   call symput('NT',nobs);
 run;
```

```
     * If NLIN converges then run delta method for either 2 or 3
       parameters;
     %if &combo=0 %then %do;
         %if &g1 > &thres %then %do;%delta(&n);%end;
         %else %do;%delta2p(&n);%end;
       %end;
     %else %if &cvstat2=0 %then %do;
         %do;%delta2p(&n);%end;
       %end;

    * Generate confidence intervals if NLIN converges;
    data c;
      set c;
        drop _type_ _status_ _name_ _iter_ _sse_;
      if &n > 1 & (&combo=0 | &cvstat2=0) then do;
        tc=tinv(0.975,&df);
        del=&sdevnew;

        * Only calculate confidence interval if gamma exceeds target
          threshold effect;
        if gamma > &thres then do;ci_h=tc*del;end;

        * If confidence interval is less than one then assign eps to zero
          which will stop the procedure;
        if ci_h ^=. & ci_h <= &binsize/2 & gamma ^=. then do;eps=0;end;
        else do; eps=1;end;
        call symput('eps',eps);

        * If confidence interval is less than two then assign eps2 to
          zero which will stop the procedure if target dose has not
          changed for three consecutive iterations;
        if ci_h ^=. & ci_h <= 1 & gamma ^=. then do;eps2=0;end;
          else do; eps2=1;end;
        call symput('eps2',eps2);
      end;
      run;
%mend;

* Check all stopping rules;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;

   * If dose multiplier has been used 6 times then stop;
   %if &count >= 6 %then %do;call symput('done',3);%end;

   * If confidence interval is less than one then stop;
   %if &eps = 0 %then %do;call symput('done',1);%end;

   * If confidence interval is less than one and the target dose has not
     changed for three consecutive iterations then stop;
   %if &eps2 = 0 %then %do;
```

```
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
  run;
%mend;


* Main macro that executes all the above stuff;

%macro runum;

 * Outer loop that determines how many sets will be executed (10 sets for
   the simulations;
 %do m=&mstrt %to &mruns;

  * Loop 2 that determines how many studies per set (100 for each
    simulation;
  %do j=1 %to &kount;

    * Initialize macro variables for each series in Loop 2;
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;
    %let b1=&B1_I;
    %let g1=1;
    %let eps=1;
    %let eps2=1;
    %let count=0;
    %let dcnt=1;

    * Initial three dose levels;
    %sims_init(numi=&numi,seed=86019398+&j+&m);
    %testum(1);

    * Inner loop has remaining dose levels with maximum number of
      iterations per study;
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
     %testum(&k);
     %epschk(&k);

     * If stopping rule met reinitialize done depart loop and write final
       iteration to data set;
     %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin: proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
 %end;
%mend;
```

```
%runum;

proc sort data=sims;by knt;run;
proc print data=sims;run;



* See summary statistics but exclude failed runs;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma B0 B1 TargetDose del dosecnt ci_h;
 run;

/***********************************************
  Use this to write data to permanent data sets, need to rename as
  appropriate

 data ltest.sims55i3f1;
  set ltest.sims55i3f1 sims;
 run;
 proc print data=ltest.sims55i3f1;run;

 ***********************************************/
proc printto;run;
```

```
Non Linear logistic shallow slope model, see Base model for complete
description of code;

%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj.LABS\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;

*************************************************************************
*****;
%let sdose= 1.25, 2.5, 5; *Intial starting dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=9; *Start for outer loop counter;
%let mruns=10; *Outer loop counter for se calc;
%let p=3; *Number of parameters to estimate;
%let g1=1; *Intial starting point for gamma;
%let eint=25; *Number oftimes to run the simulation for each NLIN run
(Inner Loop);
%let kount=100; *Number of iterations of the simulation (Outer Loop);
%let numi=3; *Number of active patients at each initial dose level;
%let numip=1; *Number of placebo patients at each initial dose level;
%let num=3; *Number of patients at each dose level;
%let nump=1; *Number of placebo patients at each dose level;
%let done=0; *Used for stopping rule;
%let binsize=1; *Smallest dose increase/decrease allowed after inital 3
doses;
*************************************************************************
******;

proc datasets library=work kill; quit;
%macro delta2p(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then ouput cvb;;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1} into covb;
    use prms; read all var {b0 b1} into parms;
    * Compute values of paritals for b0, and b1 for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(1-&thres))-parms[1])*(-1/(parms[2]#parms[2]));
      *Build parameter vector;
      beta=j(2,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      *Generate variance covariance matrix;
    delta=j(1,2,0);
```

```
    delta[1]=d_b0;
    delta[2]=d_b1;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
%macro delta(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use prms; read all var {b0 b1 gamma} into parms;
    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(parms[3]-&thres))-parms[1])*(-
1/(parms[2]#parms[2]));
    d_g=(-1/(parms[3]-&thres))*(1/parms[2]);
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
    delta[3]=d_g;
```

```
      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
/************************************************
  macros for generation of simulations
  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0461 gamma=0.6891, B0= -2.296, B1 = 0.82969 are

  the estimates modified for shallow B0

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.6891/(1+exp(2.296-0.2969*d));
    do i=1 to &numi;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
      output;
```

```
    end;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &numip;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;
%mend;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;
   mu = 0.6891/(1+exp(2.296-0.2969*&dnew));
   do i=1 to &num;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
     if result <0 then result=0;
     tabs=&dnew;
     output;
   end;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &nump;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=sim force;
%mend;

/************************************
 Compute logistic values for input
 into reg to calculate starting values
************************************/
data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;
data _null_;
 set initial;
```

```
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
*******************;

%macro testum(n);
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms b0=&b0 b1=&b1 gamma=&g1;
              mu=gamma/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     output out=pred p=pred&n;
     ods output ConvergenceStatus=conv;
    run;
    data _null_;
      set conv;
        call symput('cvstat',status);
      run;
      data _null_;
        set beta;
      hess=0;
        if trim(left(_name_)) in ("b0","b1","gamma") then do;
          if b0=. | b1=. | gamma=. then do;hess=1;end;
        end;
        call symput('hesstat',hess);
    run;
    %if &cvstat ^=0 %then %do;
       /*************************************
         If unable to estimate gamma then force
         gamma to be a value of 1.00
       *************************************/
       proc nlin data=begin outest=beta noitprint;
          parms b0=&b0 b1=&b1;
              mu=1/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
          output out=pred p=pred&n;
          ods output ConvergenceStatus=conv2;
       run;
      data _null_;
        set conv2;
          call symput('cvstat2',status);
        run;
    %end;
      %else %if &hesstat=1 %then %do;
       /*************************************
         If Hessian is singular then force
         gamma to be a value of 1.00
       *************************************/
```

```
    proc nlin data=begin outest=beta noitprint;
       parms b0=&b0 b1=&b1;
           mu=1/(1+exp(-1*(b0+b1*tabs)));
           _weight_=1/(mu*(1-mu));
           _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
       model result = mu;
       output out=pred p=pred&n;
       ods output ConvergenceStatus=conv2;
    run;
   data _null_;
    set conv2;
      call symput('cvstat2',status);
     run;
   %end;

     data _null_;
      call symput('combo',%eval(&cvstat+&hesstat));

   run;
   ods listing;

