

AN ADAPTIVE BAYESIAN APPROACH TO JOINTLY  
MODELING RESPONSE AND TOXICITY IN PHASE I  
DOSE-FINDING TRIALS

by

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University of Pittsburgh, 2007

Abstract

The Belmont Report (1979) presents ethical principles governing clinical research: respect for persons, beneficence, and justice. This dissertation attempts to improve beneficence, in particular, in early stage clinical trials, in three directions.

First, we develop a "dose-choice control panel" (DCCP) computer program. Inputs are complete population information and patient utilities. DCCP produces optimal dose assignment decisions, and helps users to explore how the population parameters and utilities affect the dose recommendation.

Second, we present a new adaptive Bayesian method for dose-finding in phase I clinical trials based on both response and toxicity. Although clinical responses are rare in cancer trials, biological responses may be common and may help decide how aggressive a phase I escalation should be. The model assumes that response and toxicity events happen depending on respective dose thresholds for the individual, assuming that the thresholds jointly follow a bivariate log-normal distribution or a mixture. The design utilizes prior information about the population threshold distribution as well as accumulated data. The next dose is assigned to maximize expected utility integrated over the current posterior distribution. The design is evaluated in a setting inspired by the Gleevec story, with population parameters equaling estimates from early

Gleevec trials. This exercise provides evidence for the value of the use of the proposed design for future clinical trials.

Third, we propose an adaptive Bayesian design based on a hierarchical pharmacokinetics/pharmacodynamic (PK/PD) model, incorporating prior knowledge and/or patient-specific measurements related to PK/PD processes. Because genetic variations or drug co-administration can lead to huge inter-individual differences in drug efficacy and toxicity, it is desirable to individualize chemotherapy dosage. Those factors influencing drug metabolism and clearance are expected to affect all PD processes downstream, leading to efficacy and toxicity outcomes, while other genetic variations or drug co-administration may affect only one PD process. Application of the design to the Gleevec and Irinotecan settings is encouraging with regard to patient protection and accuracy of estimates.

This work could improve public health by providing more accurate answers quicker, and by encouraging accrual through explicit consideration of what is best for each individual patient.

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## 1.0 INTRODUCTION

### 1.1 STATEMENT OF PROBLEM

Phase I clinical trials, generally defined as dose-finding trials, have their primary goal as the discovery of the maximum tolerated dose (MTD), which is recommended for the phase II trials to test efficacy. Both physicians and experiment researchers hope the agents demonstrate some anti-tumor effects, serving as part of rationale for launching phase II trials. However, conventional clinical response is not necessarily a useful indicator of clinical benefit. Some agents have no toxic effects at doses which provide desired biologic effects or clinical benefit, while increasing the doses of some agents may not always provide additional benefit. Traditional phase I clinical trial designs which just consider toxicity may not be effective in exploring new, potentially beneficial anti-cancer drugs.

While biomarkers may not provide true surrogate endpoint information, they are still useful because they may provide evidence that the drug has the hoped-for potential. Although changes in biomarkers during therapeutic intervention would not assist directly in the drug approval process, they may help justify proceeding to phase II trials. If an agent is safe and well-tolerated, but has no any effect on biomarkers, it may be a counterindication for phase II commitment. Consideration of toxicity alone may not be enough for dose-finding in phase I clinical trials. Augmenting toxicity data with biological endpoint data might be important.

Because genetic variations or drug co-administrations can lead to huge inter-individual differences in drug efficacy and toxicity, so it is desirable to individualize therapy. Before patient enrollment or dosage assignment, some patient specific characteristics may have already been identified to have influence on PK or PD process. These characteristics may

not lead to a dramatic difference in response or toxicity, but at least they indicate that this known information has some potential to protect patients if incorporated in the dose-finding process. The consideration of known patient information is necessary for dose-finding in phase I clinical trials. Those factors influencing drug metabolism are expected to affect all pharmacodynamic (PD) processes downstream, including both efficacy and toxicity, while other genetic variations or drug co-administrations may affect only one PD process. This suggests that a hierarchical model could help in designing an improved phase I trial incorporating specific measurements related to PK/PD processes and prior belief. On the other hand, phase I trials are small and may not contain enough information to support a highly adaptive design. The question is whether such a design could be helpful.

Although the study of dose-escalation procedures that take both response and toxicity into account is relatively new, studies of dose-escalation algorithms based only on toxicity are plentiful. These methods are divided into two categories according to different underlying philosophies in designing trials: rule-based algorithms [Storer (1989); Korn *et al.* (1994); Goodman *et al.* (1995); Molley *et al.* (1995); Durham, Flournoy and Rosenberger (1997); Simon *et al.* (1997); Leung and Wang(2001); Ivanova *et al.* (2003)], and model-based algorithms [O’Quigley *et al.*(1990); Babb *et al.* (1998), Whitehead and Brunier(1995); Gasparini and Eisele(2000); Potter (2002); Haines *et al.*(2003) ]. In general, the rule-based designs, easy to implement, are widely used in phase I clinical trials. They produce an ad-hoc estimate of the target dose, which produces a specified target toxicity probability. However, the rule-based methods do not readily yield a measure of the target dose’s accuracy. To obtain a measure of accuracy, model-based designs have been proposed in the past decade.

Some recent studies in phase I clinical trials focus on the consideration of both toxicity and efficacy [ Gooley *et al.* (1994); Thall and Russell(1998); O’Quigley, Hughes, and Fenton(2001); Braun *et al.*(2002); Thall and Cook (2004); Bekele and Shen (2005); Loke *et al* (2006) ]. All of the model-based adaptive designs introduce specific probability models to explain the relationship between dose and bivariate outcome, update the knowledge as relevant response and toxicity data accumulate, and then use this information to guide the next dose assignment. The designs are considered in the Bayesian framework, but then the operating characteristics are evaluated and ad hoc fixes are possibly introduced. All of these

indicate the designs are not full Bayesian approaches which should be decision-analytic, by combining a utility function with Bayesian posterior probabilities to form Bayesian expected utility and then to make a Bayesian decision through the maximization of Bayesian expected utility.

## 1.2 OBJECTIVE OF THE STUDY

One objective of this dissertation is to develop a "dose-choice control panel" (DCCP) for exploring decisions based on the threshold population model, and then propose a new adaptive Bayesian approach to jointly modeling response and toxicity in phase I dose-finding trials based on the solid foundation of Bayesian decision theory to address ethical concerns in phase I studies. In addition, genetic variations or drug co-administration could lead to huge inter-individual differences in drug efficacy and toxicity, making it desirable to individualize dosage according to patients' specific information. Those factors influencing drug metabolism are expected to affect all pharmacodynamic (PD) processes downstream, including both efficacy and toxicity, while other genetic variations or drug co-administrations may affect only one PD process. A hierarchical model is proposed to improve phase I trials by incorporating specific known information and prior belief. This dissertation is organized in three parts: one is the development of DCCP; the second is an adaptive Bayesian approach to jointly modeling response and toxicity in phase I dose-finding trials, and the third is knowledge-directed Bayesian design in phase I dose finding trials. The dissertation addresses the following main goals:

1. To propose a new joint model for response and toxicity thresholds;
2. To develop a "dose-choice control panel" (DCCP) for exploring decisions;
3. To develop a new adaptive Bayesian dose-finding design based on the model;
4. To compare the new design with standard designs with regard to the accuracy with optimal dose estimate and protection of patients;
5. To extend the binary outcome case to categorical outcomes;
6. To check the design robustness when thresholds follow a mixture model;

7. To apply the proposed design to Gleevec data;
8. To propose a hierarchical PK/PD model incorporating patient specific measurements related to PK/PD processes;
9. To apply this hierarchical modeling to Gleevec and Irinotecan data to check the design performance.

## 2.0 PREVIOUS APPROACHES IN PHASE I CLINICAL TRIALS

### 2.1 SINGLE OUTCOME DESIGNS

Traditional phase I trials are based on the following assumptions: 1) The clinical benefit of the drugs increases with doses increasing; 2) The toxicity of drugs increases with doses increasing; and 3) A dose which can give maximum clinical benefit with acceptable toxicity exists. Moreover, since clinical response in phase I trials are uncommon, traditional phase I clinical trials just measure the toxicities and then determine the maximum tolerated dose(MTD) which would be passed to phase II trials to test the efficacy.

Single outcome phase I trial designs based only on toxicity can be divided into two categories according to different underlying philosophies in designing the trials: rule-based design and model-based design. If the trials are designed assuming that the MTD could be obtained from the real data, only the specific dose-escalation rule is required during the whole trial and no statistical model is needed; these designs are then called rule-based designs. If the trials are designed assuming that the MTD should be estimated from the probability model using real data, a statistical model is required; these designs are called model-based designs.

#### 2.1.1 Rule-Based Designs

Rule-based designs, which only need a dose-escalation rule with no complicated statistical modeling, are simple to understand, easy to implement, and widely used in phase I clinical trials. The simple rule-based design is current standard design in phase I trials and is sometimes called "conventional design" [1].

The standard design, was first proposed for testing explosives by Anderson, McCarthy and Tukey[2], and then shown to have good property on the estimators of the median by Dixon and Mood[3, 4]. It begins with the first cohort (3 patients) at a lowest dose level often one-tenth of the  $LD_{10}$  (10% of lethal dose) in mice, which is expected to have no significant toxicity. If there is no toxicity, escalation occurs; this leads to a cohort of three patients being treated at the next higher dose level. Otherwise, an additional cohort of three patients are treated at the same dose level. Should only one of six have toxicity, escalation continues for the next cohort of three patients. Should at least two out of six patients experience toxicity, or at least two out of three patients experience toxicity in the initial cohort treated, the next three patients should be treated at the lower dose. This algorithm iterates and defines the MTD as the highest dose in which a maximum of one out of six patients experiences toxicity, meaning the highest dose with less than 1/3 toxicity. The data identify the MTD; with no statistical estimation needed, the standard design is very simple to implement.

Recent literature reports that the standard design has very poor operating characteristics [5, 6, 7, 8, 9, 10, 11, 12, 13]. One problem with the standard design is that many patients are treated at low, possibly ineffective dose levels when the initial dose level falls far below the true MTD. Another problem of the standard design is the large variability of the estimated MTD around the true MTD. The major criticism of the standard design is that it has no intrinsic property producing accurate estimates of a target quantile.

Storer compared the standard design with several simple alternatives with regard to the conservativeness of the design and the point and interval estimation of an MTD(33rd percentile) with small sample sizes. He also made two important modifications[11, 14]. He initially proposed a two-stage design. The first stage escalates doses using single patients until the first toxicity occurs; this launches second stage, which uses three-patient cohorts beginning at the next lower dose level. The two-stage design performs better than the single-stage designs, but the first stage using single patient cohorts is too aggressive; single-patient designs are also considered uncomfortable because of the variability of patients in clinical settings. Storer's second modification defines the MTD as the dose corresponding to a pre-specified toxicity probability  $\Gamma$ . In his paper, he suggested  $\Gamma = 1/3$  and proposed a logistic regression model to fit the toxicity data. The two parameters estimated from the logistic

model then determine the MTD. Although MLEs of the logistic parameters, and hence the MTD, have desirable large-sample properties, in small-sample settings this method is not well-behaved.

Standard designs rely on the rules of escalation and de-escalation, but not are designed around the target quantile. Storer's modified designs target the quantile corresponding to  $\Gamma = 1/3$ , although its intrinsic small sample properties are not desirable.

Derman (1957)[15] first demonstrated that dose levels could be centered around given quantile by randomizing the standard designs using a biased coin. Tsutakawa(1967, 1972)[16, 17] analyzed the standard design using random walk theory. Durham and Flournoy (1994)[18] described family designs where the patients are sequentially assigned to next higher, same, or lower dose level with some probability depending on the previous patients' responses. Actually, these designs are a broad extensions of standard design. Durham, Flournoy and Rosenberger (1997)[19] proposed an appropriate random walk rule for phase I clinical trials. Patients are sequentially assigned to the next higher, same or next lower dose level according to some probability distribution, which may be determined by ethical considerations as well as the patients' responses. For example, if patient  $j$  has been assigned to dose level  $x_i$ , then assign patient  $j + 1$  with the following rule: If patient  $j$  experiences a toxic response, then assign patient  $j + 1$  to level  $x_{i-1}$ ; If patient  $j$  has no toxicity, then flip a biased coin with probability of heads-up  $b$ ; If it lands head up, assign patient  $j + 1$  to level  $x_{i+1}$ , but if it lands head down, assign patient  $j + 1$  to  $x_i$ . Durham and Flournoy(1994)[18] showed that if  $b = \Gamma/(1 - \Gamma)$ , the asymptotic frequency distribution of dose assignments will be unimodally distributed around  $\mu$ , with the maximum dose level deemed tolerable. For instance, to target the 33rd percentile of the dose-response curve, select  $b = 1/2$ ; to target the 25th percentile, select  $b = 1/3$ . Durham *et al.* mentioned that the random walk rule is particularly attractive for phase I trials for several reasons: 1) The designs are simple to implement; 2) Exact finite and asymptotic distribution theory is completely worked out, allowing the experimenter to choose design parameters for the most ethical allocation scheme; and 3) Specific designs can allow the chosen design points to be distributed unimodally around a quantile of interest.

Simon *et al.*(1997)[1] proposed accelerated titration designs for phase I clinical trials in oncology. His study evaluated four designs. Design one is a standard design using a cohort

of three to six patients. Design two through design four are two stage-designs that use a single patient cohort in the first stage. Once the observation of the first dose limiting toxic effect or two grade 2 toxic effects (during their first course of treatment or during any course of treatment) occurs, the second stage using a standard design is launched. Design two through four use inpatient dose escalation if the worst toxicity is grade 0-1 in the previous course for that patient during both stages. Moreover, Simon *et al.* suggested a new method to fit the data by using the following notation:  $y_{ij} = \log(d_{ij} + \alpha D_{ij}) + \beta_i + \epsilon_{ij}$ , where  $y_{ij}$  is a latent variable denoting the toxicity experienced by  $i$ th patient during  $j$ th course,  $d_{ij}$  is the received dose by  $i$ th patient during  $j$ th course,  $D_{ij}$  is the total dose for courses previous to  $j$ ,  $\beta_i$  is a random patient effect and  $\epsilon_{ij}$ , error term, denotes the inpatient variability in toxic response for  $i$ th patient during course  $j$ . If  $y_{ij}$  is less than a specified constant  $K_1$ , then patient  $i$  is considered to have experienced less than grade 2 toxicity during course  $j$ ; if  $K_1 \leq y_{ij} < K_2$ , then grade 2 toxicity occurs; if  $K_2 \leq y_{ij} < K_3$ , then grade 3 toxicity occurs; if  $y_{ij} \geq K_3$ , then grade 4 toxicity occurs.  $\alpha, K_1, K_2, K_3$  are estimated from the fitting process. The accelerated titration designs have several advantages compared to standard design: average number of patients required for phase I trials are smaller, and fewer patients are treated at lower and untreated doses. However, accelerated titration designs are more aggressive than standard design due to the rapid escalation in the first stage, and within patient dose escalation may mask some treatment effects.

Leung and Wang (2001)[20] proposed a model-free design based on the assumption that the probability of toxicity is nondecreasing with increasing dose. The isotonic regression is fitted using cumulative subject information, and then  $q$ , the proportion of patients experiencing toxicity at each dose level, is estimated. The next patient is assigned to the dose at which  $q$  is closest to the target quantile. Simulation results show this method performs much better than commonly used methods.

Ivanova *et al.* (2003) [21] proposed three improved up-and-down designs using more information than the most recent responses, two of which are based on the "k-in-a-row" and one of which is based on "Narayana rule". The proposed methods target the dose for which  $\tau = 1 - (0.5)^{1/k}$ , where  $k$  is the number of patient, defined by researchers. The "k-in-a-row" rule is as follows: If the last response is toxic, the next patient is assigned to the next lower

dose level; if the  $k$  most recent patients are assigned to the same dose level and no toxicities are observed, then the next patient is assigned to the next higher dose level; otherwise, the next patient is assigned to the same dose level. The "Narayana rule", based on  $R$  and presented by the fraction of observed toxicities at the given dose level, is as follows: If  $R > \tau$  and at least one patient has toxicity among the last  $k$  patients at the current dose level, the next patient is assigned to the next lower dose level; if  $R < \tau$  and no patient has toxicity among the last  $k$  patients at the current dose level, the next patient is assigned to the next higher dose level; otherwise, the next patient is assigned to the current dose level. The results show that "Narayana rule" has a good property because the probability of assignment tends to zero for dose levels not closer to the target. As a result, the "Narayana rule" is better than the "k-in-a-row" rule and other designs. Many other rule-based designs have already been proposed, including the stochastic approximation methods( Robbins and Monro, 1951 [22]), but these methods are not widely used.

In general, the rule-based designs, easy to implement, are widely used in practice. Standard designs have especially become the standard methods in phase I clinical trials. Yet the rule-based methods are not designed to produce the accurate estimate which has target probability. In the past decade, therefore some model-based designs have also been proposed with the intention of producing an accurate estimate of target quantile.

### 2.1.2 Model-Guided Designs

The MTD, defined as a dose level that has certain acceptable toxicity probability, can be obtained by estimation. Many statistical designs for phase I trials have been proposed. For example, Storer[11] is the first one who suggested using a logistic regression model to get the MTD which targets the 33rd quantile, O'Quigley *et al.*[9] proposed a continual reassessment method(CRM), Babb *et al.*[31] proposed an Escalation With Overdose Control(EWOC) method, Gasparini and Eisele (2000)[35] proposed a curve-free CRM, and Whitehead and Brunier(1995)[32] introduced decision theoretic approaches.

O'Quigley *et al.* (1990) [9] proposed the continual reassessment method(CRM), the first one introducing Bayesian flavor to phase I clinical trials. Shen and O'Quigley(1996) [23]

further explored some basic asymptotic characteristics. The fundamental idea in the original CRM is to always treat patients at the dose level at which response probability, according to current knowledge, is closest to the desired level. This method proposes a dose-response function with one free parameter. The posterior mean of this parameter is updated using the prior information about the parameter, prior guesses about the probabilities of toxicity at each dose level, and all available patients' toxicity data. Probabilities of toxicity at each dose level are then computed and the dose at which the probability of toxicity is closest to the target quantile is assigned to the next patient.