/*************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";
  %if &combo=0 %then %do;
       if gamma > &thres then do;
         tdose=(log(&thres/(gamma-&thres))-b0)/b1;
               TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
      end;
      if gamma <= &thres then do;
        tdose=(log(&thres/(1-&thres))-b0)/b1;
            DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
        if &n=1 then do;
          DoseC2=2*&fdose;
        end;
        else do;
         DoseC2=2*&dnew;
            end;
            TargetDose=max(of DoseC1,DoseC2);
```

```
          if TargetDose=DoseC2 then do;call
symput('count',%eval(&count+1));end;
        end;
      %end;
    %else %if &cvstat2=0 %then %do;
      tdose=(log(&thres/(1-&thres))-b0)/b1;
        DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
      if &n=1 then do;
        DoseC2=2*&fdose;
      end;
      else do;
        DoseC2=2*&dnew;
        end;
        TargetDose=max(of DoseC1,DoseC2);
      if TargrtDose=DoseC2 then do;call
symput('count',%eval(&count+1));end;
      %end;
      %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
      if &n=1 then do;
          TargetDose=2*&fdose;
       end;
       else do;
          TargetDose=2*&dnew;
          call symput('count',%eval(&count+1));
       end;
    %end;
      if iter > 1 & TargetDose=&dnew then do;
        call symput('dcnt',%eval(&dcnt+1));
      end;
      else do; call symput('dcnt',1);end;
   run;
  data c;
    set c;
      kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;
    call symput('b0',b0);
    call symput('b1',b1);
    %if &combo=0 %then %do;
        call symput('g1',gamma);
      %end;
    %else %do; %let g1=1;%end;
    call symput('dnew',TargetDose);
   run;
        data _null;
            set begin nobs=nobs;
        call symput('DF',nobs-&p);
            call symput('NT',nobs);
          run;
    %if &combo=0 %then %do;
        %if &g1 > &thres %then %do;%delta(&n);%end;
        %else %do;%delta2p(&n);%end;

      %end;
    %else %if &cvstat2=0 %then %do;
```

```
        %do;%delta2p(&n);%end;
       %end;
    data c;
      set c;
        drop _type_ _status_ _name_ _iter_ _sse_;
      if &n > 1 & (&combo=0 | &cvstat2=0) then do;
        tc=tinv(0.975,&df);
          del=&sdevnew;
          if gamma > &thres then do;ci_h=tc*del;end;
        if ci_h ^=. & ci_h <= &binsize/2 & gamma ^=. then do;eps=0;end;
          else do; eps=1;end;
        call symput('eps',eps);
        if ci_h ^=. & ci_h <= 1 & gamma ^=. then do;eps2=0;end;
          else do; eps2=1;end;
        call symput('eps2',eps2);
      end;
      run;
%mend;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;
   %if &count >= 6 %then %do;call symput('done',3);%end;
   %if &eps = 0 %then %do;call symput('done',1);%end;
   %if &eps2 = 0 %then %do;
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
  run;
%mend;
%macro runum;
 %do m=&mstrt %to &mruns;
  %do j=1 %to &kount;
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;
    %let b1=&B1_I;
    %let g1=1;
      %let eps=1;
      %let eps2=1;
    %let count=0;
      %let dcnt=1;
    %sims_init(numi=&numi,seed=86019398+&j+&m);
    %testum(1);
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
     %testum(&k);
      %epschk(&k);
      %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin: proc append base=sims data=c force;run;
```

```
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
 %end;
%mend;
%runum;
proc sort data=sims;by knt;run;
proc print data=sims;run;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma B0 B1 TargetDose del dosecnt ci_h;
 run;
/*
 data ltest.sims55i3f3B1L;
  set ltest.sims55i3f3B1L sims;
 run;
 proc print data=ltest.sims55i3f3B1L;run;
 */
proc printto;run;
```

```
Non Linear logistic steep slope model, see Base model for complete
description of code;


%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj.LABS\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;

**************************************************************************
*****;
%let sdose= 1.25, 2.5, 5; *Intial starting dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=9; *Start for outer loop counter;
%let mruns=10; *Outer loop counter for se calc;
%let p=3; *Number of parameters to estimate;
%let g1=1; *Intial starting point for gamma;
%let eint=25; *Number of times to run the simulation for each NLIN run
(Inner Loop);
%let kount=100; *Number of iterations of the simulation (Outer Loop);
%let numi=3; *Number of active patients at each initial dose level;
%let numip=1; *Number of placebo patients at each initial dose level;
%let num=3; *Number of patients at each dose level;
%let nump=1; *Number of placebo patients at each dose level;
%let done=0; *Used for stopping rule;
%let binsize=1; *Smallest dose increase/decrease allowed after inital 3
doses;
**************************************************************************
******;

proc datasets library=work kill; quit;
%macro delta2p(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then ouput cvb;;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1} into covb;
    use prms; read all var {b0 b1} into parms;
    * Compute values of paritals for b0, and b1 for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(1-&thres))-parms[1])*(-1/(parms[2]#parms[2]));
      *Build parameter vector;
      beta=j(2,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      *Generate variance covariance matrix;
```

```
    delta=j(1,2,0);
    delta[1]=d_b0;
    delta[2]=d_b1;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
%macro delta(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use prms; read all var {b0 b1 gamma} into parms;
    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(parms[3]-&thres))-parms[1])*(-
1/(parms[2]#parms[2]));
    d_g=(-1/(parms[3]-&thres))*(1/parms[2]);
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
```

```
    delta[3]=d_g;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
/************************************************
  macros for generation of simulations

  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0461 gamma=0.6891, B0= -5, B1 = 1.8 are
  the estimates modified for steep B1 & smaller B0

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.6891/(1+exp(5-1.8*d));
    do i=1 to &numi;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
```

```
      output;
    end;
    mu = 0.6891/(1+exp(5));
    do i=1 to &numip;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;
%mend;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;
   mu = 0.6891/(1+exp(5-1.8*&dnew));
   do i=1 to &num;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
     if result <0 then result=0;
     tabs=&dnew;
     output;
   end;
    mu = 0.6891/(1+exp(5));
    do i=1 to &nump;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=sim force;
%mend;

/************************************
 Compute logistic values for input
 into reg to calculate starting values
************************************/
data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;
data _null_;
```

```
 set initial;
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
********************;

%macro testum(n);
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms b0=&b0 b1=&b1 gamma=&g1;
              mu=gamma/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     output out=pred p=pred&n;
     ods output ConvergenceStatus=conv;
    run;
    data _null_;
      set conv;
        call symput('cvstat',status);
      run;
      data _null_;
        set beta;
      hess=0;
        if trim(left(_name_)) in ("b0","b1","gamma") then do;
          if b0=. | b1=. | gamma=. then do;hess=1;end;
        end;
        call symput('hesstat',hess);
    run;
    %if &cvstat ^=0 %then %do;
       /***************************************
         If unable to estimate gamma then force
         gamma to be a value of 1.00
       ***************************************/
       proc nlin data=begin outest=beta noitprint;
          parms b0=&b0 b1=&b1;
              mu=1/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
          output out=pred p=pred&n;
          ods output ConvergenceStatus=conv2;
       run;
      data _null_;
        set conv2;
          call symput('cvstat2',status);
        run;
    %end;
      %else %if &hesstat=1 %then %do;
       /***************************************
         If Hessian is singular then force
         gamma to be a value of 1.00
```