Much of the recent literature reports properties of CRM using simulations[24, 7, 12, 25, 26, 10]. CRM has several attractive properties. One is its quantitative explanation for the probability of toxicity for the MTD. The second is its utilization of prior information about the possible toxicity at each dose level. The third is its small number of patients assigned to lower, ineffective doses. The original CRM also has several problems. One is the assignment of initial dose level. The original CRM assigns the first patient to the dose determined by prior information, usually above the lowest dose level. Most clinicians think that starting above the lowest dose is somewhat aggressive and impractical. The second problem is that the original CRM method allows the escalation of more than one dose level at a time. This raises some concern about whether the new dose level will be too toxic, although O'Quigly *et al.* suggested that this is not the case. Thirdly, because the cohort size is 1, the single patient study would take long to complete since one needs know the responses to the assigned doses of the previously entered patient before assigning the next patient. Korn *et al.* (1994) [25] and Goodman *et al.* (1995)[12]made some modifications of the original CRM; they suggested starting the study at the lowest dose level, prohibiting escalation of more than one level at a time, and stopping when a fixed number of patients had been treated at the same dose. They also suggested assigning one or more patients at each dose level to reduce the number of cohorts to complete trials. These authors provided extensive simulations to compare their CRMs to the traditional rule-based method. Concluding that two- and three-patient designs have the advantage of less toxicity and shorter study duration, they recommended two- and three-patient designs. The original CRM which has been criticized because it often tends to allocate highly toxic doses to many patients, led Ishizuka and Ohashi(2001) [27] to

propose using a mean toxicity probability  $Pr(toxicity|dose_i)$  with prior density, instead of approximate mean toxicity probability  $Pr(toxicity|dose_i)'$  with prior mean which does not reflect any variability in prior distribution. They did some simulations whose results show that the first method tends to allocate a smaller number of patients to doses higher than the maximum tolerated dose(MTD) compared with the original method.

In regard to stopping rules of CRM, Korn *et al.*[25] proposed terminating a trial if a pre-specified number of patients has been treated at the same dose level. O'Quigley *et al.* (1998) [28] discussed the stopping rule for the continual reassessment method based on the idea that continuing the study would not lead to a change in recommendation with high probability. Heyd and Karlin(1999) [29] proposed ending trials if the estimated MTD has a specified high precision. O'Quigley (2002)[30] suggested a new simple stopping rule that terminates the trials when the dose recommended to the next patient has already been allocated  $m$  times, where  $m$  is a number fixed at the beginning of the trial.

Babb et al (1998)[31] suggested an escalation with overdose control(EWOC)method. The method is fully adaptive, makes use of all the information available at the time of dose assignment, and directly addresses the ethical need to control the probability of overdosing. The authors introduced a logistic dose-toxicity model  $logit\{Pr(toxicity|dose = x)\} = \beta_0 + \beta_1x$ , where  $x$  is assigned dose,  $\beta_0$  and  $\beta_1$  are unknown parameters. The posterior joint distribution of  $\beta_0$  and  $\beta_1$  is transformed to a joint distribution of  $\gamma$  (MTD) and  $\rho_0$ (the probability of toxicity at the starting dose  $x_1$ ). The first patient receives the lowest dose, while the dose for each subsequent patient is based on the posterior marginal probability that the dose exceeding the MTD is equal to the feasibility bound,  $\alpha$ , given all of the available data. Upon completion of the trial, the MTD is estimated by minimizing the posterior expected loss with respect to a loss function. The authors also compared EWOC with four up-and-down designs, two stochastic methods, and CRM. The simulation results show that relative to CRM, EWOC overdoses a smaller proportion of patients, exhibits fewer toxicities, and estimates the MTD with slightly lower average bias and marginally higher mean square error. Relative to non-parametric methods, EWOC treats fewer patients at either subtherapeutic or severely toxic dose levels, but treats more patients at an optimal dose level.

The CRM and EWOC, two examples of Bayesian designs, are designed for different directions. The CRM assigns the dose closest to the target quantile(MTD) to the next cohort, while the EWOC passes the dose at which overdose probability is less than the pre-specified level for subsequent patients.

Whitehead and Brunier(1995)[32] proposed a decision theoretic approach for phase I trials. Similar to EWOC, their two-parameter model has a prior distribution on the parameters. The dose is picked at each stage by minimizing the asymptotic variance of the maximum likelihood estimator of MTD ( $\hat{\mu}$ ). Whitehead and Williamson (1998)[33] compared the performance of the minimum variance loss function with the original CRM loss function. The simulation results show that there is little difference in the operating characteristics. However, Sun and Tsutakawa [34] reported that the decision theoretic approaches based on the posterior variance of ( $\hat{\mu}$ ) from a logistic model tend to produce larger sampling variability, and thus the posterior variance is an undesirable criterion for design selection.

Gasparini and Eisele(2000)[35] introduced a curve-free CRM. The prior guess about the probability of toxicity  $Pr[T_i]$  at each dose level is elicited. Statistical model  $\theta_i = (1 - Pr[T_{i+1}])/(1 - Pr[T_i])$  is used with prior beta distribution on  $\theta_i$ . Then  $\theta_i$  is updated using the cumulative data information,  $Pr[T_i]$  as well. The dose allocation rule is similar to the original CRM. The simulation results show that a curve-free CRM tends to treat fewer patients at excessively toxic doses than the original CRM, but is otherwise comparable. O’Quigley(2002)[36], after comparing the curve-free CRM with the original CRM, stated that the two methods are operationally equivalent.

Potter(2002)[37] proposed a two-stage adaptive dose finding algorithm. In the first stage, doses are escalated by a factor of 1.5, and in the second stage doses are determined by a two-parameter logistic dose-response model which begins at the first instance of DLT. Setting the dose ( $d_{10}$ ) at which 10 percent of patients would experience DLT to half the dose at which the first DLT was observed and the dose( $d_{90}$ ) at which 90 percent would experience DLT to ten times  $d_{10}$  initializes the model. The performance of the new method was compared to that of rule-based methods.

Haines *et al.*(2003) [38] proposed a Bayesian design which involves constraints incorporating the optimal design points and their weights. This unified approach, which draws

ideas from decision theoretic approach by Whitehead and Brunier(1995)[32] and EWOC by Babb(1998)[31], addresses both the efficiency of estimation and the protection of patients from being assigned to highly toxic doses.

The above model-based methodologies have some similar design logic. They introduce a statistical model with some specific prior distributions on parameters, update the parameters using cumulative data information, and then allocate a dose according to certain loss function.

Model-based designs, which are widely explored, have many good properties, such as producing accurate estimates of target quantile and putting fewer patients at lower and untreated dose level. Yet, they also have the following drawbacks: 1) Special statistical model assumption beyond the regular assumption that dose-toxicity relationship is nondecreasing is required. Only if the assumptions are satisfied do the model-based methods perform well; 2) Because they are involved with complicated modeling and computational challenges in implementation, it is not easy to explain model-based designs to non-statistician researchers; and 3) Most model-based designs incorporate prior information, creating a concern about the elicitation of priors in the implementation of trials. In practice, the rule-based designs still dominate in phase I trials for two main reasons: 1) They are easy to implement; 2) No special modeling assumptions are required beyond a regular assumption that toxicity is non-decreasing with dose increasing.

## 2.2 BIVARIATE OUTCOME DESIGNS

The practice of design and implementation of phase I trials widely accept traditional clinical trial assumptions. Therefore, most statistical methods for dose-finding in phase I clinical trials determine the MTD based on the toxicity, while ignoring the response.

Although phase I clinical trials are generally defined as dose-finding trials, both the physicians and experiment researchers hope the agents demonstrate some anti-tumor effects to serve as their rational for launching phase II trials. Patients who participate in anti-cancer agent phase I trials suffer from different types of cancer; having typically exhausted

other therapeutic alternatives, they treat this as a last resort. As a result, the design and implementation of phase I clinical trials must take into account the patients' vulnerability and input.

The clinical benefit of an agent typically increases with a higher dose. While clinical benefit rarely decreases with a dose increase, some agents do have a clinical benefit plateau. If the clinical benefit plateau with an increasing dose is real for a particular agent, it is foolish to still recommend the maximum tolerated dose which has the almost same clinical benefit as the relatively lower dose. Korn [39] explored some reasons a maximum dose should not be used in this kind of situation. He first explained that the agent might be in short supply, although typically the shortage would probably be only a temporary problem. Korn also stressed that some agents will require longer-term treatment. Because phase I trials typically incorporate only short-term toxicity, long-term administration may not be required for some agents; even if long-term administration is needed, a superior strategy might be to choose a dose that is one or two doses levels below the maximum dose, but still sufficiently active. In deciding the dose that would be passed to phase II trials in this situation, both toxicity and clinical response should be taken into account.

The rapid development of molecular biology, cancer genetics, and technology makes available non-cytotoxic agents, which seem to be nontoxic at doses that achieve concentrations with desired biologic effects. Consequently, Stadler *et al.* [40] suggested a dose-escalation trial incorporating a biologic end point for the agent in addition to toxicity. Parulekar and Eisenhauer [41], after exploring this possibility for targeted, non-cytotoxic agents, reported the survey results of completed phase I trials using such agents. They found that in determining the recommended phase II dose from phase I trials, the primary basis for the recommendation is still toxicity in the majority of trials. Only two trials out of 60 used a targeted endpoint or surrogate tissue finding as the primary basis for determining the recommended phase II dose. The main reason why so few trials consider both toxicity and non-toxicity endpoints is that it is difficult to define the desired target effect in phase I trials.

From an ethical perspective, phase I trials should consider both toxicity and response, no matter which type of response occurs: clinical response, surrogate marker or regular biomarkers response. For example, in a trial of bone marrow transplantation, response

might be the nonrejection of the graft with toxicity the occurrence of graft vs.host disease. Alternatively, response may be the occurrence of a surrogate marker that is known to relate to a clinical benefit. Statistical methods for dose-finding that take into account both response and toxicity have recently been proposed.

Gooley *et al.* (1994) [42] was the first one to consider two outcomes in phase I trials; they also proposed the frequently used computer simulation procedure as a clinical trial design tool.

Thall *et al.*'s (1998) [43] TR method is a Bayesian adaptive design incorporating both response and toxicity outcomes. Bivariate binary outcomes (response (0, 1), toxicity(0, 1)) are regrouped to a trinary variable(0, 1, 2) denoting three possible situations: inefficacy(denoting no response and no toxicity), efficacy(denoting response and no toxicity), and toxicity( denoting toxicity with and without response). An proportional odds logistic regression model(PO) is then introduced, represented by  $\text{logit}(\pi_2(d, \theta)) = \mu + \beta d$  and  $\text{logit}(\pi_1(d, \theta) + \pi_2(d, \theta)) = \mu + \alpha + \beta d$ , where  $\theta = (\mu, \alpha, \beta)$ ,  $\pi_1$  denotes probability of efficacy, and  $\pi_2$  denote probability of toxicity. Standard Bayesian theory using data likelihood and prior information computes posterior distribution. The acceptable dose  $d$  is such that  $Pr\{\pi_1(d, \theta) > \underline{\pi}_1 | \mathcal{D}\} > p_1$ ,  $Pr\{\pi_2(d, \theta) < \bar{\pi}_2 | \mathcal{D}\} > p_2$ , where  $\underline{\pi}_1$  and  $\bar{\pi}_2$  are fixed lower and upper limits,  $p_1$  and  $p_2$  are fixed probability cutoffs, and  $\mathcal{D}$  is cumulative data. The authors then defined the best acceptable dose given  $\mathcal{D}$  as that having the highest probability of response. The TR method provides an ethical and practical basis for dose-finding in phase I trials, but Thall *et al.* [44] noted that the TR method can't accommodate the more general setting where it should distinguish between toxicity with and without response.

O'Quigley, Hughes and Fenton (2001)[45] proposed a two-stage dose-finding design, similar to CRM. The first stage determines an acceptable level of toxicity, starting with a low toxicity target that later may be increased; when the information on the rate of success among those patients not suffering toxic effects is collected at this dose level, the second stage uses a sequential probability ratio test to compare null and alternative values of  $Pr(E \text{ and } T^c | x) = \pi_{E|T^c}(x, \theta)\{1 - \pi_T(x, \theta)\}$ , where  $E$  denotes efficacy,  $T^c$  denotes non-toxicity,  $x$  denotes the dose, and  $\theta$  denotes the parameters. Then a decision is made as follows: 1) A negative test result leads to the further implementation; 2) A conclusion sup-

porting success rate larger than  $p_1$  closes this trial with the final recommendation for this dose level, where  $p_1$  is the promising efficacy probability; and 3) A conclusion supporting success rate less than fixed probability  $p_0$  leads to the removal of this dose level and lower dose levels from further implementation, where  $p_0$  is the unsatisfactory efficacy probability; at the same time, the target acceptable toxicity is increase from  $\theta$  to  $\theta + \delta$ , and the trials continues at the remaining dose levels.

Braun (2002)[46] extended CRM to bivariate trials in which the maximum tolerated dose is based jointly on toxicity and disease progression. Logistic regression models with subject-specific intercepts are used separately for two outcomes,  $\log(p_{1ij}/(1 - p_{1ij})) = -\alpha_i + \beta_1 x_j$  for toxicity and  $\log(p_{2ij}/(1 - p_{2ij})) = -\alpha_i + \beta_2 x_j$  for disease progression. The likelihood function includes one more parameter  $\psi$  addressing the relationship between toxicity and disease progression with the joint distribution of  $(Y, Z)$  defined as  $f(y, z|x) = k(p_1, p_2, \psi) p_1^y q_1^{(1-y)} p_2^z q_2^{(1-z)} \psi^{yz} (1 - \psi)^{(1-yz)}$ ;  $y, z \in \{0, 1\}$ ,  $0 < \psi < 1$ , where  $y$  and  $z$  denote toxicity and disease progression,  $p_1$  denotes the probability of toxicity on dose  $x$ ,  $p_2$  denotes the probability of progression on dose  $x$ ,  $q_i = 1 - p_i, i \in \{1, 2\}$ , and  $k(\cdot)$  is a normalizing constant. A three-parameter  $(\beta_1, \beta_2, \psi)$  Bayesian model is then used; the dose is chosen by minimizing a Euclidean or non-Euclidean distance from  $[E\{\pi_1(x, \beta_1, \beta_2, \psi)|\mathcal{D}\}, E\{\pi_2(x, \beta_1, \beta_2, \psi)|\mathcal{D}\}]$  to a fixed two-dimensional target.

Thall *et al.* (2004) [47] cited a major limitation of the TR method. In cases where all doses have acceptable toxicity but higher dose levels have substantially higher efficacy, the TR method does not guarantee escalation to the more desirable doses with high efficacy. Thall *et al.* proposed a new Bayesian algorithm for dose-finding based on efficacy-toxicity trade-off contours that partition the two-dimensional outcome probability domain. For trinary outcomes in addition to the PO model, the continuation ratio(CR) model is also considered, represented by  $\text{logit}(\pi_2(d, \theta)) = \mu_2 + \beta_2 d$  and  $\text{logit}(\pi_{1|2^c}(d, \theta)) = \mu_1 + \beta_1 d$ , where  $\theta = (\mu_1, \mu_2, \beta_1, \beta_2)$ ,  $\pi_2$  denoting probability of toxicity and  $\pi_{1|2^c}$  denoting probability of efficacy given non-toxicity. For bivariate binary outcomes, a bivariate binary model is introduced in terms of marginal probability and one association parameter  $\psi$ , represented by  $\text{logit}(\pi_T(x, \theta)) = \mu_T + \beta_T d$  for toxicity and  $\text{logit}(\pi_E(x, \theta)) = \mu_E + \beta_{E,1} d + \beta_{E,2} d^2$  for efficacy, where  $\theta = (\mu_T, \beta_T, \mu_E, \beta_{E,1}, \beta_{E,2}, \psi)$ . Then this model is written by  $\pi_{a,b} =$

$(\pi_E)^a(1 - \pi_E)^{1-a}(\pi_T)^b(1 - \pi_T)^{1-b} + (-1)^{a+b}\pi_E(1 - \pi_E)\pi_T(1 - \pi_T)((e^\psi - 1)/(e^\psi + 1))$ . Decision rule is based on the desirability of the pair  $\pi(d, \theta)$  in the two dimensional domain. Simulation results show that this method has high probabilities of making correct decisions and treats most patients at dose with desirable efficacy-toxicity trade-offs.

Bekeleet *al.*(2005) [49] proposed a Bayesian approach to phase I/II dose-finding oncology trials by jointly modeling a binary toxicity( $T$ ) and a continuous biomarker expression outcome( $W$ ). The joint distribution of  $(W^*, T)$ , which is assumed to have a bivariate normal distribution in terms of covariance parameter  $\rho$  and marginal distributions, is introduced, represented by  $W^* \sim Normal(X_i\beta_{W^*}, \sigma_{W^*}^2)$  and  $Pr(T_i = 1|x_i = d_k) = \Phi(X_i\beta_z) = \Phi(\beta_{Z,k})$  where  $W^*$  is the transformed  $W$ . Dose  $d_k$  will be acceptable if  $Pr(h^{-1}(\beta_{W,k}) > W_{min}^*|data, n_k \geq m) > \delta_1$  and  $Pr(\Phi(\beta_{Z,k}) < \pi_t|data, n_k \geq m) > \delta_2$  or  $Pr(\Phi(\beta_{Z,k-1}) < \pi_t|data, n_k < m, n_{k-1} \geq m) > \delta_3$ , where  $m$  is a fixed integer between 1 and 6,  $n_k$  is the number of patients evaluated at dose  $d_k$ ,  $\delta_1, \delta_2$  and  $\delta_3$  are prespecified threshold probabilities,  $W_{min}^*$  is the lowest biomarker expression level of clinical interest,  $\pi_t$  is a maximum acceptable toxicity probability,  $h^{-1}(\beta_{W,k})$  is the biomarker expression level for the  $k$ th dose, and  $\Phi(\beta_{Z,k})$  is the probability of toxicity for the  $k$ th dose. The probability of allocating the next patient among the acceptable doses is proportional to the Euclidean distance from  $[E(h^{-1}(\beta_{W,k})|data), E(\Phi(\beta_{Z,k})|data)]$  to the optimal point( $W_{max}^*, 0$ ). Extensive simulation results show that the design chooses the preferred dose using both toxicity and expression outcomes.

To determine the optimal dose, Loke *et al* (2006) [50] suggested a Bayesian dose finding design for dual endpoint that makes use of an "implicit weights implementation method" combined with Bayesian inference on the patient outcomes that incorporate both toxicity and efficacy. Assuming the independence in the probability of toxicity and efficacy we model the patient response for all four combinations of outcome, represented by  $y = (y_{1l}, y_{2l}, y_{3l}, y_{4l})$ , where  $l$  denotes the dose level ( $l = 1, \dots, m$ ). The prior of the four probabilities is assumed to follow a Dirichlet distribution with random variable  $\theta$ , where  $0 \leq \theta_{il} \leq 1$  and  $\sum_{i=1}^4 \theta_{il} = 1$ . This leads to the conjugate Dirichlet posterior distribution  $p_l(\theta|\alpha + y) = \frac{\Gamma(\sum_{i=1}^4 \alpha_{il} + y_{il})}{\prod_{i=1}^4 \Gamma(\alpha_{il} + y_{il})} \theta_{1l}^{\alpha_{1l} + y_{1l} - 1} \dots \theta_{4l}^{\alpha_{4l} + y_{4l} - 1}$ , where  $\alpha = (\alpha_{1l}, \alpha_{2l}, \alpha_{3l}, \alpha_{4l})$ , reflecting clinical opinion. The form of utility weights, depending on the desired target probability value, reflects the trade-off between toxicity and efficacy in the decision to escalate or de-escalate the dose

level. The optimal action to be taken is the one which maximizes the expected value of the utility with respect to the posterior distribution.

All of the above bivariate outcome designs share some commonalities: 1) As model-based designs, they utilize different statistical models; 2) As adaptive designs, they use current cumulative data to update underlying parameters and then, according to certain decision rules, choose an optimal dose and assign it to the next cohort; 3) Decision rules are clearly defined on both toxicity and response; and 4) The involvement of complicated computation causes computational challenges in the implementation.

### 2.3 PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) MODELING IN DRUG DEVELOPMENT

Pharmacokinetics considers the absorption, distribution, metabolism, and elimination of drugs over time, describing the relationship between drug inflow and drug concentrations at intended sites. Pharmacokinetics data consist of drug concentrations along with known measured times and dosage regimens. Pharmacodynamics considers drug concentrations and the corresponding responses, describing the relationship between drug concentrations and pharmacological effects. Pharmacodynamics data consist of individual responses along with associated drug concentrations or dosage regimen. Population PK/PD data consist of a collection of PK/PD data on a group of individuals along with individual-specific covariates, for example, age, sex, genotype. Pharmacokinetic/pharmacodynamic(PK/PD) modeling, which considers the dose-exposure-effect relationship and aims to explore the within and inter variability in PK or PD data, gained much attention in drug development in the past decades. Exposure can be the drug concentration vs. time profile, or a summary measure such as area under the concentration curve (AUC) or maximum concentration (C<sub>max</sub>). Effect may be a pharmacological marker, a measure of efficacy or safety.

Sheiner *et al.* [51, 52] proposed a framework for considering the role of PK/PD modeling in drug development and discussed its current and potential impact on that activity. Population PK/PD model consists of two separate sub-models: a PK model for drug concentration

as a function of time  $t$ , dose, individual random effects, and measurement error, and a PD model for drug effect as a function of the true concentration at time  $t$ , individual random effects, and measurement error. Hierarchical model approach has gained much popularity among PK/PD models, establishing within-individual exchangeability, independence, and predictiveness, by conditioning on individual-specific covariates, dosage regimens, and parameters. Thus, take PK model as an example, the minimal hierarchical model for drug concentration  $Y_i$  is:

$$[Y_i|X_i, D_i; \Theta] = \int [Y_i, \theta_i|X_i, D_i; \Theta]d\theta_i = \int [Y_i|D_i; \theta_i][\theta_i|X_i; \Theta]d\theta_i \quad (2.1)$$

where  $\theta_i$  is the set of PK parameters of individual  $i$  for PK model (for example, volume of distribution, clearance), and  $\Theta$  consists of not only population means of  $\theta$ , but also interindividual variance and other parameters quantifying the magnitude of errors in measurement of the PK observations in  $Y_i$ .

This model is called hierarchical because at the first level, the distribution of individual elements of  $Y_i$  depends on individual-specific parameters  $\theta_i$  and design  $D_i$  (dosage, time), whereas at the second level of the hierarchy, the distribution of  $\theta_i$  depends on population parameters  $\Theta$  and baseline covariates  $X_i$ . A Bayesian approach adds a third level to the hierarchy: a prior distribution on  $\Theta$  has its own hyperparameters.

The PD hierarchical model is similar to the above PK hierarchical model, and the only difference is that PK and PD models take different nonlinear functions. PK models are typically nonlinear functions of unknown individual-specific parameters  $\theta$  and defined in terms of differential equations that describe the drug inflow rate between a sequence of compartments that model the body. PK data would be fitted as one-compartment, two-compartment or three compartment model. PD models are nonlinear functions of individual-specific parameters  $\phi$  and the mainstay of PD modeling is  $E_{max}$  model, which assumes the following relationship exists between drug concentration( $C$ ) and drug effect( $E$ ).

$$E = E_0 + E_{max}C^\gamma/(C^\gamma + C_{50}^\gamma) \quad (2.2)$$

where  $E_0$  is the baseline effect,  $E_{\max}$  is the maximum effect,  $C_{50}$  is the drug concentration that results in 50% of the maximal effect, and  $\gamma$  is the slope parameter that determines the slope of the concentration-response curve, so  $\phi_i = (E_{0i}, E_{\max i}, C_{50i}, \gamma_i)$ .

It is very common to model PK/PD data from multiple individuals as a two-level hierarchy, allowing the variability in concentration/effects to be divided into within-individual variability and inter-individual variability. The following is the detailed interpretation for the two-level hierarchy model in mathematical notation:

At the first level, the observations of each individual are modeled conditional on individual specific PK and PD parameters. Let  $Y_{ij}$  and  $Z_{ij}$  denote the observed concentration and the observed effect of individual  $i$  at time  $t_{ij}$ . Let  $\theta_i$  and  $\phi_i$  denote the PK and PD parameters of individual  $i$ . Let  $D_{ij}$  and  $X_{ij}$  denote the administered dose and true concentration of individual  $i$  at time  $t_{ij}$ . Let  $f_{PK}$  and  $f_{PD}$  denote the predicted drug concentration and response from PK and PD model, respectively. Let  $\epsilon_{PKij}$  and  $\epsilon_{PDij}$  denote the error terms, which are independently and identically distributed normal random variables with mean zero and variance depending on  $f_{PK}$  and  $f_{PD}$  respectively.

$$Y_{ij} = f_{PK}(\theta_i, D_{ij}) + \epsilon_{PKij} = f_{PKij} + \epsilon_{PKij} \quad (2.3)$$

$$Z_{ij} = f_{PD}(\phi_i, X_{ij}) + \epsilon_{PDij} = f_{PDij} + \epsilon_{PDij} \quad (2.4)$$

Inter-individual variability is modeled at the second stage by assuming that individual-specific PK and PD parameters  $(\theta_i, \phi_i)$  depend on population parameters  $(\Theta, \Phi)$  and covariates  $x_i$ . We assume that

$$\theta_i = \mu_\theta + x_i' \beta_\theta + \delta_{PKi} \quad (2.5)$$

$$\phi_i = \mu_\phi + x_i'' \beta_\phi + \delta_{PDi} \quad (2.6)$$

where  $\mu_\theta$  and  $\mu_\phi$  are population means of  $\theta_i$  and  $\phi_i$ ,  $x_i$  denotes the covariates of the individual  $i$ ,  $x_i'$  and  $x_i''$  are subsets of covariates of individual  $i$ ,  $\beta_\theta$  and  $\beta_\phi$  are corresponding population regression coefficients,  $\mu_\theta$  and  $\mu_\phi$  represent the intercept terms. Actually not all of the PK/PD models consider the specific covariates. The random  $\delta_{PKi}$  and  $\delta_{PDi}$  are independent and multivariate normally distributed with zero mean, and variance-covariance matrices  $\Sigma_\theta$  and  $\Sigma_\phi$  respectively.

Let  $Y$  and  $Z$  denote all PK and PD data. Let  $\Theta$  denote  $(\mu_\theta, \Sigma_\theta)$ , the PK population parameters. Let  $\Phi$  denote  $(\mu_\phi, \Sigma_\phi)$ , the PD population parameters. The marginal likelihood for the population parameters can be written as:

$$L(\Theta, \Phi|Y, Z) = p(Y, Z; \Theta, \Phi) = \prod_i \int \int p(y_i; \theta_i) p(z_i; \theta_i, \phi_i) p(\theta_i; \Theta) p(\phi_i; \Phi) d\theta_i d\phi_i \quad (2.7)$$

For example,  $\theta_i$  could be  $(CL_i, V_i)$  and  $\phi_i$  could be  $(E_{0i}, E_{\max i}, C_{50i}, \gamma_i)$ .

Joint PK/PD data may be analyzed in a number of ways. The simplest approach is to substitute the observed concentrations into PD model without considering PK modeling. A slightly more refined approach is to first model the PK data and then to substitute in the fitted concentration. The drawbacks of this approach are: 1) The uncertainty in the fitted concentrations is not considered; 2) There is no feedback from the PK model, so the PD data will not aid in the estimation of PK parameters.

When PK/PD data are to be modeled by a nonlinear hierarchical model, there are several challenges: 1) The choice of sampling times, number of samples, and number of individuals still remains a challenge; 2) Prior information is required in the hierarchical model, so the elicitation of prior is also a challenge; and 3) If specific covariates are also considered, the choice of which elements should be included at the second stage for the modeling of  $\theta_i$  and  $\phi_i$  is somewhat difficult. Now some software programs to deal with population analysis are available and the best known software is NONMEM( Non-Linear Mixed Effect Model). Population approach is increasingly recognized as a useful tool in PK/PD modeling[53, 54]. In oncology, the population approach has been increasingly applied both for PK and PD models[55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65].

### **3.0 AN INTERFACE FOR EXPLORING DECISIONS WHEN KNOWLEDGE IS COMPLETE**

#### **3.1 INTRODUCTION TO "DOSE-CHOICE CONTROL PANEL" (DCCP)**

The Belmont Report (1979) presents ethical principles governing clinical research: respect for persons, beneficence, and justice. In early stage clinical trials, clinicians and researchers should make decisions about dose assignment based on patients' values, preferences, and first and foremost the principle of doing what is best for patients or at least not purposefully or knowingly doing them harm. Imagine this scenario: One patient is enrolled for the treatment, and our job is to choose the dose. Suppose we have complete population information and utilities elicited from patient representing one's values and preferences, we could make a decision based on complete population information and utilities. Thus we have developed a "dose-choice control panel" (DCCP) computer program based on the above scenario. Inputs are complete population information and patient utilities. DCCP produces optimal dose assignment decisions, and helps users to explore how the population parameters and utilities affect the dose recommendation. This chapter describes the population model, the utility assumptions, and the interface. Some applications are described in which the models and utilities were critiqued, resulting in a richer, more realistic framework. The resulting enhancements include new parameters added to address bimodality, treatment refractoriness, and response-limiting event, as well as broader utility functions, which will be described below.

### 3.2 THRESHOLD-BASED POPULATION MODEL

The patient response and toxicity outcomes will be notated as follows: R=response, r=no response, T=toxicity, t=no toxicity. Our model is based on the assumption that a particular effect of treatment(R or T) occurs if the dose exceeds that patient's threshold dose for that type of effect( $\theta_R$  or  $\theta_T$ ). For a particular patient who is assigned to a particular dose  $i$ , one of the four possible outcomes ( $rt$ ,  $rT$ ,  $Rt$ , and  $RT$ ) could occur with corresponding probabilities ( $Pr[rt|Dose_i]$ ,  $Pr[rT|Dose_i]$ ,  $Pr[Rt|Dose_i]$ , and  $Pr[RT|Dose_i]$ ). These probabilities also depend on the joint distribution of  $\theta_R$  and  $\theta_T$ , which is parameterized by a parameter  $\varphi$ . Below, we will write this as  $Pr[jk|\phi]$  when the emphasis is on  $\varphi$ , where  $j, k$  are response and toxicity outcomes.

Different individuals have different thresholds for response and toxicity. The individual thresholds for response ( $\theta_R$ ) and toxicity ( $\theta_T$ ) are assumed to jointly follow a bivariate log-normal distribution with  $\varphi$  equal to  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$ .

$$(\log\theta_R, \log\theta_T) \sim Normal \left[ \begin{pmatrix} \mu_R \\ \mu_T \end{pmatrix}, \begin{pmatrix} \sigma_R^2 & \sigma_R\sigma_T\rho \\ \sigma_R\sigma_T\rho & \sigma_T^2 \end{pmatrix} \right] \quad (3.1)$$

Because response and toxicity occur depending on their respective thresholds, for any individual one of four possible outcomes could happen with corresponding probabilities. The contour plot of Figure 1.A shows this (Figures and Tables are shown at the end of each chapter).

### 3.3 UTILITIES BASED ON BINARY OUTCOMES

Our approach is based on Bayesian decision theory. Bayesian decision theory starts with a valuation of all possible outcomes, represented by a utility function, which assigns a number to each outcome. The principle of decision-making is to maximize the expected utility over unknown parameters and future possibilities. This section introduces a utility function for

response and toxicity outcomes. In this case, the decision to be made is the dose to be given. Let

$$U(\theta_R, \theta_T, dose) = \begin{cases} U_{rt} & \text{if } \theta_R > dose, \theta_T > dose \\ U_{rT} & \text{if } \theta_R > dose, \theta_T \leq dose \\ U_{Rt} & \text{if } \theta_R \leq dose, \theta_T > dose \\ U_{RT} & \text{if } \theta_R \leq dose, \theta_T \leq dose \end{cases} \quad (3.2)$$

Note that the above utility function  $U$  is a piece-wise constant function over dose. For example, the case  $\theta_R > dose, \theta_T > dose$  corresponds to the patient having no response and toxicity  $rt$ ;  $U_{rt}$  denotes the utility given to outcome  $rt$ . We will set  $U_{rt}$  equal to 0, as a reference, because  $rt$  is the outcome if dose is 0 or patient is not enrolled in the trial. Table 1 demonstrates the utility function in terms of outcomes.

### 3.4 DOSE CHOICE

We are considering the choice of dose for a patient. Therefore, we need the probability of each outcome for the enrolled patient as a function of dose.

$$\begin{aligned} EU &= E_{\theta_R, \theta_T | \varphi} [U(\theta_R, \theta_T, dose)] \\ &= \int_{\theta_R} \int_{\theta_T} U(\theta_R, \theta_T, dose) f(\theta_R, \theta_T | \varphi) d\theta_R d\theta_T \\ &= \sum_{j=r}^R \sum_{k=t}^T U_{jk} Pr[jk | \varphi] \end{aligned}$$

In the  $\theta_R, \theta_T$  plane, the point (dose, dose) divides the plane into quadrants, corresponding to the four outcomes.  $Pr[jk | \varphi]$  is calculated by integrating the bivariate log-normal density over the corresponding quadrant. Figure 1.B demonstrates how the corresponding probabilities and EU change with increasing dose under fixed  $\varphi$ .

The dose assigned to the enrolled patient should be Optimal Dose ( $OPT$ ), which maximizes expected utility (EU).

### 3.5 DCCP INTERFACE

The DCCP interface was developed to explore how the population parameters and utilities affect the EU and dose recommendation. This is currently implemented with the statistical language R, with "live" interactive graphics using Tierney's TKRLOT package from the University of Iowa.

The DCCP interface is made up of four parts, with the upper left demonstrating the contour plot for population distribution of  $(\theta_R, \theta_T)$ , the lower left allowing the users to set the population threshold parameters, the upper right displaying probabilities and EU, and the lower right allowing the users to control the utilities. The parameters  $\varphi=(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$  govern the joint distribution of thresholds, and in this exploratory tool the user sets the parameters as they were known. We have added parameters (Pr(refractory), K(response-limiting event), *proportion*,  $\mu_{ratio}$ ,  $\sigma_{ratio}$ ) to be discussed later. We consider four specific utility functions here: simple utility function, additive utility function, aggressive utility function, and cautious utility function. The simple utility function places positive utility only on co-occurrence of response and non-toxicity without considering individual ethical concern. The additive utility function assumes  $U_{RT} = U_R + U_T$ , where  $U_R = U_{Rt} - U_{rt}$  and  $U_T = U_{rT} - U_{rt}$ . The aggressive utility function puts more utility on  $RT$  based on the assumption that the badness of toxicity is tolerable if response occurs. The cautious utility function puts negative utility on  $RT$  based on the assumption that the badness of toxicity is intolerable even if the response does occur. Table 2 displays these utility functions.

### 3.6 USING DCCP TO CRITIQUE THE MODEL AND UTILITIES

Bayesian decision theory will make sense if the inputted models and utilities make sense. On working with the DCCP interface, results that did not make sense helped us to modify both model and utilities.

### 3.6.1 Bimodality

According to the literature of pharmacokinetics and pharmacogenetics reporting the existence of multimodality among population thresholds,  $Proportion$ ,  $\mu_{ratio}$ , and  $\sigma_{ratio}$  are introduced to express the bimodality of thresholds, with proportion denoting the proportion of the second sub-population, also called minor population, and  $(\mu_{ratio}, \sigma_{ratio})$  denoting the ratio of means and standard deviations in two sub-populations. The screen shot in Figure 2 demonstrates the control panel under the cases that  $(\theta_R, \theta_T)$  follow a mixture model with the proportions of minor population and main population respectively 0.2 and 0.8.

### 3.6.2 Refractoriness and Response-limiting Event

On working with the DCCP interface, we have found that as dose increases indefinitely the probability of response tends to 1. This does not reflect the reality in certain circumstances, leading to the necessary modifications of the model.

Given the knowledge about refractoriness,  $Pr(\text{refractory})$  is introduced to express a degree of patient heterogeneity for pharmacodynamics, with the presence of the probability that one's disease is refractory (unresponsive at any dose). Because clinical practice or competition of patient outcomes may lead to patient experiencing certain events which exclude response,  $K(\text{response-limiting event})$  is introduced to describe the dose-response parameters for experiencing a response-limiting event (RLE), a toxicity or other event that excludes response. Inspired by Simon's paper (1997),  $\theta_K$  is defined as  $\theta_K = \theta_T \exp(K)$ , where  $\theta_K$  is called threshold of RLE, and  $K$  is a positive number. With the introduction of  $K$ , the original RT region is divided into two parts: RT and RLE. When  $\theta_R \leq dose$  and  $\theta_T \leq dose < \theta_K$ , RT occurs; when  $\theta_R \leq dose$  and  $\theta_T \leq \theta_K \leq dose$ , RLE occurs. The final rT region will be made up of two parts: RLE and original rT.

$Pr(\text{refractory})$  and  $K(\text{response-limiting event})$  cause tailing off of probabilities in the right-side graph. The screen shots in the Figure 3 and Figure 4 are control panels for exploring the above two situations. Figure 3 and Figure 4 respectively assume that the probability of refractory is 0.3 and  $K(\text{response-limiting event})$  is 2, addressing certain degree of patient heterogeneity for pharmacodynamics.