```
    ****************************************/
    proc nlin data=begin outest=beta noitprint;
       parms b0=&b0 b1=&b1;
           mu=1/(1+exp(-1*(b0+b1*tabs)));
           _weight_=1/(mu*(1-mu));
           _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
       model result = mu;
       output out=pred p=pred&n;
       ods output ConvergenceStatus=conv2;
    run;
   data _null_;
    set conv2;
      call symput('cvstat2',status);
     run;
   %end;

     data _null_;
      call symput('combo',%eval(&cvstat+&hesstat));
   run;
   ods listing;

/*************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";
  %if &combo=0 %then %do;
       if gamma > &thres then do;
         tdose=(log(&thres/(gamma-&thres))-b0)/b1;
               TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
      end;
      if gamma <= &thres then do;
        tdose=(log(&thres/(1-&thres))-b0)/b1;
            DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
        if &n=1 then do;
          DoseC2=2*&fdose;
        end;
        else do;
         DoseC2=2*&dnew;
            end;
            TargetDose=max(of DoseC1,DoseC2);
```

```
          if TargetDose=DoseC2 then do;call
symput('count',%eval(&count+1));end;
         end;
       %end;
     %else %if &cvstat2=0 %then %do;
       tdose=(log(&thres/(1-&thres))-b0)/b1;
         DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
       if &n=1 then do;
         DoseC2=2*&fdose;
       end;
       else do;
         DoseC2=2*&dnew;
         end;
         TargetDose=max(of DoseC1,DoseC2);
       if TargrtDose=DoseC2 then do;call
symput('count',%eval(&count+1));end;
       %end;
       %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
       if &n=1 then do;
           TargetDose=2*&fdose;
        end;
        else do;
           TargetDose=2*&dnew;
           call symput('count',%eval(&count+1));
        end;
     %end;
       if iter > 1 & TargetDose=&dnew then do;
         call symput('dcnt',%eval(&dcnt+1));
       end;
       else do; call symput('dcnt',1);end;
    run;
   data c;
     set c;
       kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;
     call symput('b0',b0);
     call symput('b1',b1);
     %if &combo=0 %then %do;
         call symput('g1',gamma);
       %end;
     %else %do; %let g1=1;%end;
     call symput('dnew',TargetDose);
    run;
          data _null;
              set begin nobs=nobs;
          call symput('DF',nobs-&p);
              call symput('NT',nobs);
            run;
     %if &combo=0 %then %do;
         %if &g1 > &thres %then %do;%delta(&n);%end;
         %else %do;%delta2p(&n);%end;
       %end;
     %else %if &cvstat2=0 %then %do;
         %do;%delta2p(&n);%end;
```

```
      %end;
    data c;
      set c;
        drop _type_ _status_ _name_ _iter_ _sse_;
      if &n > 1 & (&combo=0 | &cvstat2=0) then do;
        tc=tinv(0.975,&df);
          del=&sdevnew;
          if gamma > &thres then do;ci_h=tc*del;end;
        if ci_h ^=. & ci_h <= &binsize/2 & gamma ^=. then do;eps=0;end;
          else do; eps=1;end;
        call symput('eps',eps);
        if ci_h ^=. & ci_h <= 1 & gamma ^=. then do;eps2=0;end;
          else do; eps2=1;end;
        call symput('eps2',eps2);
      end;
      run;
%mend;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;
   %if &count >= 6 %then %do;call symput('done',3);%end;
   %if &eps = 0 %then %do;call symput('done',1);%end;
   %if &eps2 = 0 %then %do;
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
  run;
%mend;
%macro runum;
 %do m=&mstrt %to &mruns;
  %do j=1 %to &kount;
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;
    %let b1=&B1_I;
    %let g1=1;
      %let eps=1;
      %let eps2=1;
    %let count=0;
      %let dcnt=1;
    %sims_init(numi=&numi,seed=86019398+&j+&m);
    %testum(1);
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
     %testum(&k);
      %epschk(&k);
      %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin: proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
```

```
  %end;
 %end;
%mend;
%runum;
proc sort data=sims;by knt;run;
proc print data=sims;run;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma B0 B1 TargetDose del dosecnt ci_h;
 run;
/*
 data ltest.sims55i3f3B1;
  set ltest.sims55i3f3B1 sims;
 run;
 proc print data=ltest.sims55i3f3B1;run;
 */
proc printto;run;
```

```
Michael-Menten model, see Base non-linear logistic model for complete
description of code;

%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj.LABS\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;
*****************************************************************2***
*****;
%let sdose= 1.25, 2.5, 5; *Intial starting dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=9; *Start for outer loop counter;
%let mruns=10; *Outer loop counter for se calc;
%let p=3; *Number of parameters to estimate;
%let g1=1; *Intial starting point for gamma;
%let eint=25; *Number of times to run the simulation for each NLIN run
(Inner Loop);
%let kount=100; *Number of iterations of the simulation (Outer Loop);
%let numi=1; *Number of active patients at each initial dose level;
%let numip=1; *Number of placebo patients at each initial dose level;
%let num=3; *Number of patients at each dose level;
%let nump=1; *0Number of placebo patients at each dose level;
%let done=0; *Used for stopping rule;
%let binsize=1; *Smallest dose increase/decrease allowed after inital 3
doses;
*****************************************************************
******;

proc datasets library=work kill; quit;
%macro delta2p(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" & upcase(_name_) in ("ALPHA","THETA") then
output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{alpha theta} into covb;
    use prms; read all var {alpha theta} into parms;
    * Compute values of paritals for b0, and b1 for each ED;
    d_a1 = -(parms[2])/(1 - &thres + parms[1])**2;
    d_t1 = (&thres-parms[1])/(1-&thres + parms[1]);
      *Build parameter vector;
      beta=j(2,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      *Generate variance covariance matrix;
```

```
    delta=j(1,2,0);
    delta[1]=d_a1;
    delta[2]=d_t1;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
%macro delta(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{alpha theta gamma} into covb;
    use prms; read all var {alpha theta gamma} into parms;
    * Compute values of paritals for alpha, theta and gamma for each ED;
    d_a1 = -(parms[2]#parms[3])/((parms[3] - &thres + parms[1])**2);
    d_t1 = (&thres-parms[1])/(parms[3]-&thres + parms[1]);
    d_g  = -(parms[2]*(&thres-parms[1]))/(parms[3] - &thres +
parms[1])**2;;
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_a1;
    delta[2]=d_t1;
```

```
    delta[3]=d_g;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
/************************************************
  macros for generation of simulations
  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0358 gamma=0.7752, ALPHA= 0.0592, THETA = 4.4556 are
  the estimates from the clinical trail data run

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.0592 + (0.7752*d)/(4.4556+d);
    do i=1 to &numi;
      result=mu+sqrt(0.0358*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
      output;
```

```
    end;
    mu = 0.0592;
    do i=1 to &numip;
      result=mu+sqrt(0.0358*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;run;quit;
%mend;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;
    mu = 0.0592 + (0.7752*&dnew)/(4.4556+&dnew);
   do i=1 to &num;
      result=mu+sqrt(0.0358*mu*(1-mu))*rannor(&seed);
     if result <0 then result=0;
     tabs=&dnew;
     output;
   end;
    mu = 0.0592;
    do i=1 to &nump;
      result=mu+sqrt(0.0358*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=sim force;run;quit;
%mend;

%macro testum(n);
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms  alpha=&b0 theta=&b1 gamma=&g1;
          mu = alpha + ((gamma*tabs)/(theta + tabs));
              _weight_= 1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     ods output ConvergenceStatus=conv;
    run;
    data _null_;
      set conv;
        call symput('cvstat',status);
      run;
      data _null_;
        set beta;
```