### 3.6.3 Critiquing Utilities

Working on this interface, we have found that optimizing patient's outcome on simple utility function which places positive utility only on the co-occurrence of response and non-toxicity leads to wrong recommendations, even it is commonly used in the literature. The difference between simple utility function and additive utility function is the penalty for rT's. This is especially meaningful under the cases where responses are rare or none, however, rT's are fairly common. The screen shot in Figure 5 demonstrates this situation. Simple utility function allows escalation in the face of rT's (there is no penalty for rT's), while additive utility function will not (there is penalty for rT's). Additive utility function, aggressive utility function, and cautious utility function could address ethical concerns, making the dose recommendations more ethical.

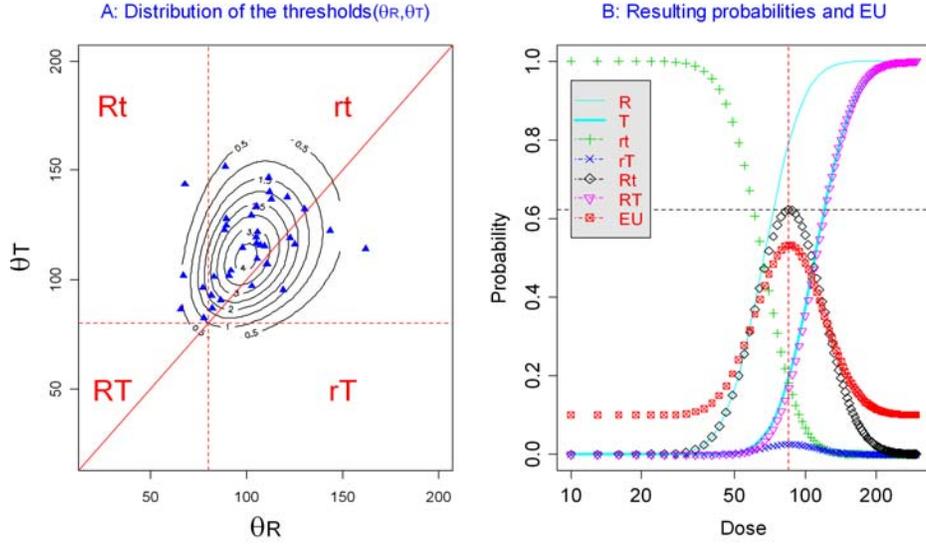


Figure 1: *Contour Plot, Resulting Probabilities and EU*

Note: The diagonal line in the contour plot represents possible assigned doses. Along this diagonal line, the vertical and horizontal lines divide the whole population into four subgroups ( $rt$ ,  $rT$ ,  $Rt$ , and  $RT$ ). Expected Utility(EU) is the expectation of utility function over the population thresholds.

Table 1: *Utility Function*

Outcome	$t$	T
$r$	$U_{rt}$	$U_{rT}$
R	$U_{Rt}$	$U_{RT}$

Table 2: Four Utility Functions

$U_{simple}$		$U_{additive}$		$U_{aggressive}$		$U_{cautious}$	
Outcome	$t$ T	Outcome	$t$ T	Outcome	$t$ T	Outcome	$t$ T
$r$	0 0	$r$	0 -1	$r$	0 -1	$r$	0 -1
R	1 0	R	1 0	R	1 1	R	1 -1

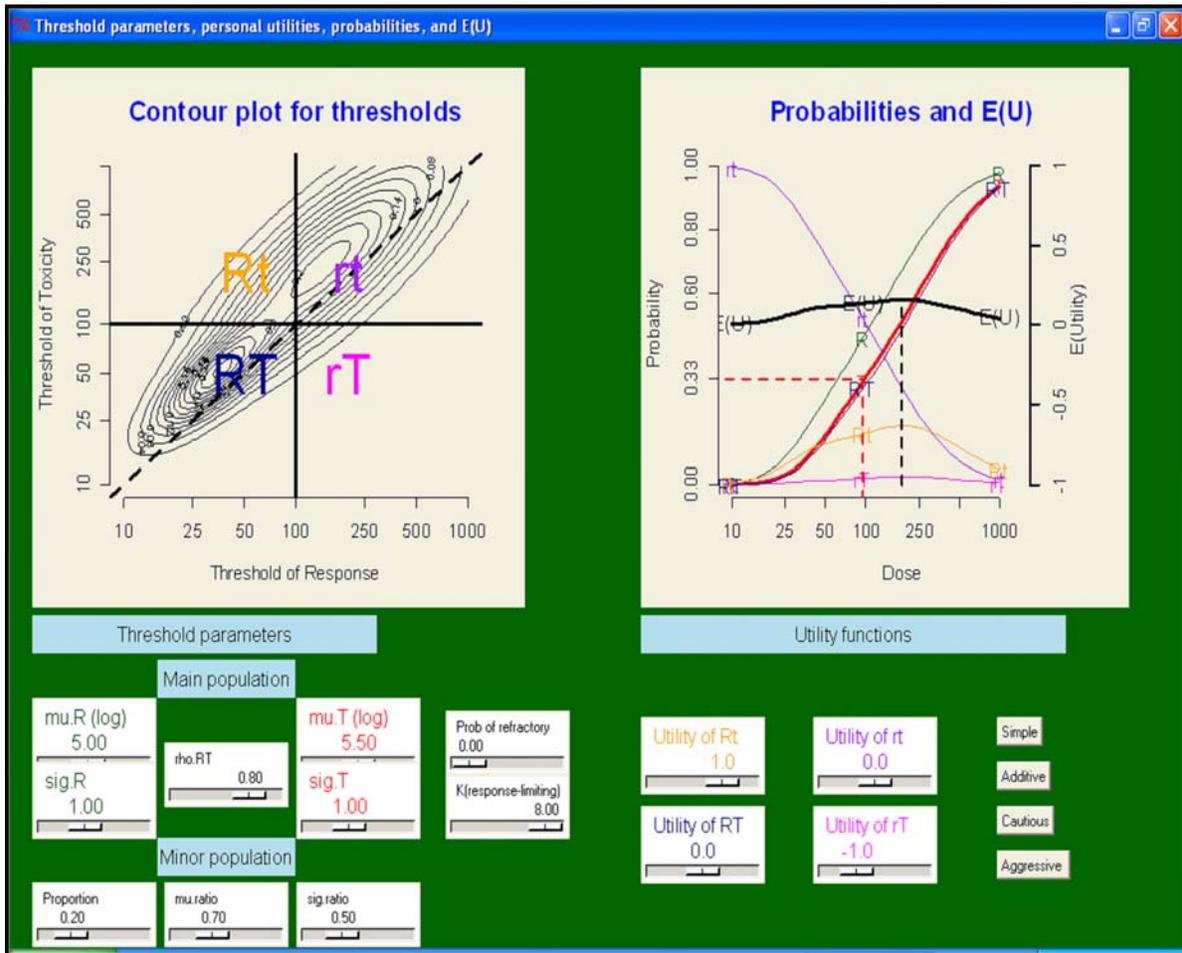


Figure 2: Interface with Bimodality

Note: Thresholds follow a bimodal log-normal distribution with a proportion of second sub-population (minor population) 0.2. The ratios of mean and standard deviation in main and minor populations are set as 0.7 and 0.5.

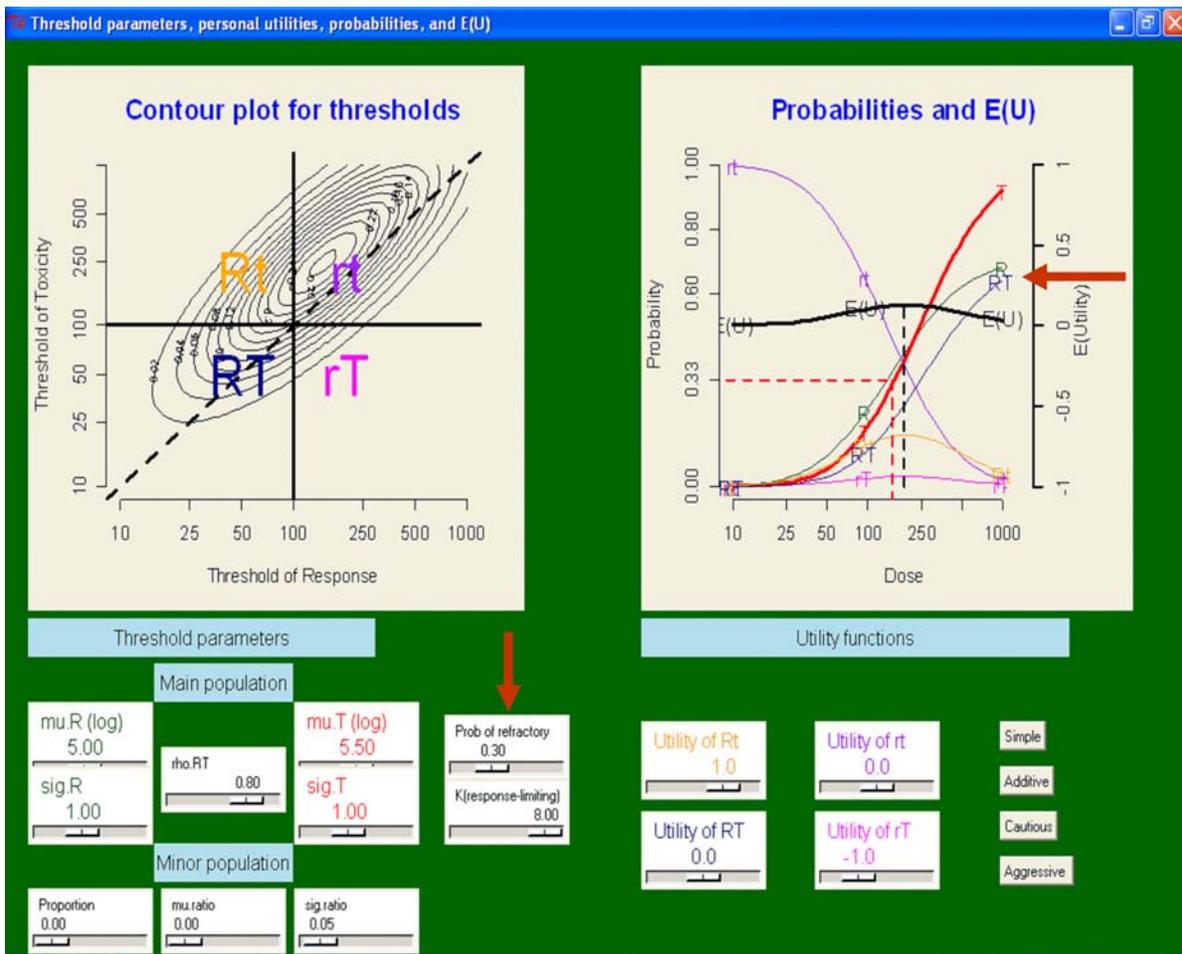


Figure 3: *Interface with Certain Probability of Refractory*

Note: The probability of refractory is set as 0.3. Both  $Pr[R]$  and  $Pr[RT]$  tail off because of the probability of refractory.

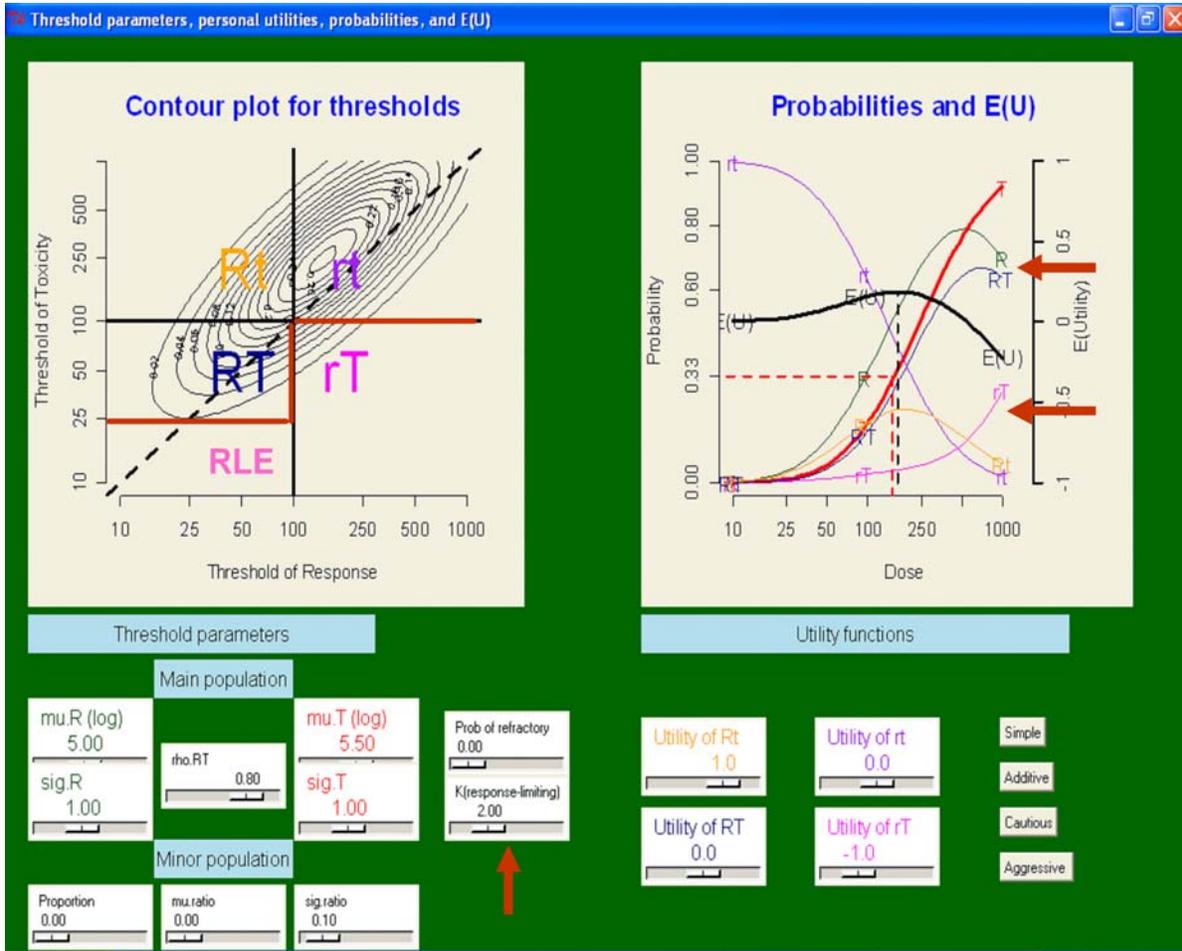


Figure 4: *Interface with Response-Limiting Event*

Note: With the introduction of  $K$ , the original  $RT$  region is divided into two parts:  $RT$  and  $RLE$ . The final  $rT$  region will be made up of two parts:  $RLE$  and original  $rT$ . Both  $Pr[R]$  and  $Pr[RT]$  tail off because response-limiting event excludes certain chance of response.  $Pr[rT]$  increases because of the addition of  $RLE$ .

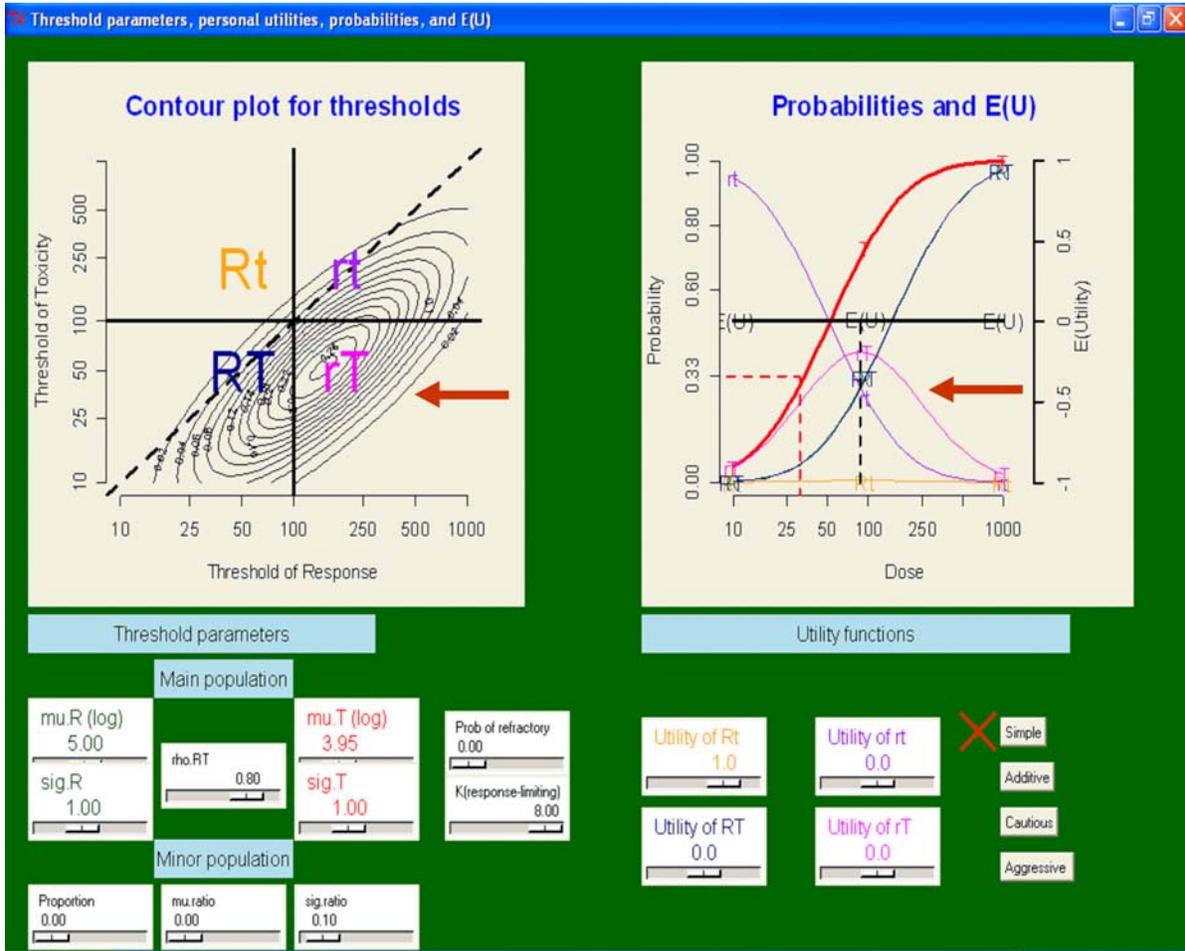


Figure 5: *Interface with Simple Utility Function*

Note: Simple utility function allows escalation in the face of  $rT$ 's (there is no penalty for  $rT$ 's). Under the cases where responses are rare or none, however,  $rT$ 's are fairly common, simple utility function could lead to wrong recommendations.