```
  hess=0;
    if trim(left(_name_)) in ("aplha","theta","gamma") then do;
      if alpha=. | theta=. | gamma=. then do;hess=1;end;
    end;
    call symput('hesstat',hess);
run;
%if &cvstat ^=0 %then %do;
   /***************************************
     If unable to estimate gamma then force
     gamma to be a value of 1.00
   ***************************************/
   proc nlin data=begin outest=beta noitprint;
      parms alpha=&b0 theta=&b1;
      mu = alpha + (tabs/(theta + tabs));
          _weight_=1/(mu*(1-mu));
          _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
      model result = mu;
      ods output ConvergenceStatus=conv2;
   run;
  data _null_;
    set conv2;
      call symput('cvstat2',status);
    run;
%end;
  %else %if &hesstat=1 %then %do;
   /***************************************
     If Hessian is singular then force
     gamma to be a value of 1.00
   ***************************************/
   proc nlin data=begin outest=beta noitprint;
      parms alpha=&b0 theta=&b1;
      mu = alpha + (tabs/(theta + tabs));
          _weight_=1/(mu*(1-mu));
          _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
      model result = mu;
      ods output ConvergenceStatus=conv2;
   run;
  data _null_;
   set conv2;
     call symput('cvstat2',status);
    run;
  %end;

    data _null_;
     call symput('combo',%eval(&cvstat+&hesstat));
  run;
  ods listing;

/************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
```

```
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";
  %if &combo=0 %then %do;

       tdose= theta*(&thres - alpha)/(gamma - &thres + alpha);
       if round(tdose,1) > 0 then do;
               TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
      end;
      if round(tdose,1) <= 0 then do;
        if &n=1 then do;
          DoseC2=2*&fdose;
        end;
        else do;
         DoseC2=2*&dnew;
            end;
            TargetDose=DoseC2;
        call symput('count',%eval(&count+1));
      end;
    %end;
  %else %if &cvstat2=0 %then %do;
    tdose=theta*(&thres - alpha)/(1 - &thres + alpha);
      if round(tdose,1) > 0 then do;
         DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
         TargetDose=DoseC1;
         end;
    if round(tdose,1) <= 0 then do;
      if &n=1 then do;
        DoseC2=2*&fdose;
      end;
      else do;
       DoseC2=2*&dnew;
        end;
        TargetDose=DoseC2;
      call symput('count',%eval(&count+1));
      end;
    %end;
    %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
    if &n=1 then do;
        TargetDose=2*&fdose;
     end;
     else do;
        TargetDose=2*&dnew;
        call symput('count',%eval(&count+1));
     end;
```

```
     %end;
       if iter > 1 & TargetDose=&dnew then do;
         call symput('dcnt',%eval(&dcnt+1));
       end;
       else do; call symput('dcnt',1);end;
    run;
   data c;
     set c;
       kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;
     call symput('b0',alpha);
     call symput('b1',theta);
     %if &combo=0 %then %do;
         call symput('g1',gamma);
       %end;
     %else %do; %let g1=1;%end;
     call symput('dnew',TargetDose);
    run;
          data _null;
              set begin nobs=nobs;
          call symput('DF',nobs-&p);
              call symput('NT',nobs);
            run;
     %if &combo=0 %then %do;
         %if tdose > 0 %then %do;%delta(&n);%end;
         %else %do;%delta2p(&n);%end;
       %end;
     %else %if &cvstat2=0 %then %do;
         %do;%delta2p(&n);%end;
       %end;
    data c;
      set c;
        drop _type_ _status_ _name_ _iter_ _sse_;
      if &n > 1 & (&combo=0 | &cvstat2=0) then do;
        tc=tinv(0.975,&df);
          del=&sdevnew;
          ci_h=tc*del;
        if ci_h ^=. & ci_h <= &binsize/2 /*& gamma ^=.*/ then
do;eps=0;end;
          else do; eps=1;end;
        call symput('eps',eps);
        if ci_h ^=. & ci_h <= 1 /*& gamma ^=.*/ then do;eps2=0;end;
          else do; eps2=1;end;
        call symput('eps2',eps2);
      end;
      run;
%mend;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;
   %if &count >= 6 %then %do;call symput('done',3);%end;
   %if &eps = 0 %then %do;call symput('done',1);%end;
   %if &eps2 = 0 %then %do;
```

```
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
  run;
%mend;
%macro runum;
 %do m=&mstrt %to &mruns;
  %do j=1 %to &kount;
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b1=4;
    %let b0=.1;
    %let g1=1;
      %let eps=1;
      %let eps2=1;
    %let count=0;
      %let dcnt=1;
    %sims_init(numi=&numi,seed=8601998+&j+&m);
    %testum(1);
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
     %testum(&k);
      %epschk(&k);
      %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin: proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
 %end;
%mend;
%runum;
proc sort data=sims;by knt;run;
proc print data=sims;run;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma alpha theta TargetDose del dosecnt ci_h;
 run;
/*
 data ltest.sims55michmen;
  set ltest.sims55michmen sims;
 run;
 proc print data=ltest.sims55michmen;run;
 */
proc printto;run;
```

```
Gompertz model, see Base non-linear logistic model for complete
description of code;

%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;
*************************************************************************2***
*****;
%let sdose= 1.25, 2.5, 5; *Intial starting dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=9; *Start for outer loop counter;
%let mruns=10; *Outer loop counter for se calc;
%let p=3; *Number of parameters to estimate;
%let g1=1; *Intial starting point for gamma;
%let eint=25; *Number of times to run the simulation for each NLIN run
(Inner Loop);
%let kount=100; *Number of iterations of the simulation (Outer Loop);
%let numi=1; *Number of active patients at each initial dose level;
%let numip=1; *Number of placebo patients at each initial dose level;
%let num=3; *Number of patients at each dose level;
%let nump=1; *Number of placebo patients at each dose level;
%let done=0; *Used for stopping rule;
%let binsize=1; *Smallest dose increase/decrease allowed after inital 3
doses;
*************************************************************************
******;

proc datasets library=work kill; quit;
%macro delta2p(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" & upcase(_name_) in ("B0","B1") then output
cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1} into covb;
    use prms; read all var {b0 b1} into parms;
    * Compute values of paritals for b0, and b1 for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(-log(&thres))+parms[1])*(1/(parms[2]#parms[2]));
      *Build parameter vector;
      beta=j(2,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      *Generate variance covariance matrix;
    delta=j(1,2,0);
```

```
    delta[1]=d_b0;
    delta[2]=d_b1;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;

    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;

  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
%macro delta(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use prms; read all var {b0 b1 gamma} into parms;
    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(log(parms[3]/&thres))+parms[1])*(1/(parms[2]#parms[2]));
    d_g=(-1/log(parms[3]/&thres))*(1/(parms[3]*parms[2]));
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
```

```
    delta[3]=d_g;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
/************************************************
  macros for generation of simulations
  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0461 gamma=0.6366, B0= -0.6804, B1 = 0.3812 are
  the estimates from the "TRUTH" from the profile
  using dose levels up to 4 Tablets

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.6366*(exp(-exp(0.6804-0.3812*d)));
    do i=1 to &numi;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
```

```
      output;
    end;
    mu = 0.6366*(exp(-exp(0.6804)));
    do i=1 to &numip;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;
%mend;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;
    mu = 0.6366*(exp(-exp(.6804-0.3812*&dnew)));
   do i=1 to &num;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
     if result <0 then result=0;
     tabs=&dnew;
     output;
   end;
    mu = 0.6366*(exp(-exp(.6804)));
    do i=1 to &nump;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=sim force;
%mend;

/*************************************
 Compute logistic values for input
 into reg to calculate starting values
*************************************/
data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;
data _null_;
```

```
 set initial;
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
********************;

%macro testum(n);
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms b0=&b0 b1=&b1 gamma=&g1;
          mu = gamma*(exp(-exp(-b0-b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     ods output ConvergenceStatus=conv;
    run;
    data _null_;
      set conv;
        call symput('cvstat',status);
      run;
      data _null_;
        set beta;
      hess=0;
        if trim(left(_name_)) in ("b0","b1","gamma") then do;
          if b0=. | b1=. | gamma=. then do;hess=1;end;
        end;
        call symput('hesstat',hess);
    run;
    %if &cvstat ^=0 %then %do;
       /***************************************
         If unable to estimate gamma then force
         gamma to be a value of 1.00
       ***************************************/
       proc nlin data=begin outest=beta noitprint;
          parms b0=&b0 b1=&b1;
          mu = (exp(-exp(-b0-b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
          ods output ConvergenceStatus=conv2;
       run;
      data _null_;
        set conv2;
          call symput('cvstat2',status);
        run;
    %end;
      %else %if &hesstat=1 %then %do;
       /***************************************
         If Hessian is singular then force
         gamma to be a value of 1.00
       ***************************************/
       proc nlin data=begin outest=beta noitprint;
```

```
      parms b0=&b0 b1=&b1;
      mu = (exp(-exp(-b0-b1*tabs)));
          _weight_=1/(mu*(1-mu));
          _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
      model result = mu;
      ods output ConvergenceStatus=conv2;
   run;
  data _null_;
   set conv2;
     call symput('cvstat2',status);
    run;
  %end;

    data _null_;
     call symput('combo',%eval(&cvstat+&hesstat));
  run;
  ods listing;

/*************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";
  %if &combo=0 %then %do;
       if gamma > &thres then do;
         tdose=(-log(log(gamma/&thres))-b0)/b1;
               TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
      end;
      if gamma <= &thres then do;
        if &n=1 then do;
          DoseC2=2*&fdose;
        end;
        else do;
         DoseC2=2*&dnew;
            end;
            TargetDose=DoseC2;
        call symput('count',%eval(&count+1));
      end;
    %end;
  %else %if &cvstat2=0 %then %do;
    tdose=(-log(-log(&thres))-b0)/b1;
      DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
```

```
      if &n=1 then do;
        DoseC2=2*&fdose;
      end;
      else do;
        DoseC2=2*&dnew;
        end;
        TargetDose=max(of DoseC1,DoseC2);
      if TargrtDose=DoseC2 then do;call
symput('count',%eval(&count+1));end;
      %end;
      %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
      if &n=1 then do;
          TargetDose=2*&fdose;
       end;
       else do;
          TargetDose=2*&dnew;
          call symput('count',%eval(&count+1));
       end;
     %end;
      if iter > 1 & TargetDose=&dnew then do;
        call symput('dcnt',%eval(&dcnt+1));
      end;
      else do; call symput('dcnt',1);end;
    run;
   data c;
     set c;
       kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;
     call symput('b0',b0);
     call symput('b1',b1);
     %if &combo=0 %then %do;
         call symput('g1',gamma);
       %end;
     %else %do; %let g1=1;%end;
     call symput('dnew',TargetDose);
    run;
          data _null;
              set begin nobs=nobs;
          call symput('DF',nobs-&p);
              call symput('NT',nobs);
            run;
     %if &combo=0 %then %do;
         %if &g1 > &thres %then %do;%delta(&n);%end;
         %else %do;%delta2p(&n);%end;
       %end;
     %else %if &cvstat2=0 %then %do;
         %do;%delta2p(&n);%end;
       %end;
    data c;
      set c;
        drop _type_ _status_ _name_ _iter_ _sse_;
      if &n > 1 & (&combo=0 | &cvstat2=0) then do;

        tc=tinv(0.975,&df);
```

```
          del=&sdevnew;
          if gamma > &thres then do;ci_h=tc*del;end;
        if ci_h ^=. & ci_h <= &binsize/2 & gamma ^=. then do;eps=0;end;
          else do; eps=1;end;
        call symput('eps',eps);
        if ci_h ^=. & ci_h <= 1 & gamma ^=. then do;eps2=0;end;
          else do; eps2=1;end;
        call symput('eps2',eps2);
      end;
      run;
%mend;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;
   %if &count >= 6 %then %do;call symput('done',3);%end;
   %if &eps = 0 %then %do;call symput('done',1);%end;
   %if &eps2 = 0 %then %do;
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
  run;
%mend;
%macro runum;
 %do m=&mstrt %to &mruns;
  %do j=1 %to &kount;
      %if &m=2 %then %if &j=22 %then %let j=%eval(&j+1);
      %if &m=4 %then %if &j=20 %then %let j=%eval(&j+1);
      %if &m=6 %then %if &j=18 %then %let j=%eval(&j+1);
      %if &m=8 %then %if &j=16 %then %let j=%eval(&j+1);
      %if &m=10 %then %if &j=14 %then %let j=%eval(&j+1);
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;
    %let b1=&B1_I;
    %let g1=1;
      %let eps=1;
      %let eps2=1;
    %let count=0;
      %let dcnt=1;
    %sims_init(numi=&numi,seed=86019398+&j+&m);
    %testum(1);
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
     %testum(&k);
      %epschk(&k);
      %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin:proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
```

```
 %end;
%mend;
%runum;
proc sort data=sims;by knt;run;
proc print data=sims;run;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma B0 B1 TargetDose del dosecnt ci_h;
 run;
/*
 data ltest.sims55gompertz;
  set ltest.sims55gompertz sims;
 run;
 proc print data=ltest.sims55gompertz;run;
 */
proc printto;run;
```

```
Base Logistic model plus safety addition, see Base non-linear logistic
model for complete description of code;

%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj.LABS\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;

*************************************************************************
*****;
%let sdose= 1.25, 2.5, 5; *Intial starting dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=1; *Start for outer loop counter;
%let mruns=1; *Outer loop counter for se calc;
%let p=3; *Number of parameters to estimate;
%let g1=1; *Intial starting point for gamma;
%let eint=25; *Number of times to run the simulation for each NLIN run
(Inner Loop);
%let kount=25; *Number of iterations of the simulation (Outer Loop);
%let numi=1; *Number of active patients at each initial dose level;
%let numip=1; *Number of placebo patients at each initial dose level;
%let num=3; *Number of patients at each dose level;
%let nump=1; *Number of placebo patients at each dose level;
%let done=0; *Used for stopping rule;
%let binsize=1; *Smallest dose increase/decrease allowed after inital 3
doses;
*************************************************************************
******;

proc datasets library=work kill; quit;
%macro delta2p(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" & upcase(_name_) ^= "GAMMA" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1} into covb;
    use prms; read all var {b0 b1} into parms;
    * Compute values of paritals for b0, and b1 for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(1-&thres))-parms[1])*(-1/(parms[2]#parms[2]));
      *Build parameter vector;
      beta=j(2,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      *Generate variance covariance matrix;
    delta=j(1,2,0);
```

```
    delta[1]=d_b0;
    delta[2]=d_b1;