## 4.0 A NEW MODEL-GUIDED PHASE I DESIGN INCORPORATING RESPONSE INFORMATION

### 4.1 BACKGROUND

The usual phase I, II and III anti-cancer drug clinical trials are based on the following assumptions: 1) The agent has toxic effects; 2) The agent shrinks the tumor; 3) Toxicity and anti-tumor activity are dose dependent with a monotonic dose-response relationship; 4) The agent shrinks the tumor much better under certain acceptable toxicity; 5) Shrinkage of tumor size is generally related with prolonged life or better quality of life. The higher the shrinkage rate, the more likely the agent will be potentially beneficial. In exploring new anti-cancer drugs, phase I trials focus on the toxicity. The primary goal of phase I trials is to find the maximum tolerated dose (MTD) and then recommend this dose for the phase II trials. Phase II trials, which are performed in small number of patients, usually focus on the efficacy measured by the percentage of tumor shrinkage. Finally, large-scale randomized phase III trials are launched to assess the clinical benefit using endpoints like recurrence free survival, disease free survival, or overall survival; phase III trials sometimes assess quality of life. Because these traditional clinical trial assumptions have been widely accepted, the above drug development scheme has been used for several decades.

Although phase I clinical trials are defined as dose-finding trials, both the physicians and experiment researchers hope the agents demonstrate some anti-tumor effects which are part of rationale for launching phase II trials. In general patients who participate in anti-cancer agent phase I trials suffer from different types of cancer, have typically exhausted other therapeutic alternatives, treat this as a last resort to their vulnerable situations, so beneficial response should also be taken into account from the viewpoint of the patient in the

design and implementation of phase I clinical trials. However, conventional clinical response is not necessarily a useful indicator of clinical benefit. For example, interest in cytostatic agents, which inhibit tumor growth or the development of metastases, has rapidly increased as molecular biology has introduced more sophistication into anti-cancer drug development. Some agents have no toxic effects at doses which provide desired biologic effects or clinical benefit, while increasing the doses of some agents may not always provide additional benefit. So for cytostatic agents traditional phase I clinical trial designs which just consider toxicity may not be effective in exploring new potential beneficial anti-cancer drugs.

Phase I trials are often relatively small, typically 30 or fewer patients, and of a duration too short to measure genuine clinical benefit. Often investigators measure clinical or laboratory markers during phase I trials with the hope of obtaining suggestive data that can help determine if phase II trials are warranted. Recently, biomarkers have been intensely studied to explain the results of clinical trials by relating the effects of drugs on molecular and cellular pathways to clinical responses. Some special biomarkers, called surrogate biomarkers, could be used as substitutes for clinical endpoints. Most biomarkers may not provide true surrogate endpoint information, but are still useful because they may indicate downstream effects consistent with the investigator's therapeutic model, and provide confirmation that the drug has the hoped-for potential. Although changes in biomarkers during therapeutic intervention would not assist directly in the drug approval process, it may help justify proceeding to phase II trials. If an agent is safe and well tolerated, but has no any effect on biomarkers, it may be a counterindication for phase II commitment. So consideration of toxicity alone may not be enough for dose-finding in phase I clinical trials. Augmenting toxicity data with biological endpoint data might be important.

Some recent studies in phase I clinical trials have focused on the consideration of both toxicity and efficacy (Gooley *et al.* (1994); Thall and Russell (1998); O'Quigley, Hughes, and Fenton (2001); Braun *et al.* (2002); Thall and Cook (2004); Bekele and Shen (2005); Loke *et al.* (2006) ) [42, 43, 45, 46, 47, 49, 50]. All of the model-based adaptive designs introduce specific probability model, such as the logistic regression model, to explain the relationship between dose and bivariate outcome, update the knowledge as relevant response and toxicity data accumulate, and then use this information to guide the next dose assignment. The

designs are considered in the Bayesian framework, but then the operating characteristics are evaluated and ad hoc fixes are possibly introduced. All of these indicate the designs are not full Bayesian approaches which should be decision-analytic, by combining utility function with Bayesian posterior probabilities to form Bayesian expected utility and then to make a Bayesian decision through the maximization of Bayesian expected utility.

Only if Bayesian decision theory is correctly used and the prior distribution and the utility function are sensible will the resulting clinical trial designs be both sensible and ethical.

We propose a new adaptive dose-finding algorithm using full Bayesian approaches to choose the best optimal dose which would be passed to the phase II trials. As a result, we organize chapter four as follows: 1) Section 4.2 addresses the proposed clinical trial design; 2) Section 4.3 focuses on the comparison of three computational methods, the comparison of designs with and without incorporating toxicity, and the characteristics of ethical designs; 3) Section 4.4 presents the extension of basic bivariate binary case; 4) Section 4.5 gives the design robustness check; 5) Section 4.6 explores some possible applications; and 6) Section 4.7 concludes with a discussion.

## **4.2 PROPOSED CLINICAL TRIAL DESIGN**

### **4.2.1 The Principle**

An adaptive Bayesian approach provides a framework for incorporating current cumulative data and prior information, making decisions sequentially in implementing the whole trial. Cumulative data should include responses and toxicities for all previous patients. While prior information should reflect some prior beliefs about the particular drug from the researchers, it should not be so informative as to dominate the observed data.

The correct ethical decision for each potential patient should be made to maximize the expected utility using all prior cumulative information, the driving principle of the proposed design.

### 4.2.2 Probability Model and Posterior Distribution

Assuming individual thresholds for response and toxicity  $(\theta_R, \theta_T)$  follow a bivariate log-normal distribution,  $(\log\theta_R, \log\theta_T)$  follow a bivariate normal distribution with five parameters.

$$(\log\theta_R, \log\theta_T) \sim N \left[ \begin{pmatrix} \mu_R \\ \mu_T \end{pmatrix}, \begin{pmatrix} \sigma_R^2 & \sigma_R\sigma_T\rho \\ \sigma_R\sigma_T\rho & \sigma_T^2 \end{pmatrix} \right] \quad (4.1)$$

For any given dose  $i$ , four probabilities exist:

$$\begin{aligned} P_{irt} &= Pr[\text{no Response, no Toxicity}] = Pr[\theta_R > \text{dose}_i, \theta_T > \text{dose}_i] \\ P_{irT} &= Pr[\text{no Response, Toxicity}] = Pr[\theta_R > \text{dose}_i, \theta_T \leq \text{dose}_i] \\ P_{iRt} &= Pr[\text{Response, no Toxicity}] = Pr[\theta_R \leq \text{dose}_i, \theta_T > \text{dose}_i] \\ P_{iRT} &= Pr[\text{Response, Toxicity}] = Pr[\theta_R \leq \text{dose}_i, \theta_T \leq \text{dose}_i] \end{aligned} \quad (4.2)$$

We specify the prior distributions for the parameters, with means following normal distributions and variance covariance matrix following Inverse-Wishart distribution.

$$\begin{aligned} \mu_R &\sim N(\mu_{\mu_R}, \sigma_{\mu_R}) \\ \mu_T &\sim N(\mu_{\mu_T}, \sigma_{\mu_T}) \\ \begin{pmatrix} \sigma_R^2 & \sigma_R\sigma_T\rho \\ \sigma_R\sigma_T\rho & \sigma_T^2 \end{pmatrix} &\sim W^{-1} \left[ \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, 2 \right] \end{aligned} \quad (4.3)$$

Denote by  $R_m$  the response of the  $m$ th patient where  $R_m = R$  if response occurs and  $R_m = r$ , otherwise. Denote by  $T_m$  the toxicity of the  $m$ th patient where  $T_m = T$  if toxicity occurs and  $T_m = t$ , otherwise. Denote by  $Dose_m$  the assigned dose of the  $m$ th patient.

The data after observation of  $n$  patients is  $\mathcal{D}_n = \{(Dose_m, R_m, T_m), m = 1, 2, \dots, n\}$  and the likelihood function of  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$  given  $\mathcal{D}_n$  is

$$L(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho | \mathcal{D}_n) = \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}^{n_{ijk}} \quad (4.4)$$

We incorporate prior information about  $\mu_R, \mu_T, \sigma_R, \sigma_T$  and  $\rho$  through a prior density function  $\pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$  defined as

$$\pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho) = \pi(\mu_R)\pi(\mu_T)\pi(\sigma_R, \sigma_T, \rho) \quad (4.5)$$

Through the application of Bayesian theorem the joint posterior distribution of  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$  given  $\mathcal{D}_n$  is :

$$\begin{aligned} \pi^*(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho) &\propto L(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho | \mathcal{D}_n) \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho) \\ &= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}^{n_{ijk}} \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho) \end{aligned} \quad (4.6)$$

### 4.2.3 Decision Rule

Because dose-finding trials are based on toxicity alone, the decision rule is to choose the dose for which the probability of toxicity is closest to the target toxicity quantile. For the dose-finding trials which incorporate both toxicity and response, the commonly used decision rule is to select the dose for which the probability of response and probability of toxicity are closest to the target response and toxicity quantile. For the proposed adaptive Bayesian method for dose-finding, a full Bayesian decision-analytic approach is used. Upon completion of updating cumulative patient outcome information, we can estimate the optimal dose by maximizing the Bayesian expected utility with the choice of utility function  $U$ .

The general Bayesian expected utility is defined as the expectation of utility function with respect to the posterior distribution, i.e,  $E_\theta[U(\theta, a)] = \int_{\Theta} U(\theta, a) f(\theta|x) d\theta$ . The utility function  $U(\theta, a)$  represents the utility by the decision maker if the action  $a \in \mathcal{A}$  is taken and the real state of nature is  $\theta \in \Theta$ . The clinical researchers determine utilities based on the drugs and the goals of the trials.  $f(\theta|x)$  represents the posterior distribution of  $\theta$ .

For each trial, experimenters have different standards about how to define the response, toxicity, and optimal dose. Moreover, different experimenters have varying opinions on the choice of a design. Some prefer the designs that put patients at considerable risk but maximize the probability of response, while others think the study should be a conservative one based on ethical concerns with a design that avoid treatment at toxic doses. Aggressive

trials make it possible to give more utility to  $RT$ . For example, patients enrolled in phase I cancer trials consider participating in the study as the last resort, after they have failed all conventional therapy. In this case, patients prefer to get the relatively aggressive dose which may have a better response. Conservative trials, giving more utility to  $rt$ , possibly avoid treatment at excessively toxic doses. If pharmaceutical companies sponsor a trial, the utilities may simply focus on  $Rt$ , the most desirable outcome.

Let  $\theta$  denote  $(\theta_R, \theta_T)$ ,  $\varphi$  denote  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$ , and  $\mathcal{D}_n$  denote the data observed to the current time, then the Bayesian expected utility for the next patient is:

$$\begin{aligned}
E(U|Dose) &= E_\varphi[E_{\theta|\varphi}[U(\theta, dose)]] \\
&= \int_\varphi \int_{\theta_R} \int_{\theta_T} U(\theta_R, \theta_T, dose) f(\theta_R, \theta_T|\varphi) \pi^*(\varphi|\mathcal{D}_n) d\theta_R d\theta_T d\varphi \\
&= \int_\varphi \sum_{j=r}^R \sum_{k=t}^T U_{jk} P_{jk}(Dose|\varphi) \pi^*(\varphi|\mathcal{D}_n) d\varphi \\
&= \sum_{j=r}^R \sum_{k=t}^T U_{jk} \int_\varphi P_{jk}(Dose|\varphi) \pi^*(\varphi|\mathcal{D}_n) d\varphi \\
&= \sum_{j=r}^R \sum_{k=t}^T U_{jk} E_\varphi[P_{jk}(Dose|\varphi)] \tag{4.7}
\end{aligned}$$

A Bayes action is an action which maximizes Bayesian expected utility. For the above equation, the Bayesian action is best dose choice for the next patient.

The optimal dose  $OPT_n$  is estimated by maximizing  $E(U|Dose)$ , Hence the  $(n + 1)th$  patient ( $\forall n = 1, 2, \dots, N$ ) receives the dose

$$\begin{aligned}
OPT_n &= \arg \max_{dose} E(U|Dose) \\
&= \arg \max_{dose} \sum_{j=r}^R \sum_{k=t}^T U_{jk} E_\varphi[P_{jk}(Dose|\varphi)] \tag{4.8}
\end{aligned}$$

Calculating the multiple integrations  $E_\varphi[P_{jk}(Dose|\varphi)]$  over  $\varphi$  is very complicated. Three practical approaches are available to deal with the multiple integrations over  $\varphi$ .

The first is to substitute the posterior mean  $\hat{\varphi}$  from MCMC sample for  $\varphi$ .

$$\hat{E}_\varphi[P_{jk}(Dose|\varphi)] = P_{jk}(Dose|\hat{\varphi}) = P_{jk}(Dose|\sum_{z=1}^Z \varphi_z/Z) \tag{4.9}$$

where  $\varphi_1, \varphi_2, \dots, \varphi_Z$  are i.i.d samples from the posterior distribution of  $\pi^*(\varphi|\mathcal{D}_n)$ . Because there is no closed form for this posterior distribution, the MCMC sample draws are used instead of the exact samples.

The second one is to use the Monte Carlo sampling to estimate  $E_\varphi[P_{jk}(Dose|\varphi)]$ . The Monte Carlo method approximates  $E_\varphi[P_{jk}(Dose|\varphi)]$  as

$$\hat{E}_\varphi[P_{jk}(Dose|\varphi)] = \frac{1}{Z} \sum_{z=1}^Z P_{jk}(Dose|\varphi_z) \quad (4.10)$$

where  $\varphi_1, \varphi_2, \dots, \varphi_Z$  are i.i.d samples from the posterior distribution of  $\pi^*(\varphi|\mathcal{D})$ .

The third approach is to use importance sampling to estimate  $E_\varphi[P_{jk}(Dose|\varphi)]$ .

$$\hat{E}_\varphi[P_{jk}(Dose|\varphi)] = \sum_{z=1}^Z w_z [P_{jk}(Dose|\varphi_z)] / \sum_{z=1}^Z w_z \quad (4.11)$$

where  $\varphi_1, \varphi_2, \dots, \varphi_Z$  are i.i.d samples from sampling distribution  $I(\varphi)$ ,  $g(\varphi)$  is the true posterior distribution of  $\varphi$  up to constant and  $w_z = g(\varphi_z)/I(\varphi_z)$ .

## 4.2.4 Calculation of the Posterior

### 4.2.4.1 MCMC

The Bayesian approach can combine the information from the data and prior, so the Bayesian statistical inference should be based on the posterior, but dealing with the posterior distribution directly is often problematic. In the past twenty years Markov Chain Monte Carlo(MCMC) methods have been widely used to deal with posterior distribution. The principle of MCMC is to construct a Markov Chain and it has a specified equilibrium distribution  $\pi$  that is the joint posterior probability distributions of the parameters of the model. The parameters are assigned arbitrary initial values, and the chain is simulated until its distribution appears to converge, and then, once it converges, the simulated observations can be used as the observations from the posterior distributions, and then make inference about the parameters.

There are two popular methods for setting up Markov Chain: the Gibbs sampler algorithm and Metropolis-Hastings algorithm.

The Gibbs sampler algorithm requires directly generating sample values from the full conditional distributions  $p(\varphi_i|\varphi_{j \neq i}, y), i = 1, \dots, k$ , and it does produce a Markov chain with

the joint posterior density as its stationary distribution. The advantages of Gibbs sampler are that it is easy to implement numerically and the convergence to target distribution is guaranteed as long as the full conditional distributions are correctly defined. But the potential problem with Gibbs sampler is that if the model is complicated it is not easy to figure out the full conditional distributions. The Gibbs sampler requires the conditional distributions.

The most general MCMC approach is the Metropolis-Hastings algorithm and in fact Gibbs sampler is just a special case of Metropolis-Hastings algorithm. The Metropolis-Hastings algorithm has one major advantage over the Gibbs sampler that the full conditional distributions are not required. But the trade-off of this method are that it is inefficient compared to Gibbs sampler for which the acceptance rate is 1, and the convergence is not guaranteed. The MH algorithm is based on proposing a new candidate point according to an arbitrary proposal density function and then accepting this proposed candidate according to the particular acceptance probability that depends on the current point, candidate point, proposal density and target density( true joint posterior density). Suppose we wish to simulate from the multivariate posterior  $p(\varphi|x)$ ( target density function). Let  $q(\varphi, \varphi_{can})$  be an arbitrary proposal probability density function that describes the probability of proposing  $\varphi_{can}$  given that the current point is  $\varphi$ . The following are basic ideas and steps for Metropolis-Hastings algorithm:

1. Let the current point be  $\varphi_l$ .
2. Generate a new candidate  $\varphi_{can}$  from the proposal density  $q(\varphi_l, \varphi_{can})$ .
3. Generate uniform variable  $U$  from Uniform(0,1).
4. Calculate acceptance rate  $\alpha$ ,

$$\alpha = \min\left(1, \frac{p(\varphi_{can}|x)q(\varphi_{can}, \varphi_l)}{p(\varphi_l|x)q(\varphi_l, \varphi_{can})}\right) \quad (4.12)$$

5. If  $U \leq \alpha$  then set

$$\varphi_{l+1} = \varphi_{can}$$

else set

$$\varphi_{l+1} = \varphi_l$$

6. Repeat the previous steps to obtain the sequence  $\varphi_0, \varphi_1, \varphi_2, \varphi_3 \dots$ , where  $\varphi_0$  denotes an arbitrary starting value.
7. Discard the burn-in values (up to  $\varphi_m$ ) obtained before algorithm converges. Then  $\varphi_{m+1}, \varphi_{m+2} \dots$  is a correlated sequence from the required posterior distribution  $p(\varphi|x)$ .

After getting  $\varphi_{m+1}, \varphi_{m+2}, \dots, \varphi_{m+L}$ , the random sequence

$$\bar{g}(\varphi_L) = \frac{1}{L} \sum_{l=1}^L g(\varphi_{m+l}) \quad (4.13)$$

converges almost surely to  $E_\pi g(\varphi)$  as  $L \rightarrow \infty$ . As long as  $L$  is large enough,  $\frac{1}{L} \sum_{l=1}^L g(\varphi_{m+l})$  can be a good estimator for  $E_\pi g(\varphi)$ . Because it is difficult to know exactly how large a value of  $L$  should be used, intuition usually determines its value. Moreover, the mean square error of this estimator can also be estimated. That is,

$$M\hat{S}E = E\left[\frac{1}{L} \sum_{l=1}^L g(\varphi_{m+l}) - E_\pi g(\varphi)\right]^2 \quad (4.14)$$

The acceptance probability  $\alpha$  is in the form of a ratio that includes  $p(\varphi_{can}|x)/p(\varphi_l|x)$ . Thus, the big advantage of the Metropolis-Hastings algorithm is that even if the posterior is known only up to a constant, the algorithm can still be used because the constant cancels out. In general, any proposal density  $q(\varphi, \varphi_{can})$  can be used, but if the proposal density is chosen naively, the efficiency of the chain may be poor. A popular implementation is the Random Walk sampler where the proposal distribution is symmetric with respect to  $\varphi_l$ :

$$\varphi_{can} = \varphi_l + \epsilon$$

where  $\epsilon \sim \text{Distribution}(0, \sigma^2)$ . For example:

$$\varphi_{can} \sim \text{Normal}(\varphi_l, \sigma^2)$$

or

$$\varphi_{can} \sim \text{Uniform}(\varphi_l - \Delta, \varphi_l + \Delta)$$

The parameters  $\sigma^2$  or  $\Delta$  are tuning parameters and can be chosen to achieve the desired acceptance rate.