      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
%macro delta(n);
  data cvb prms;
   set beta;
   if upcase(_type_)="COVB" then output cvb;
   if upcase(_type_)="FINAL" then output prms;
  run;
  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use prms; read all var {b0 b1 gamma} into parms;
    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(parms[3]-&thres))-parms[1])*(-
1/(parms[2]#parms[2]));
    d_g=(-1/(parms[3]-&thres))*(1/parms[2]);
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
    delta[3]=d_g;
```

```
      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
    *print beta;
    *print covb;
    *print var_ed;
    create devchk from var_ed [colname='vars'];
      append from var_ed;
  quit;
  run;
  %if &n=1 %then %do;
    data _null_;
        set devchk;
      call symput('sdevnew',vars);
    run;
  %end;
  %else %do;
    data _null_;
        set devchk;
      call symput('sdevold',&sdevnew);
        call symput('sdevnew',vars);
    run;
  %end;
  %put sdevnew: &sdevnew;
  %put sdevold: &sdevold;
  run;
%mend;
/************************************************
  macros for generation of simulations
  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0461 gamma=0.6891, B0= -2.296, B1 = 0.5979 are
  the estimates from the "TRUTH" from the profile
  using dose levels up to 4 Tablets

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.6891/(1+exp(2.296-0.5979*d));
    do i=1 to &numi;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
      output;
```

```
    end;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &numip;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;
%mend;
%macro sims(num,seed);
  %global sd;
  data sim;
   drop i mu;
   mu = 0.6891/(1+exp(2.296-0.5979*&dnew));
   do i=1 to &num;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
     if result <0 then result=0;

     tabs=&dnew;
     output;
   end;
    mu = 0.6891/(1+exp(2.296));
    do i=1 to &nump;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   call symput('sd',&seed);
  run;
  proc append base=b2 data=sim force;
%mend;
%macro safetychk(n,num,seed,dse);
  data aechk;
    retain aeY 0;
      if &n=2 then do d=&sdose;
        do i = 1 to &numi;
       mu = 1/(1+exp(-(d-12.5)/2.547));
         ae=ranuni(&seed);
         if ae <= mu then aeY+1;
         output;
        end;
      if aeY > 0 then call symput('aestop',1);
    end;
      else do;
       mu = 1/(1+exp(-(&dse-12.5)/2.547));
         do i=1 to &num;
           ae=ranuni(&seed);
           if ae <= mu then aeY+1;
```

```
          output;
        end;
        aepct=(&&AE&dse+aeY)/(&&BIN&dse+&num);
        call symput("aePCT",aepct);
        call symput("BIN&dse",%eval(&&BIN&dse+&num));
        call symput("AE&dse",&&AE&dse+aeY);
      end;
      if aeY > 0 then call symput('AEX',aeY);
      else call symput('AEX',0);
   run;
%mend;

data _null_;
 put "&AEPCT";
run;
/************************************
 Compute logistic values for input
 into reg to calculate starting values
************************************/
data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;
data _null_;
 set initial;
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
********************;


%macro testum(n);
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms b0=&b0 b1=&b1 gamma=&g1;
              mu=gamma/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     output out=pred p=pred&n;
     ods output ConvergenceStatus=conv;
    run;
    data _null_;
      set conv;
        call symput('cvstat',status);
```

```
  run;
  data _null_;
    set beta;
  hess=0;
    if trim(left(_name_)) in ("b0","b1","gamma") then do;
      if b0=. | b1=. | gamma=. then do;hess=1;end;
    end;
    call symput('hesstat',hess);
run;
%if &cvstat ^=0 %then %do;
   /****************************************
     If unable to estimate gamma then force
     gamma to be a value of 1.00
   ****************************************/
   proc nlin data=begin outest=beta noitprint;
      parms b0=&b0 b1=&b1;
          mu=1/(1+exp(-1*(b0+b1*tabs)));
          _weight_=1/(mu*(1-mu));
          _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
      model result = mu;
      output out=pred p=pred&n;
      ods output ConvergenceStatus=conv2;
   run;
  data _null_;
    set conv2;
      call symput('cvstat2',status);
    run;
%end;
  %else %if &hesstat=1 %then %do;
   /****************************************
     If Hessian is singular then force
     gamma to be a value of 1.00
   ****************************************/
   proc nlin data=begin outest=beta noitprint;
      parms b0=&b0 b1=&b1;
          mu=1/(1+exp(-1*(b0+b1*tabs)));
          _weight_=1/(mu*(1-mu));
          _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
      model result = mu;
      output out=pred p=pred&n;
      ods output ConvergenceStatus=conv2;
   run;
  data _null_;
   set conv2;
     call symput('cvstat2',status);
    run;
  %end;

    data _null_;
     call symput('combo',%eval(&cvstat+&hesstat));
  run;
  ods listing;
```

```
/*************************************************************
 Generate the new Target Dose from the parameter estimates
 from the NLIN logistic run.

 If gamma less than or equal to the threshold then the
 new dose is computed as two times previous dose.

 If gamma is greater than the threshold then the new dose is
 computed for the parameter estimates of the most recent
 NLIN run
*************************************************************/

data c;
  set beta;
  iter=&n;dosecnt=&n+2;knt=&m;
  if upcase(_type_)="FINAL";
  %if &combo=0 %then %do;
       if gamma > &thres then do;
         tdose=(log(&thres/(gamma-&thres))-b0)/b1;
               TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
      end;
      if gamma <= &thres then do;
        tdose=(log(&thres/(1-&thres))-b0)/b1;
            DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
        if &n=1 then do;
          DoseC2=&dmult*&fdose;
        end;
        else do;
         DoseC2=&dmult*&dnew;
            end;
            TargetDose=max(of DoseC1,DoseC2);
        if TargetDose=DoseC2 then do;
         call symput('count',%eval(&count+1));end;
        end;
    %end;
  %else %if &cvstat2=0 %then %do;
    tdose=(log(&thres/(1-&thres))-b0)/b1;
      DoseC1=round((round(tdose,1)/&binsize),1)*&binsize;
    if &n=1 then do;
      DoseC2=&dmult*&fdose;
    end;
    else do;
      DoseC2=&dmult*&dnew;
      end;
      TargetDose=max(of DoseC1,DoseC2);
    if TargrtDose=DoseC2 then do;
       call symput('count',%eval(&count+1));end;
    %end;
    %if &combo ^=0 %then %if &cvstat2^=0 %then %do;
    if &n=1 then do;
        TargetDose=&dmult*&fdose;
     end;
     else do;
```

```
        TargetDose=&dmult*&dnew;
        call symput('count',%eval(&count+1));
     end;
  %end;
    if iter > 1 & TargetDose=&dnew then do;
      call symput('dcnt',%eval(&dcnt+1));
    end;
    else do; call symput('dcnt',1);end;
 run;
data c;
  set c;
    kount=&count;convs=&cvstat;hessian=&hesstat;tc=0;ci_h=.;eps=1;
  call symput('b0',b0);
  call symput('b1',b1);
  %if &combo=0 %then %do;
      call symput('g1',gamma);
    %end;
  %else %do; %let g1=1;%end;
    %if &wallchk=1 %then %do;
      if TargetDose >= &wall then do;
       call symput('wallchk',0);
       call symput('dnew',&wall);
       call symput('wall',9999);
    end;
      else do;call symput('dnew',TargetDose);end;
  %end;
    %if &wallchk=0 %then %do;call symput('dnew',TargetDose);%end;
 run;
       data _null;
           set begin nobs=nobs;
       call symput('DF',nobs-&p);
           call symput('NT',nobs);
         run;
  %if &combo=0 %then %do;
      %if &g1 > &thres %then %do;%delta(&n);%end;
      %else %do;%delta2p(&n);%end;
    %end;
  %else %if &cvstat2=0 %then %do;
      %do;%delta2p(&n);%end;
    %end;
 data c;
   set c;
     drop _type_ _status_ _name_ _iter_ _sse_;
   if &n > 1 & (&combo=0 | &cvstat2=0) then do;
     tc=tinv(0.975,&df);
       del=&sdevnew;
       if gamma > &thres then do;ci_h=tc*del;end;
     if ci_h ^=. & ci_h <= &binsize/2 & gamma ^=. then do;eps=0;end;
       else do; eps=1;end;
     call symput('eps',eps);
     if ci_h ^=. & ci_h <= 1 & gamma ^=. then do;eps2=0;end;
       else do; eps2=1;end;
     call symput('eps2',eps2);
```

```
      end;
      run;
%mend;
%macro epschk(n);
  %global done;
  data _null_;
   %if &n >= 3 %then %do;
   %if &count >= 6 %then %do;call symput('done',3);%end;
   %if &eps = 0 %then %do;call symput('done',1);%end;
   %if &eps2 = 0 %then %do;
     %if &dcnt >= 3 %then %do;call symput('done',2);%end;
    %end;
   %end;
   %if &aestop =1 %then %do;call symput('done',4);%end;
  run;
  data c; set c; done=&done;run;
%mend;
%macro doseadj(n);
  %if &AEX >=1 %then %do;
     data _null_;
       call symput('wall',&dnew);
       call symput('aecnt',%eval(&aecnt+&AEX));
       call symput('wallchk',1);
     run;
     data c;
         set c;
         if &n=2 then do;n=2+(&k-1);end;
         else do;n=(&k-1)*3;end;
         ae_p=&aecnt/n;
         ndmult=&dmult*.5;
         newdose=min(TargetDose,&wall,&dnew);
         call symput('dnew',newdose);
       call symput('dmult',ndmult);
         if &aePCT >=1/3 then call symput('aestop',1);
         if ae_p >= 1/3 then call symput('aestop',1);
     run;
  %end;
%mend;
%macro runum;
 %do m=&mstrt %to &mruns;
  %do j=1 %to &kount;
    %let cvstat2=0;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;

    %let b1=&B1_I;
    %let g1=1;
      %let eps=1;
      %let eps2=1;
    %let count=0;
      %let dcnt=1;
```

```
      %let AEX=0;
      %let aePCT=0;
      %let aecnt=0;
      %let aestop=0;
    %let dmult=2; * Dose Multiplier;
      %let wall=9999;
      %let wallchk=0;
      data _null_;
        %do q=1 %to 50;
           call symput("BIN&q",0);
             call symput("AE&q",0);
        %end;
      run;
    %sims_init(numi=&numi,seed=86019398+&j+&m);
    %testum(1);
    %do k = 2 %to &eint;
      %sims(num=&num,seed=9302468+&m+&j*&k);
      %safetychk(n=&k,num=&num,seed=9302468+&m+&j*&k,dse=&dnew);
      %testum(&k);
      %doseadj(&k);
      %epschk(&k);proc append base=sims data=c force;run;
      %if &done ^=0 %then %do;%let done=0;%goto fin;%end;
    %end;
   %fin: proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
 %end;
%mend;
%runum;
proc sort data=sims;by knt;run;
proc print data=sims;run;
proc means data=sims n mean stderr min max clm;
 where kount^=6;
 by knt;
 var gamma B0 B1 TargetDose del dosecnt ci_h;
 run;
/*
 data ltest.sims55i3f1AE;
  set ltest.sims55i3f1AE sims;
 run;
 proc print data=ltest.sims55i3f1AE;run;
 */
proc printto;run;
```

```
Fixed Dose model, see Base non-linear logistic model for complete
description of code;

*%let path = f:\Disertation;
%let path= C:\Documents and Settings\davenpmj.LABS\My
Documents\School\Disertation;
libname ltest "&path";
proc printto log="&path\sim.log" new;run;
goptions reset=all;
goptions device=win rotate=landscape vsize=8 hsize=10.5 ftext=simplex;
options symbolgen macrogen mprint;

*************************************************************************
*****;
%let sdose= 0.5, 1, 2, 4, 8, 16; * dose levels;
*%let sdose= 1.25, 2.5, 5, 7, 6, 6, 5, 5, 5, 10; * dose levels;
%let fdose=5; *High starting dose level;
%let thres=0.55;
%let mstrt=1; *Start for outer loop counter;
%let mruns=10; *Outer loop counter for se calc;
%let p=3; *Number of parameters estimated;
%let kount=100; *Number of iterations of the simulation (Outer Loop);
%let numi=5; *Number of active patients at each dose level;
%let numip=1; *Number of placebo patients at each dose level;
%let binsize=1;
*************************************************************************
******;

proc datasets library=work kill; quit;

%macro delta;
  data cvb;
   set beta;
   if upcase(_type_)="COVB";
  run;
  proc iml;
    use cvb; read all var{b0 b1 gamma} into covb;
    use c; read point 1 var {b0 b1 gamma} into parms;
    * Compute values of paritals for b0, b1 and gamma for each ED;
    d_b0 = -1/parms[2];
    d_b1=(log(&thres/(parms[3]-&thres))-parms[1])*(-
1/(parms[2]#parms[2]));
    d_g=(-1/(parms[3]-&thres))*(1/parms[2]);
      *Build parameter vector;
      beta=j(3,1,0);
      beta[1,1]=parms[1];
      beta[2,1]=parms[2];
      beta[3,1]=parms[3];
      *Generate variance covariance matrix;
    delta=j(1,3,0);
    delta[1]=d_b0;
    delta[2]=d_b1;
    delta[3]=d_g;
```

```
      * Calculate variance of ED target;
    var_ed=delta*covb*delta`;
      sdev=sqrt(var_ed);
    *print beta;
    *print covb;
    *print var_ed sdev;
    create devchk from var_ed [colname='vars'];
      append from sdev;
  quit;
  run;
    data _null_;
        set devchk;
      call symput('sdevs',vars);
    run;
%mend;
/************************************************
  macros for generation of simulations
  the variance component (tau) is the variance
  observed from the given data using a non-linear
  logistic with a quasi-likelihood assumption of
  variance showing a bionomial distribution.

  tau= 0.0461 gamma=0.6891, B0= -2.296, B1 = 0.5979 are
  the estimates from the "TRUTH" from the profile
  using dose levels up 100 mg

  run with steep slope B1=1.8 and long shelp B0=-5

  resulting supression values can not be less
  than zero.
************************************************/

%macro sims_init(numi,seed);
  %global sd;
  data siminit;
   drop i mu d;
   do d=&sdose;
    mu = 0.6891/(1+exp(5-1.8*d));
    do i=1 to &numi;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=d;
      output;
    end;
    mu = 0.6891/(1+exp(5));
    do i=1 to &numip;
      result=mu+sqrt(0.0461*mu*(1-mu))*rannor(&seed);
      if result <0 then result=0;
      tabs=0;
      output;
    end;
   end;
```

```
   call symput('sd',&seed);
  run;
  proc append base=b2 data=siminit force;
%mend;