For the proposed method, the joint posterior distribution is :

$$\begin{aligned}\pi^*(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho | \mathcal{D}_n) &\propto L(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho | \mathcal{D}_n) \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho) \\ &= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}^{n_{ijk}} \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)\end{aligned}$$

The following basic steps implement MCMC to get the simulated samples:

1. To simplify the computation procedures, the symmetric proposal distributions  $q(\cdot)$  are used at  $(l + 1)_{th}$  iteration,

$$\mu_{R_{can}} \sim Normal(\mu_{R_l}, \sigma_{\mu_R}) \quad (4.15)$$

$$\mu_{T_{can}} \sim Normal(\mu_{T_l}, \sigma_{\mu_T}) \quad (4.16)$$

$$\sigma_{R_{can}} \sim Normal(\sigma_{R_l}, \sigma_{\sigma_R}) \quad (4.17)$$

$$\sigma_{T_{can}} \sim Normal(\sigma_{T_l}, \sigma_{\sigma_T}) \quad (4.18)$$

$$\rho_{can} \sim Uniform(\rho_l - \sigma_\rho, \rho_l + \sigma_\rho) \quad (4.19)$$

2. Generate uniform variables  $U$  from Uniform(0,1).
3. If  $U \leq \alpha$  then set

$$\varphi_{l+1}^s = \varphi_{can}^s$$

else set

$$\varphi_{l+1}^s = \varphi_l^s$$

where

$$\alpha = \min\left(1, \frac{\pi^*(\varphi_{can}^s | \varphi^{-s}, \mathcal{D}_n)}{\pi^*(\varphi_l^s | \varphi^{-s}, \mathcal{D}_n)}\right) \quad (4.20)$$

Note 1:  $\varphi = (\varphi^1, \varphi^2, \varphi^3, \varphi^4, \varphi^5) = (\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$

Note 2:  $\varphi^s$  is the  $s_{th}$  element of  $\varphi$ , where  $s = 1, 2, \dots, 5$

Note 3:  $\pi^*(\varphi | \mathcal{D}_n)$  : posterior distribution of  $\pi^*(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho | \mathcal{D}_n)$

4. Repeat the previous steps to obtain the sequence  $\varphi_0, \varphi_1, \varphi_2, \varphi_3 \dots$ , where  $\varphi_0$  denotes an arbitrary starting value and then discard burn-ins.

In implementing MCMC, the standard deviations of the five parameters are chosen so that the acceptance rate is around 20 – 40%.

#### 4.2.4.2 Importance Sampling

Importance sampling is a technique for numerically approximating an integral. Consider the following integral

$$J(y) = E_x f(y|x) = \int f(y|x)g(x)dx \quad (4.21)$$

It is assumed to sample directly from  $g(x)$ . Importance sampling is used when direct sampling from  $g(x)$  is not possible. Let  $I(x)$  be a density that is easy to sample from and approximates  $g(x)$ . Importance sampling approximates  $J(y)$  as:

1. Draw  $x_1, x_2, \dots, x_Z$  from  $I(x)$ ;
2.  $\hat{J}(y) = \sum_{z=1}^Z w_z f(y|x_z) / \sum_{z=1}^Z w_z$ .

where  $w_z = g(x_z)/I(x_z)$ .

If the support of  $I(x)$  includes the support of  $g(x)$ , the tail of  $I(x)$  does not decay faster than the tail of  $g(x)$  and  $J(y)$  exists and is finite, then  $\hat{J}(y) \xrightarrow{a.s.} J(y)$ .

For the proposed adaptive Bayesian design,

$$\begin{aligned} E_\varphi[P_{jk}(Dose|\varphi)] &= \int_\varphi P_{jk}(Dose|\varphi)\pi^*(\varphi|\mathcal{D}_n)d\varphi \\ &\propto \int_\varphi P_{jk}(Dose|\varphi)\pi(\varphi)L(\varphi|\mathcal{D}_n)d\varphi \\ &= \int_\varphi P_{jk}(Dose|\varphi)\pi(\varphi) \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}(\varphi)^{n_{ijk}} d\varphi \end{aligned} \quad (4.22)$$

True distribution  $g(\varphi)$  could be defined as:

$$g(\varphi) = \pi(\varphi) \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}(\varphi)^{n_{ijk}} \quad (4.23)$$

Sampling distribution  $I(\varphi)$  could be defined as:

$$I(\varphi) = \pi(\varphi) \quad (4.24)$$

Draw  $\varphi_1, \varphi_2, \dots, \varphi_Z$  from  $I(\varphi)$ , then

$$\hat{E}_\varphi[P_{jk}(Dose|\varphi)] = \sum_{i=1}^Z w_z [P_{jk}(Dose|\varphi_z)] / \sum_{i=1}^Z w_z \quad (4.25)$$

where

$$\begin{aligned} w_z &= g(\varphi_z) / I(\varphi_z) \\ &= \pi(\varphi_z) \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}(\varphi_z)^{n_{ijk}} / \pi(\varphi_z) \\ &= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T P_{ijk}(\varphi_z)^{n_{ijk}} \end{aligned} \quad (4.26)$$

#### 4.2.5 Choice of Prior

One of the important steps in dose-finding trials is to elicit the hyperparameters before implementing trials. The hyperparameters should reflect some prior beliefs about the particular drug from the researchers, but should not be so informative as to dominate the observed data information. The vague prior information should be combined with the individual data to estimate parameters.

The choice of prior is very debatable. Most statistical frequentists and clinicians think it is impractical and aggressive to assign the first patient to a dose determined by prior, unless that dose is the lowest, which is often one-tenth of  $LD_{10}$  in mice. Statistical Bayesians hold different opinions; they think the prior should be from the pre-clinical information. Before implementing phase I trials, the experimenter should already have enough information about the pre-selected dose levels from the animal studies and previous studies, to provide the guess of the probabilities of toxicity and response.

This proposed method assumes that  $\mu_R$  and  $\mu_T$  follow normal distributions and that hyperparameters are from the prior information. The variance-covariance matrix is assumed to follow the Inverse-Wishart( $R, \rho$ ) distribution. To represent vague prior knowledge, the degree of freedom  $\rho$  for this distribution should be as small as possible (i.e. 2, the rank of  $\Sigma$ ).

The scale matrix  $R$ , which is specified as  $\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$ , represents an assessment of the order of

the magnitude of covariance matrix. Except for cases with very few individuals, the choice of  $R$  has little effect on the posterior estimate of  $\Sigma$ .

### 4.3 RESULTS

To ensure the appropriateness of the dose-finding algorithm, before implementing trials simulation studies should be conducted to check the operating characteristics. Only after simulations show satisfactory results should the proposed algorithm be applied to real trials. All of the simulations are run using R on the Opteron Cluster machine in the Pittsburgh Supercomputing Center.

#### 4.3.1 Comparison of Three Computational Methods

Because three methods are proposed for the calculation of expected utility, the most important step in the implementation of the proposed design, it is necessary to make a comparison for future recommendations.

Assuming individual thresholds for response and toxicity ( $\theta_R, \theta_T$ ) follow a bivariate log-normal distribution, ( $\log\theta_R, \log\theta_T$ ) follow a bivariate normal distribution with five parameters ( $\mu_R, \mu_T, \sigma_R, \sigma_T, \rho$ ).  $N$  individual response and toxicity thresholds are generated from the log-bivariate-normal distribution with the above five given parameters and in these simulations  $N$  is set as 50.

Before implementing trials, we collect some pre-clinical information about these five parameters. Prior information should be vague enough to not dominate the dose assignment. Its influence on dose assignment should decrease as more subjects are enrolled in the trials because the data should speak louder than the prior information. The prior should also be clearly and sufficiently defined so that it takes power to determine the first several dose assignments, especially the first dose assignment.

Mean of response threshold( $\mu_R$ ) and mean of toxicity threshold( $\mu_T$ ) are assumed to independently follow a normal distribution. Standard deviation of response threshold( $\sigma_R$ ),

standard deviation of toxicity threshold( $\sigma_T$ ) , and correlation of the two thresholds( $\rho$ ) are assumed to follow an inverse-Wishart distribution with scale matrix  $R$  which is specified as  $\begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$  and degree of freedom  $\rho$  which is specified as 2.

With no data available for the first dose assignment, the prior determines the optimal dose. The likelihood for  $\varphi$  ( $\mu_R, \mu_T, \sigma_R, \sigma_T, \rho$ ) after  $n$  patients have been observed is denoted as  $L(\varphi|\mathcal{D}_n)$ . The likelihood  $L(\varphi|\mathcal{D}_n)$  and prior distribution  $\pi(\varphi)$  are used to compute the posterior distribution  $\pi^*(\varphi|\mathcal{D}_n)$  via standard Bayesian theory. The optimal dose  $opt_n$  is estimated by maximizing  $E(U|Dose)$ , and then  $\hat{opt}_n$  is assigned to the  $(n + 1)th$  patient, whose outcome depends on the following rules:

1. If the individual response threshold  $\theta_{R_{n+1}}$  is less than optimal dose  $\hat{opt}_n$ , response occurs;
2. If the individual toxicity threshold  $\theta_{T_{n+1}}$  is less than optimal dose  $\hat{opt}_n$ , toxicity occurs.

The simple study design considered here repeats the above process until 50 patients have been observed. The final recommended optimal dose should be the last optimal dose; moreover, it should be compared with the true optimal dose and optimal dose range. The approach described here can be used to guide study design choices, but this topic is beyond the scope of this section.

Three different methods are explored to calculate  $E_\varphi[P_{jk}(Dose|\varphi)]$ : MCMC with posterior mean, MCMC with MCMC sample, and importance sampling. For MCMC methods, the length of chain is 5000, the burn-in is 3000, and the thinning is 10 for every patient in this adaptive simulation. The burn-in is chosen as 3000 because the chain appears to reach equivalence before this point. Importance sampling draws 1000 independent samples  $\varphi_i$  from the prior distribution  $\pi(\varphi)$ , and the corresponding weights  $w_i$  are the corresponding ratios of  $\pi^*(\varphi|\mathcal{D}_n)/\pi(\varphi)$ .

Three scenarios are constructed for the comparison, while for simplicity the simple utility function which only focuses on the co-occurrence of response and non-toxicity is used. Table 3 demonstrates the OPT, corresponding  $Pr[Rt]$  and OPT range under different scenarios. To test the robustness of the proposed design against priors, Table 4 constructs several different prior guesses. All possible combinations of different scenarios and different priors run 100 simulations. For all of the three different computational methods, simulation results are

Table 3: *Scenarios for Comparison of Three Computational Methods*

Scenario	$\mu_R$	$\mu_T$	$\sigma_R$	$\sigma_T$	$\rho$	OPT	$Pr[Rt]$	OPT range
1	3.5	4.5	1	1	0	54.60	0.478	39.80 ~ 74.90
2	4	6	2	2	0.5	148.41	0.419	76.74 ~ 287.02
3	3	9	1	1.5	0.8	244.87	0.984	92.17 ~ 837.45

Note: OPT range is defined as the doses for which the expected utility exceeds 95% of the maximum EU.

similar. As more patients are enrolled in the trial, optimal doses approach the true optimal dose range. For example, the true optimal dose, which is based on the underlying parameters of scenario 1, is 54.60 with corresponding probability of response and non-toxicity 0.478, and the true optimal dose range is 39.80 ~ 74.90. Three different priors test the robustness of proposed design, with the first producing the first dose assignment 665.18, the second yielding the first dose assignment 244.64 and the third creating the first dose-assignment 311.09. As more patients are enrolled in the trial, optimal doses approach the true optimal dose range 39.80 ~ 74.90, although different priors produce different first dose assignments. Table 5 summarizes the estimated optimal doses for scenario 1 based on 100 simulations.

### 4.3.2 Comparison of Designs with and without Incorporating Response Information

An important goal of phase I trials is to find the appropriate dose which would be passed to phase II trials for the test of efficacy. In the case of cytotoxic chemotherapy agents, it is usually assumed that higher doses are the most effective and the toxicity is the surrogate for efficacy. The dose-response and dose-toxicity curves are closer to each other and mono-tonic. The dose at which 33 % of patients experience toxicity, the usual threshold for an acceptable level of toxicity, must be considered optimal: raising the dose leads to a significant increase in toxicity; lowering the dose leads to a large decrease in response. Based on the above

Table 4: *Priors*

Prior	$\mu_{\mu_R}$	$\mu_{\mu_T}$	$\sigma_{\mu_R}$	$\sigma_{\mu_T}$
1	5	8	3	3
2	3	9	3	3
3	4	8	3	3

Note: Three priors are very vague in order not to dominate the dose assignment.

assumption, phase I cancer clinical trials commonly use the standard MTD design.

For cancer vaccines, cytostatic agents and some herbal medications, the toxicity rate is very low, while the response rate is somewhat high. The dose corresponding to a 33% toxicity rate is far from optimal: the dose can be substantially decreased without a significant effect on response. Moreover, the response of agent could be maximized almost without toxicity. This poses challenges for the standard MTD design. This study proposes an adaptive Bayesian approach to jointly model response and toxicity, with the process of continually examining the cumulative data, updating current knowledge about parameters, and modifying optimal dose by maximizing Bayesian expected utility. Adaptive Bayesian design with cohort size 3, compared to adaptive Bayesian design with cohort size 1, provides an opportunity of speeding up the trials.

This Bayesian approach, due to its complexity, also necessitates some novel, easier to implement non-parametric designs considering both response and toxicity. The goal is to choose OPT maximizing utility.

Up-down design is based on commonly-used standard MTD design. Since toxicity is also considered in the next dose assignment, it could be called Up-down design (3+3,R's and T's). Three patients are treated at one dose level, and the next dose assignment is based on the current cohort outcomes. Four possible outcomes are given different dose-increment values.  $rt, rT, Rt, RT$  are respectively assigned to 1,  $-1, 0, -1$ . If the summation of dose-increment

values is greater than 0, then the next cohort of three patients is treated at the next higher dose. If the summation of dose-increment values is less than 0, then the next cohort of three patients is treated at the next lower dose. If the summation of dose-increment values is 0, then the next cohort of three patients is treated at the same dose level. The optimal dose  $OPT$  is the dose maximizing  $U(dose_m)$

$$\begin{aligned}
 OPT &= \arg \max_{dose_m} U(dose_m) \\
 &= \arg \max_{dose_m} \sum_{j=r}^R \sum_{k=t}^T U_{jk} n_{m_{jk}} / n_m
 \end{aligned} \tag{4.27}$$

where  $n_m$  denotes the number of patients assigned to dose  $m$ ,  $n_{m_{jk}}$  denotes the number of patients experiencing  $jk$  at dose  $m$ , and  $U_{jk}$  denotes the utility for patient outcome  $jk$ .

Accelerated design (1+3, R's and T's) is a modification of the above up-down design(3+3, R's and T's). Accelerated design treats one patient per dose level until the first toxicity occurs; the above up-down design , which treats three patients per dose level, is then launched. At the acceleration stage, the following rule applies: if  $rt$  occurs, the next patient is treated at the next higher dose. If  $Rt$  occurs, the next patient is treated at the same dose. This design provides the opportunity of speeding up the trial and reduce the number of patients assigned to lower doses. The determination of  $OPT$  for accelerated design is the same as the above up-down design.

To evaluate the proposed Bayesian adaptive design as compared to three non-parametric designs with regard to accuracy of optimal dose estimate and protection of patients, a series of simulation studies from a wide range of scenarios are performed. For any particular scenario and design, 500 simulations are conducted to reliably assess the performance of these designs.

In order to make the simulations more well-grounded the true parameters  $\mu_T$  and  $\sigma_T$  are from Dr. Richard Simons paper. Figure 6 displays functions of  $Pr[R]$  and  $Pr[T]$  over doses under different scenarios. To make plots more readable, the dose in the plots are rescaled with the original dose divided by the starting dose. The right panel has a bigger  $\mu_R$  compared to the left panel and the lower panel has a bigger  $\mu_T$  compared to the upper panel.

For the adaptive Bayesian design, individual thresholds for response and toxicity are generated from bivariate log-normal distribution with given parameters under different scenarios. The prior distributions for the parameters of interest are specified as follows.  $\mu_R$  and  $\mu_T$  are assumed to follow independently normal distributions with mean  $\mu_{\mu_R}=5$ ,  $\mu_{\mu_T}=8$ , and standard deviation  $\sigma_{\mu_R} = 3$ ,  $\sigma_{\mu_T} = 3$ . The process of updating knowledge of parameters and maximizing Bayesian expected utility is repeated until all the pre-specified patients have been observed. For three other designs, including standard MTD design (3+3, T's only), accelerated design (1+3, R's and T's), and up-down design (3+3, R's and T's), 20 fixed dose levels are pre-specified according to the modified Fibonacci series, with the first dose levels the tenth of  $LD_{10}$ . In the design simulations considered here, sample size is fixed as 30 and simple utility function focusing on response and non-toxicity is used.

Adaptive Bayesian designs produce continuous OPT through maximization of Bayesian expected utility; three alternative designs recommend one of the fixed dose levels at the end of each simulation. The comparison of five designs with regard to the accuracy of estimate and patient protection is based on 500 simulation results. Figure 7 demonstrates the accuracy of estimates among the five designs. These plots show that the CDF curves of adaptive Bayesian designs always cross true OPT lines and are steeper than three other curves, implying that the final recommended OPTs are always closer to the true OPTs. However, alternative designs starting dosage and pre-specified dose levels play an important role in the final recommendations. For example, in scenarios 5 and 6, a starting dose, 10th of  $LD_{10}$ , much lower than true OPTs, and a fixed sample size (30) are not enough to locate the OPT.

Figure 8 demonstrates the patient protection among the five designs. The bars representing adaptive Bayesian designs corresponding to Rt, the desirable outcome, are always higher among these five designs, with the bar representing adaptive Bayesian design with cohort size 1 reaching the highest. The bars representing adaptive Bayesian designs corresponding to rt, the undertreated outcome, are always lower among these five designs, with the bar representing adaptive Bayesian design with cohort size 1 reaching the lowest. These simulation results show that the Bayesian adaptive design, compared to three alternative designs, is helpful in protecting patients. Sometimes, standard MTD design protects patients.

### 4.3.3 Ethical Designs (Exploring Priors and Utilities)

The proposed adaptive Bayesian design uses full Bayesian decision analysis, in the sense of combining utility function and Bayesian posterior probability to form Expected Utility and taking Bayesian action by maximizing EU. Only if Bayesian decision theory is correctly used and the prior distribution and the utility function are sensible will the resulting clinical trial designs be both sensible and ethical; otherwise, the designs may be suboptimal or could lead to wrong conclusions.

Six scenarios, combinations of three response rates and two correlations, are constructed with  $\mu_T = 4.7$  and  $\sigma_T = 0.18$  using the real trial information from Dr. Simon's paper. Three response levels are high, good, and poor, respectively, denoting that the marginal probabilities of response at the dose level with  $Pr[T] = 0.33$  are 90%, 50%, and 20%. The two types of correlation are zero correlation and positive correlation with  $\rho$  equal to 0.9. Figure 9 shows the contour plots of the six scenarios.

This study constructs four priors with the goal of identifying the role of prior information in the ethical and optimal designs, as shown in Table 6. The four priors are combinations of different  $\mu_{\mu_T}$  and different  $\sigma_{\mu_R}$  and  $\sigma_{\mu_T}$ . The first two priors represent vague prior information with bigger  $\sigma_{\mu_R}$  and  $\sigma_{\mu_T}$ , the third prior represents optimistic prior information with a bigger  $\mu_{\mu_T}$  and smaller  $\sigma_{\mu_R}$  and  $\sigma_{\mu_T}$ , while the fourth prior represents pessimistic prior information with a smaller  $\mu_{\mu_T}$  and smaller  $\sigma_{\mu_R}$  and  $\sigma_{\mu_T}$ .

Four types of utility functions address ethical considerations:  $U_{simple}$ ,  $U_{additive}$ ,  $U_{aggressive}$ , and  $U_{cautious}$ . Figure 10 demonstrates four utility curves over dose under six scenarios. EU are the Expected Utilities given the true five parameters. Under high response scenarios, the shapes of four EU are similar with narrow concave-down areas; under good response scenarios, the shapes of four EU are different, with  $EU_{simple}$  concave-down and three other EU irregular and flat; Under poor response scenarios, the  $EU_{simple}$  is very flat, and three other EU are convex-up. The underlying reasons for these discrepancies include: 1) Expected Utility assigns four utilities to four different outcomes depending on the comparison of thresholds and assigned dose; and 2) The shapes of four probability curves over dose vary on the underlying parameters.

Three criteria summarized the operating characteristics of six scenarios based on 500 simulations: final recommended OPT, number of patients experiencing four different outcomes, and the  $EU$  at final recommended OPT. The following are simulation results:

1) Under high response scenarios, the optimal dose ranges, at which  $EU$  exceeds 95% of the maximum of  $EU$ , are narrow, while under poor response scenarios, optimal dose ranges are broad because of the broad and irregular  $EU$  shapes. The recommended optimal doses under poor response scenarios have greater variations when compared to those under high response scenarios.

2) Different utility functions, which are used to address different ethical concerns in the trials, lead to different final OPT recommendations. The OPTs from additive utility function are smaller than those from aggressive utility function, but larger than those from cautious utility function. These properties show very well, especially under the high response and good response scenarios.

3) The final OPT recommendations have little difference under four priors which test the sensibleness of the designs; even the third prior distribution is narrow. These properties show very well, especially under the high response and good response scenarios. However, the distribution of patient outcomes under prior 3 varies from those under other priors. For example, when cautious utility function is used, the means (standard deviations) of number of patients experiencing ( $rt$ ,  $rT$ ,  $Rt$ ,  $RT$ ) are 2.83(1.1), 0(0), 23.43(1.87), 3.73(0.94) under prior 3 and 5.96(2.46), 0(0), 21.81(2.87), 2.22(0.64) under prior 1 based on fixed sample size 30.

4) As far as patient protection is concerned, more patients experience  $RT$  for  $U_{aggressive}$  usage and more patients experience  $rt$  for  $U_{cautious}$  usage. Under poor response scenarios, simple utility function could lead to negative patient experience, with more patients experiencing  $rT$ , the worst desirable outcome. Additive utility function, aggressive utility function, and conservative utility function addressing different ethical concerns could improve patient experience with fewer patients experiencing  $rT$  and more patients experiencing  $rt$  or  $RT$ .

5) The  $EU$  at the final recommended OPT is closer to the  $\max(U)$  with good accuracy.

Factorial analysis was used to test the main effects and interaction effects of four variables including response (three levels), correlation (two levels), prior (four types), and utility function (four types). Factorial MANOVA was used to determine whether or not four categorical

variables and their interactions significantly affect the linear combinations of the number of patients experiencing four different outcomes. The  $EU$  at final recommended OPT and final recommended dose used factorial ANOVA to determine which of the variables and their interactions have significant effects on them. For the numbers of patients experiencing four different outcomes, all of the main effects and their interactions are significant with  $p \leq 0.01$ , same for the  $EU$  at final recommended OPT and final recommended OPT. These results demonstrate that different response levels, correlations, priors, and utility functions have significant effects on the number of patients experiencing four different outcomes, final recommended OPT, and the corresponding  $EU$ . Moreover, the effect of one variable on the dependent variables (number of patients,  $EU$  and  $OPT$ ) varies according to other variables.

#### 4.4 EXTENSION OF BINARY CASE TO CATEGORICAL CASE

The above binary outcome model now extends to a categorical outcome model. A toxicity is defined as an adverse event that is possibly, probably or definitely related to the treatment. The "Common Terminology Criteria for Adverse Events"(CTCAE) v3.0 grades toxicities with the following rule: 0=no toxicity, 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5=death. Most phase I trials define "toxicity" as the toxicity grade equal to or greater than 3. Although convenient to reduce the ordinal scale of toxicity to a binary variable for which grades 0, 1 or 2 are "no toxicity" and grades 3 or 4 are "toxicity", doing this potentially discards useful information. It is assumed that the probability of toxicity increases with dose increasing; therefore, grade 2 toxicity should provide different information about dose-escalation from grade 0 toxicity. If grade 2 toxicity occurs at dose level  $i$ , it gives a warning that the toxicity may occur at the next higher dose level. Distinguishing between grade 0, 1 or 2 toxicity rather than combining them would make the dose-escalation more reliable.

Assume there are three different toxicity levels:  $T_0$ (toxicity grade  $\leq 1$ ),  $T_1$ (toxicity grade = 2), and  $T_2$ (toxicity grade  $\geq 3$ ). The response variable is still divided into two levels,  $r$ (no response) and  $R$ (response).

Assume that every individual has two different toxicity thresholds( $\theta_{T_1}, \theta_{T_2}$ ), the first for  $T_1$ , the other for  $T_2$ . Moreover, because the two thresholds follow log-normal distributions with the same standard deviation but different means (similar to Simon et al's paper, 1997), the following occurs:  $\log(\theta_{T_1}) \sim Normal(\mu_T, \sigma_T)$  and  $\log(\theta_{T_2}) = K_T + \log(\theta_{T_1})$ , where  $K_T$  is the difference of  $\log(\theta_{T_1})$  and  $\log(\theta_{T_2})$ .

At any given dose  $i$ , if  $\theta_{T_1} > dose_i$ , then  $T_0$  occurs ; if  $\theta_{T_2} > dose_i$  and  $\theta_{T_1} \leq dose_i$ , then  $T_1$  occurs; if  $\theta_{T_2} \leq dose_i$ , then  $T_2$  occurs. Let  $\theta_{T_2} = \theta_{T_1} \exp(K_T)$ , then the following rules exist: 1) If  $\theta_{T_1} > dose_i$ , then  $T_0$  occurs; 2) If  $dose_i \exp(-K_T) < \theta_{T_1} \leq dose_i$ , then  $T_1$  occurs; and 3) If  $\theta_{T_1} \leq dose_i \exp(-K_T)$ , then  $T_2$  occurs.

We can model the categorical outcome case by not only using the bivariate normal distribution of  $(\log\theta_R, \log\theta_{T_1})$  but also introducing one more parameter  $K_T$ , which is used to distinguish the threshold of  $T_1$  and  $T_2$ . Figure 11 demonstrates the contour plot of  $(\theta_R, \theta_{T_1})$  and possible patient outcomes given the assigned dose.

We model the probability of response ( $R$ ) and toxicity( $T$ ) at given dose  $i$  based on the above assumptions. For any given dose  $i$ , there exist six probabilities:

$$\begin{aligned}
P_{irT_0} &= Pr[\theta_R > dose_i, \theta_{T_1} > dose_i] \\
P_{irT_1} &= Pr[\theta_R > dose_i, dose_i \exp(-K_T) < \theta_{T_1} \leq dose_i] \\
P_{irT_2} &= Pr[\theta_R > dose_i, \theta_{T_1} \leq dose_i \exp(-K_T)] \\
P_{iRT_0} &= Pr[\theta_R \leq dose_i, \theta_{T_1} > dose_i] \\
P_{iRT_1} &= Pr[\theta_R \leq dose_i, dose_i \exp(-K_T) < \theta_{T_1} \leq dose_i] \\
P_{iRT_2} &= Pr[\theta_R \leq dose_i, \theta_{T_1} \leq dose_i \exp(-K_T)]
\end{aligned} \tag{4.28}$$

The data after observation of  $n$  patients is  $\mathcal{D}_n = \{(Dose_m, R_m, T_m), m = 1, 2, \dots, n\}$ , and the likelihood function of  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T)$  given  $\mathcal{D}_n$  is

$$L(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T | \mathcal{D}_n) = \prod_{i=1}^n \prod_{j=r}^R \prod_{k=T_0}^{T_1, T_2} P_{ijk}^{n_{ijk}} \tag{4.29}$$

Through the application of Bayesian theorem, the joint posterior distribution of  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T)$  given  $\mathcal{D}_n$  is :

$$\begin{aligned}\pi^*(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T | \mathcal{D}_n) &\propto L(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T | \mathcal{D}_n) \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T) \\ &= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=T_0}^{T_1, T_2} P_{ijk}^{n_{ijk}} \pi(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T)\end{aligned}\quad (4.30)$$

By letting  $\theta$  denote  $(\theta_R, \theta_T)$ ,  $\varphi$  denote  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho, K_T)$ , and  $\mathcal{D}_n$  denote the data observed to the current time, Bayesian expected utility for the next patient is:

$$\begin{aligned}E(U|dose) &= E_\varphi[E_{\theta|\varphi}[U(\theta, dose)]] \\ &= \int_\varphi \int_{\theta_R} \int_{\theta_T} U(\theta_R, \theta_T, dose) f(\theta_R, \theta_T | \varphi) \pi^*(\varphi | \mathcal{D}_n) d\theta_R d\theta_T d\varphi \\ &= \int_\varphi \sum_{j=r}^R \sum_{k=T_0}^{T_1, T_2} U_{jk} P_{jk}(\varphi) \pi^*(\varphi | \mathcal{D}_n) d\varphi \\ &= E_\varphi \left[ \sum_{j=r}^R \sum_{k=T_0}^{T_1, T_2} U_{jk} P_{jk}(\varphi) \right] \\ &= \sum_{j=r}^R \sum_{k=T_0}^{T_1, T_2} U_{jk} E_\varphi [P_{jk}(\varphi)]\end{aligned}\quad (4.31)$$

$E(U|dose)$  is then maximized to get the optimal dose  $opt_n$ . Hence, the  $(n+1)th$  patient ( $\forall n = 1, 2, \dots, N$ ) receives the dose

$$\begin{aligned}OPT_n &= \arg \max_{dose} E(U|dose) \\ &= \arg \max_{dose} \sum_{j=r}^R \sum_{k=T_0}^{T_1, T_2} U_{jk} E_\varphi [P_{jk}(\varphi)]\end{aligned}\quad (4.32)$$

The categorical outcome model which considers the grades of toxicity is an extension of the bivariate binary model by introducing one more parameter  $K_T$  that distinguishes the threshold of  $T_1$  and  $T_2$ . The optimal dose is calculated by maximizing the expected utility which gives certain utilities to  $P_{irT_0}$ ,  $P_{irT_1}$ ,  $P_{irT_2}$ ,  $P_{iRT_0}$ ,  $P_{iRT_1}$  and  $P_{iRT_2}$ .

Six scenarios are constructed, with Table 7 showing the corresponding simulation results based on 100 simulations. Columns 2-7 give the underlying parameters, and column 8 is the utility function that introduces three different utility functions. Columns 9 and 10 list

the corresponding true OPT and OPT range. The last column is the mean and standard deviation of the final recommended OPT, which shows that the estimate of OPT has good accuracy (mean close to true OPT and small SD).

#### 4.5 ROBUSTNESS OF DESIGN PERFORMANCE TO MODEL MISSPECIFICATION

Drug response and toxicity within population are determined by a number of polymorphisms in genes encoding drug metabolism enzymes. Population studies typically reveal either a unimodal or bimodal distribution in the activity of these enzymes. A unimodal population distribution occurs when the population only has polymorphisms causing small variations in the activity of drug-cleaning enzymes. A bimodal population distribution occurs when a subset of population possesses mutations or polymorphisms eliminating or dramatically decreasing the activity of drug metabolism enzymes, whereas most other have polymorphisms causing slighter variations in activity [76]. Based on the study of population polymorphisms, thresholds for response and toxicity might follow a unimodal distribution for most agents and a bimodal distribution for some agents. Figure 12 clearly demonstrates population distribution in the activity of drug metabolism enzymes and corresponding distribution of thresholds.

The proposed adaptive Bayesian approach assumes that thresholds for response and toxicity follow a bivariate log-normal distribution for a therapeutic agent. This may not be applicable for some agents because of some unknown genetic variations which are related with changes of thresholds for response and toxicity. The whole population may be made up of several sub-populations following different density functions; the thresholds for response and toxicity in the whole population might follow a mixture model for some specific agents. Figure 13 explicitly shows the distribution of thresholds for response and toxicity. The whole population is made up of two sub-populations, with 10% following the first density function  $f_1(\theta_R, \theta_T)$  and 90% following the second density function  $f_2(\theta_R, \theta_T)$ . Thresholds for response

and toxicity may thus follow a mixture model that is:

$$(\theta_R, \theta_T) \sim p * f_1(\theta_R, \theta_T | \varphi_1) + (1 - p) * f_2(\theta_R, \theta_T | \varphi_2) \quad (4.33)$$

where  $p$  is the proportion of first group,  $\varphi_1$  and  $\varphi_2$  are the underlying parameters for the two sub-populations.

Appendix A gives a detailed mathematical description of the two models with one based on the Gaussian distribution and the other on the mixture model. Simulations should be conducted to check the robustness of proposed method when the basic model assumptions are violated. Individuals with specific thresholds should be sampled from a known mixture model and then assigned to the estimated current optimal doses which maximize expected utility based on the bivariate log-normal distribution assumption. A comparison of the assigned doses to patients' thresholds generates the outcomes of patients. The true optimal dose should be based on a mixture model assumption whose four probabilities,  $P_{irt}$ ,  $P_{irT}$ ,  $P_{iRt}$ , and  $P_{iRT}$ , are mixtures of two parts:  $p * P_{ijk}(\varphi_1) + (1 - p) * P_{ijk}(\varphi_2)$ ,  $\forall j = r, R, k = t, T$ , where  $P_{ijk}(\varphi_1)$  is the probability for the first distribution, and  $P_{ijk}(\varphi_2)$  is the probability for the second distribution.

To simplify the simulations, assume that the means of thresholds have the same ratio for two subpopulations as well as standard deviations of thresholds. Therefore,  $\varphi_2$  is  $(\mu_R, \mu_T, \sigma_R, \sigma_T, \rho)$  and  $\varphi_1$  is  $((\mu_R * \mu_{ratio}), (\mu_T * \mu_{ratio}), (\sigma_R * \sigma_{ratio}), (\sigma_T * \sigma_{ratio}), \rho)$ . Different  $\rho$  and  $p$  construct six scenarios with Figure 14 demonstrating the corresponding contour plots.

Table 8 demonstrates the simulation results using additive utility function. Columns 2-8 give the underlying parameters and column 9 is the proportion of first group. Columns 10 and 11 list the corresponding true OPT and OPT range. The last column, the mean and standard deviation of the final recommended OPT, shows that the estimate of OPT has good accuracy (mean close to true OPT and small SD).

Table 5: *Results of Scenario 1 for Comparison of Three Methods*

M	Prior	$\overline{opt}_{10th}(sd)$	$\overline{opt}_{20th}(sd)$	$\overline{opt}_{30th}(sd)$	$\overline{opt}_{40th}(sd)$	$\overline{opt}_{50th}(sd)$	$opt$	opt range
1	1	77.12(18.02)	72.23(12.38)	67.34(10.37)	62.3(9.31)	56.43(8.23)	54.60	39.80~74.90
	2	75.56(19.32)	65.23(13.45)	60.18 (8.34)	58.12(9.39)	57.22(5.62)	54.60	39.80~74.90
	3	68.56(20.47)	62.34(12.97)	63.45(9.98)	58.45(8.23)	58.26(5.39)	54.60	39.80~74.90
2	1	77.20(22.34)	58.49(14.28)	55.34(13.28)	56.72(9.37)	54.32(5.23)	54.60	39.80~74.90
	2	68.29(19.7)	62.34(12.82)	58.23(9.26)	58.19(8.12)	56.34(6.16)	54.60	39.80~74.90
	3	89.23(25.4)	67.87(14.27)	63.28(10.26)	59.23(9.24)	56.87(4.12)	54.60	39.80~74.90
3	1	71.34(19.23)	59.21(12.31)	58.98(9.51)	58.23(8.24)	56.39(4.23)	54.60	39.80~74.90
	2	82.83(22.94)	64.29(10.27)	60.23( 9.14)	61.34(8.17)	58.32(6.21)	54.60	39.80~74.90
	3	71.93(17.8)	62.19(13.4)	65.75(12.73)	58.12(9.32)	54.23(6.23)	54.60	39.80~74.90

*Note:*

Method 1 (M1): MCMC with posterior mean

Method 2 (M2): MCMC with MCMC sample

Method 3 (M3): Importance sampling

$opt$ : Optimal dose

opt range: Optimal dose range

$\overline{opt}_{ith}(sd)(\forall i = 10, 20, 30, 40, 50)$  : The average of estimated optimal doses and corresponding standard deviation of the estimated optimal doses assigned to  $ith$  patient.