/************************************
 Compute logistic values for input
 into reg to calculate starting values
************************************/
data a;
 set ltest.masked;
 if result=0 then delete;
 if dose <=50;
 lres=log(result/(1-result));
 tabs=dose/5;
run;
proc reg data=a outest=initial noprint;
 model lres=tabs;
 run;
 quit;
data _null_;
 set initial;
 call symput('B0_I',Intercept);
 call symput('B1_I',tabs);
run;
********************;

%macro testum;
   data begin;set b2;run;
   ods listing close;
   proc nlin data=begin outest=beta noitprint;
     parms b0=&b0 b1=&b1 gamma=&g1;
              mu=gamma/(1+exp(-1*(b0+b1*tabs)));
              _weight_=1/(mu*(1-mu));
              _loss_=-(result*log(mu/(1-mu))+log(1-mu))/_weight_;
          model result = mu;
     ods output ConvergenceStatus=conv;
   run;quit;
   ods listing;

   data c;
     set beta;
     if upcase(_type_)="FINAL";tc=.;del=.;ci_h=.;knt=&m;
     if gamma > &thres then do;
        tdose=(log(&thres/(gamma-&thres))-b0)/b1;
            TargetDose=round((round(tdose,1)/&binsize),1)*&binsize;
     end;
    run;
       data _null;
        set begin nobs=nobs;
      call symput('DF',nobs-&p);
        call symput('NT',nobs);
       run;
```

```
       data _null_;
        set beta;
        if gamma <= &thres then do;%let g0=1;end;
        else do;call symput('g0',0);end;
    run;

      %if &g0=0 %then %do;
     %delta;
      data c;
        set c;
          tc=tinv(0.975,&df);
          del=&sdevs;
          ci_h=tc*del;
      run;
    %end;
%mend;

%macro runum;
  %do m=&mstrt %to &mruns;
   %do k=1 %to &kount;
    %let sdevnew=0;
    %let sdevold=0;
    %let dnew=0;
    %let b0=&B0_I;
    %let b1=&B1_I;
    %let g1=1;
    %sims_init(numi=&numi,seed=81193098+&k+10*&m);
    %testum;
    proc append base=sims data=c force;run;
    proc datasets library=work memtype=data;delete b2; quit;
  %end;
  %end;
%mend;
%runum;

data ltest.sim21fdt5p1v3;
 set sims;
run;
proc print data=ltest.sim21fdt5p1v3;run;
proc printto;run;

*proc print data=sims;run;
```

VITA

James Michael Davenport was born in Long Beach, California on August 28, 1958 and is a citizen of the United States of America residing in Ashland, Virginia. Prior earned degrees are a B.Sc., Mathematics in 1982 and an M.S., Statistics in 1984 both from the University of Arkansas in Fayetteville, Arkansas. Mike has more than 20 years of diverse clinical (GCP), preclinical (GLP) drug research/ development and device manufacturing experience for small and large pharmaceutical companies including 10 years at PPD Development. For the past 12 years Mike has had extensive experience in the pharmacokinetic aspects of drug development. Currently he is the Director of Biometrics and Clinical Pharmacology for PPD Development. A list of publications and presentations is listed below.

Dall, Desmond M.; Learmonth, Ian D.; Solomon, Michael I.; Miles, Anthony W.; Davenport J. Michael: Fracture and Loosening of Charnley Femoral Stems. J. Bone Joint Surgery (Br.), Vol. 75-b, No. 2, March 1993, pg. 259-265.

Solomon, Michael I.: Dall, Desmond M.; Learmonth, Ian D.; Davenport, J. Michael: Survivorship of Cemented Total Hip Arthroplasty in Patients 50 Years of Age or Younger. J. Arthroplasty, Vol. 7, Supplement 1992, pg. 347-352.

Jordan, Louis R.; Keblish, Peter A.; Collier, John; Greenwald, A. Seth; Davenport, J. Michael: Successful Use of a Metal-Backed Rotating Anatomic Patella in TKA: Biomechanical Rationale and Clinical Experience. Presented as an Exhibit and Paper at

the American Academy of Orthopaedic Surgeons meeting, San Francisco, California, 1993.

Sorrells, R. Barry; Fenning, John B.; Davenport, J. Michael: Comparison of the Clinical Results and Survivorship of Noncemented Cruciate Sacrificing Versus Cruciate Sparing Total Knee Replacements. Presented as an Exhibit and Paper at the American Academy of Orthopaedic Surgeons meeting, San Francisco, California, 1993.

Sorrells, R. Barry; Buechel, Frederick F.; Voorhorst, Paul E.; Peoples, Stephen J.; Davenport, J. Michael: Clinical Results and Survivorship of Cemented and Uncemented Cruciate Sacrificing Total Knee Replacements. Presented as an Exhibit and Paper at the American Academy of Orthopaedic Surgeons meeting, Washington, DC, 1992.

Rorabeck, Cecil H.; Kirk, Patrick G.; Kelman, David C.; Voorhorst, Paul E.; Davenport, J. Michael: Comparison of the Miller Galante I Total Knee Arthroplasty with Anatomic Modular Knee Total Knee Arthroplasty. Presented at the American Academy of Orthopaedic Surgeons meeting, Washington, DC, 1992.

James, Charles M.; Fenning, John B.; Davenport, J. Michael; Peoples, Stephen J.; Greenwald, A. Seth: Two to Five Year Clinical and Radiographic Results of a Cementless Porous Coated Acetabular Cup. Presented as an Exhibit and Paper at the American Academy of Orthopaedic Surgeons meeting, Anaheim, CA, 1991.

Davenport, J. Michael; Peoples, Stephen J.: Survival Analysis. Provided as handouts with Exhibits at American Academy of Orthopaedic Surgeons, Anaheim, CA, 1991; Washington, DC, 1992; and San Francisco, CA, 1993.

Davenport, J. Michael; Friddle, Nancy S.; Hastings, Cheryl K.; Peoples, Stephen J.: Voorhorst, Paul E.: Multicenter Clinical Results of Cemented and Cementless Mobile Bearing Total Knee Replacement -- The Cruciate Sacrificing LCS Knee. White paper, January 1992.

Dall, Desmond M.; Learmonth, Ian D.; Solomon, Michael; Davenport, J. Michael: 811 Charnley Hips Followed for 3-17 Years. Acta Orthopaedica Scandinavica, Vol. 64 (3), 1993, pgs. 252-256.

Gunsolley, J.C., Elswick, R.K., Davenport, J.M.: Equivalence and Superiority Testing In Regeneration Clinical Trials. J. Peridontology, Vol. 69 (5), 1998, pgs. 521-527.

Noonan, P.K., Davenport, J. M., Reynolds, L., Natarajan, S. BA/BE Assessment of Estradiol and Metabolites: Dependency on Analytical Methodology. Poster/Podium presentation. American Association of Pharmaceutical Scientists Annual Meeting, Indianapolis, IN. October 2000.

Noonan, P.K., Davenport, J. M.: Rate of Exposure and Other Metrics in BA/BE Studies. Poster/Podium presentation. American Association of Pharmaceutical Scientists Annual Meeting, Denver, CO, October 2001.

Christopher R., Davenport J.M., Gwaltney S., Kaldor S., Kassel D., Lee B., Navre M., Shi L., Stafford L., Xu R., Zhang Z. [452-P] Pharmacokinetic and Pharmacodynamic Profiles of SYR-322, a Novel Inhibitor of Dipeptidyl Peptidase-IV, in Rats, Dogs, and Monkeys. Poster presentation at the American Diabetes Association Annual Meeting, June 2006