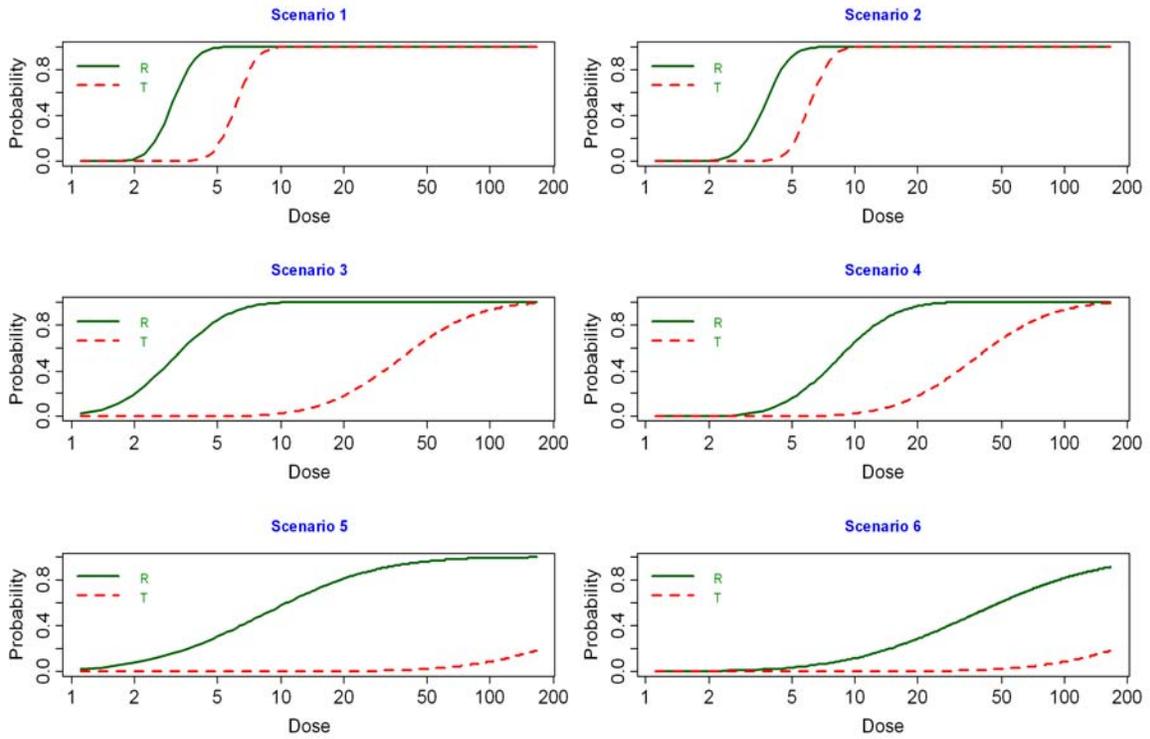


Figure 6: *Probabilities under Six Different Scenarios*

Note: The right panel has a bigger  $\mu_R$  compared to the left panel and the lower panel has a bigger  $\mu_T$  compared to the upper panel.

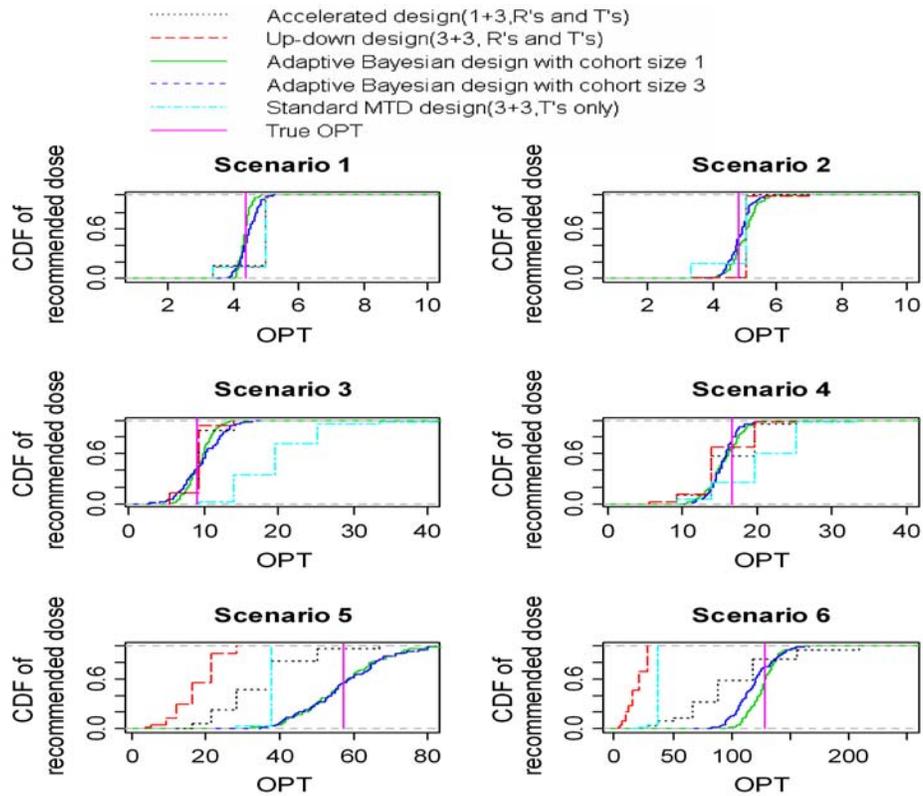


Figure 7: *Comparison of Accuracy of Estimates among Five Designs*

Note: The CDF curves of adaptive Bayesian designs always cross true OPT lines and are steeper than three other curves, implying that the final recommended OPTs are always closer to the true OPTs.

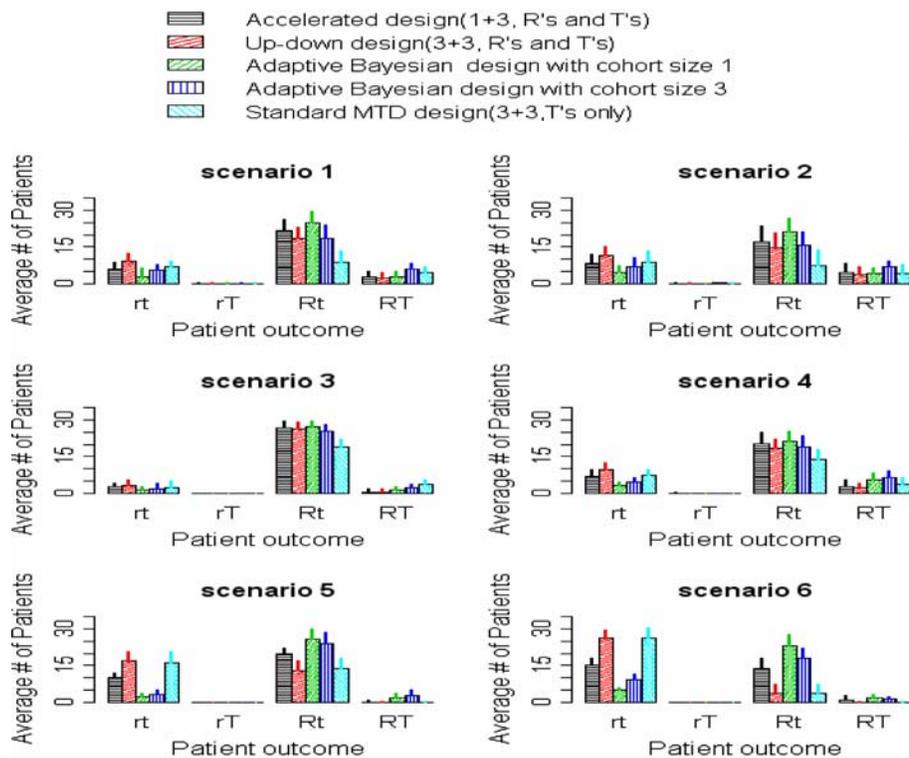


Figure 8: *Comparison of Patient Protection among Five Designs*

Note: The bars representing adaptive Bayesian designs corresponding to Rt, the desirable outcome, are always higher among these five designs; The bars representing adaptive Bayesian designs corresponding to rt, the undesirable and under-treated outcome, are always lower among these five designs.

Table 6: *Priors for the Ethical Designs*

Prior	$\mu_{\mu_R}$	$\mu_{\mu_T}$	$\sigma_{\mu_R}$	$\sigma_{\mu_T}$
Vague prior	5	8	3	3
Vague prior	5	4	3	3
Optimistic and narrow prior	5	8	1	1
Pessimistic and narrow prior	5	4	1	1

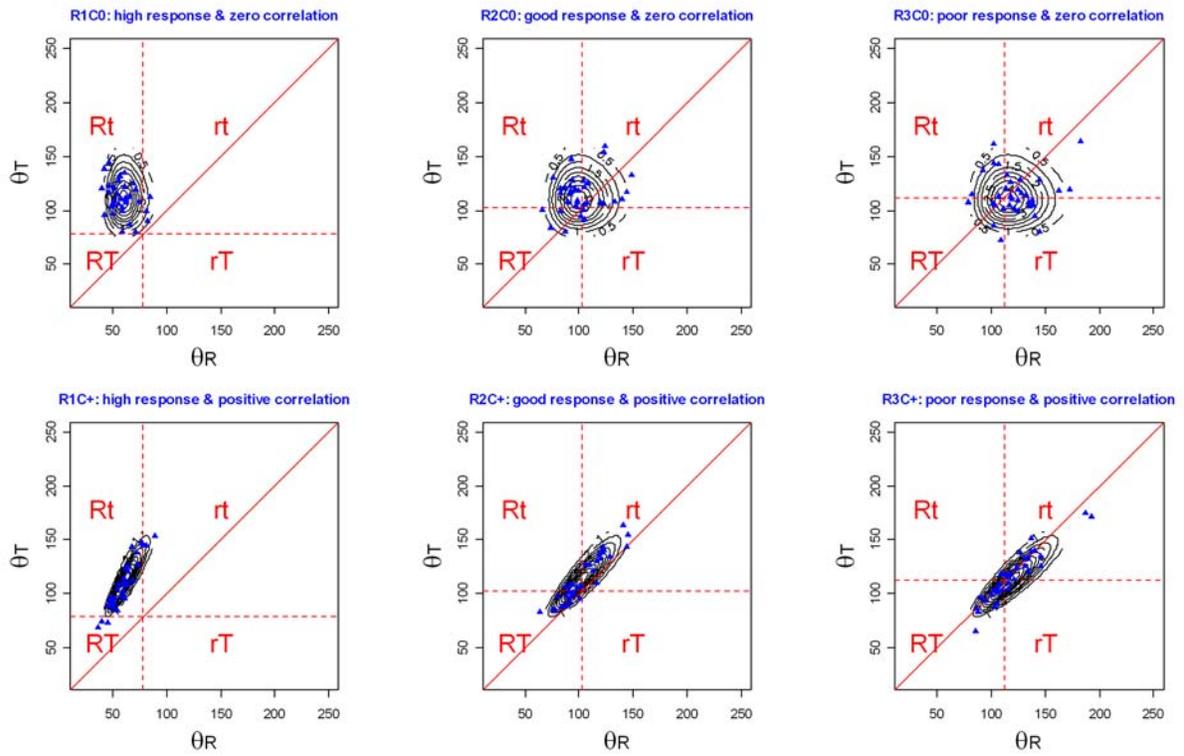


Figure 9: *Contour Plots of Six Scenarios*

Note: Three response levels are high, good, and poor, respectively, denoting that the marginal probabilities of response at the dose level with  $Pr[T] = 0.33$  are 90%, 50%, and 20%. The two types of correlation are zero correlation and positive correlation with  $\rho$  equal to 0.9.

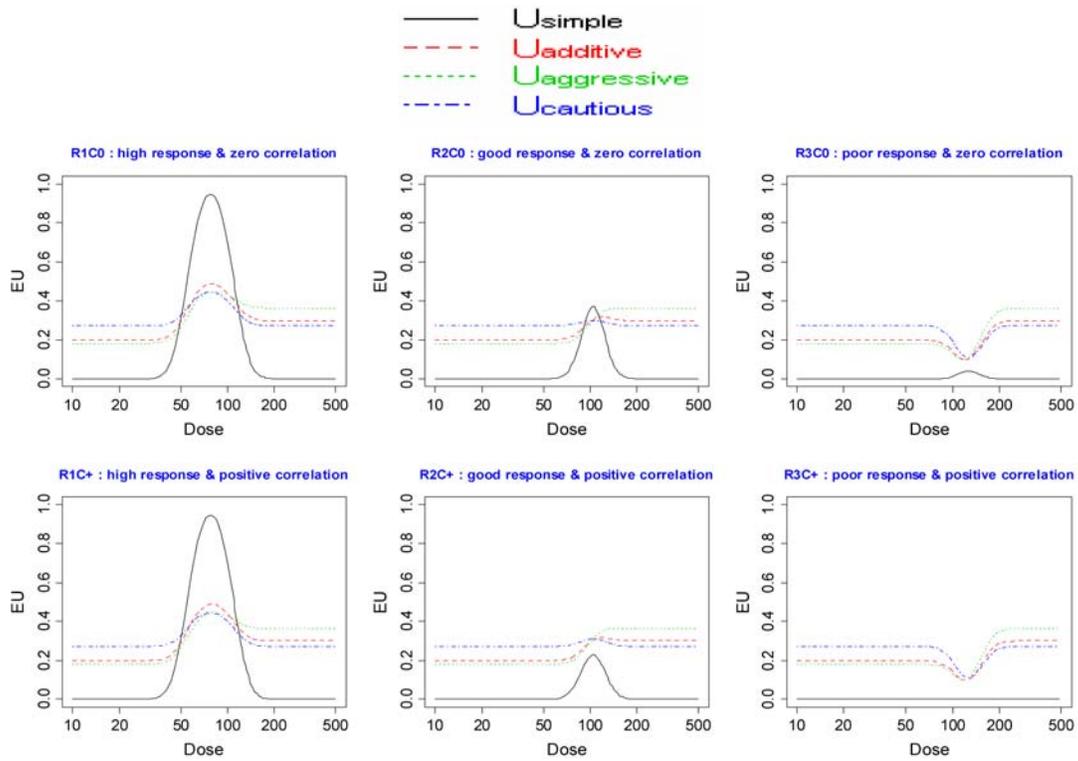


Figure 10: *Four EUs under Six Scenarios*

Note: Under high response scenarios, the shapes of  $EU$  are similar with narrow concave-down areas; under good response scenarios, the shapes of  $EU$  are different, with  $EU_{simple}$  concave-down and three other  $EU$  irregular and flat; Under poor response scenarios, the  $EU_{simple}$  is very flat, and three other are convex-up.

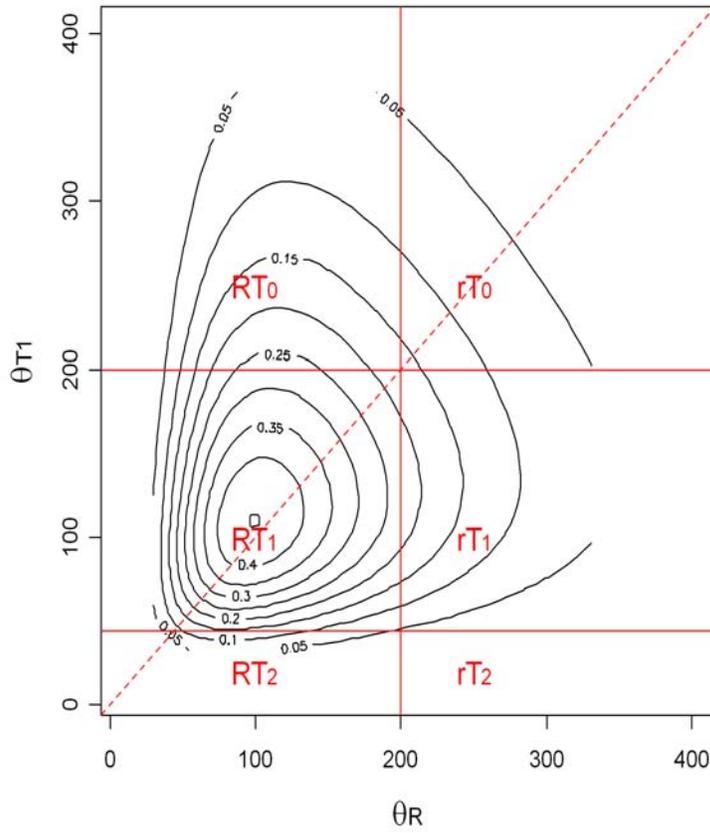


Figure 11: *Distribution of Thresholds  $(\theta_R, \theta_{T_1})$*

Note: The diagonal line in the contour plot represents possible assigned doses. Along this diagonal line, the vertical and horizontal lines divide the whole population into six subgroups ( $rT_0$ ,  $rT_1$ ,  $rT_2$ ,  $RT_0$ ,  $RT_1$  and  $RT_2$ ).

Table 7: *Simulation Results for Categorical Outcome Model*

Scenario	$\mu_R$	$\mu_T$	$\sigma_R$	$\sigma_T$	$\rho$	$K_t$	Utility	OPT	OPT range	$\overline{opt}_{est}(SD)$
1	4	4.5	0.18	0.18	0	0.2	(0.2,0,0,0.3,0.3,0.2)	78.08	63.66 ~ 94.87	77.23(5.81)
2	4	4.5	0.18	0.18	0	0.2	(0.1,0,0,0.6,0.3,0)	71.86	65.20 ~ 79.35	72.38(3.82)
3	4	4.5	0.18	0.18	0	0.2	(0,0,0,0.5,0.5,0)	77.48	69.20 ~ 86.75	80.38(4.36)
4	4	5.8	0.68	0.68	0.3	0.7	(0.2,0,0,0.3,0.3,0.2)	192.00	94.39 ~ 387.68	182.18 (37.87)
5	4	5.8	0.68	0.68	0.3	0.7	(0.1,0,0,0.6,0.3,0)	146.94	103.00 ~ 210.42	132.92( 22.84)
6	4	5.8	0.68	0.68	0.3	0.7	(0,0,0,0.5,0.5,0)	190.57	128.05 ~ 283.61	178.26 (32.91)

Note:  $K_t$  is the difference between  $\theta_{T_1}$  and  $\theta_{T_2}$ .  $OPT$  is the true OPT and  $OPT$  range is the doses at which EU exceeds 95% of maximum of EU.  $\overline{opt}_{est}(SD)$  denotes the mean and standard deviation of the final recommended OPT, implying the estimate of OPT has good accuracy (mean close to true OPT and small SD).

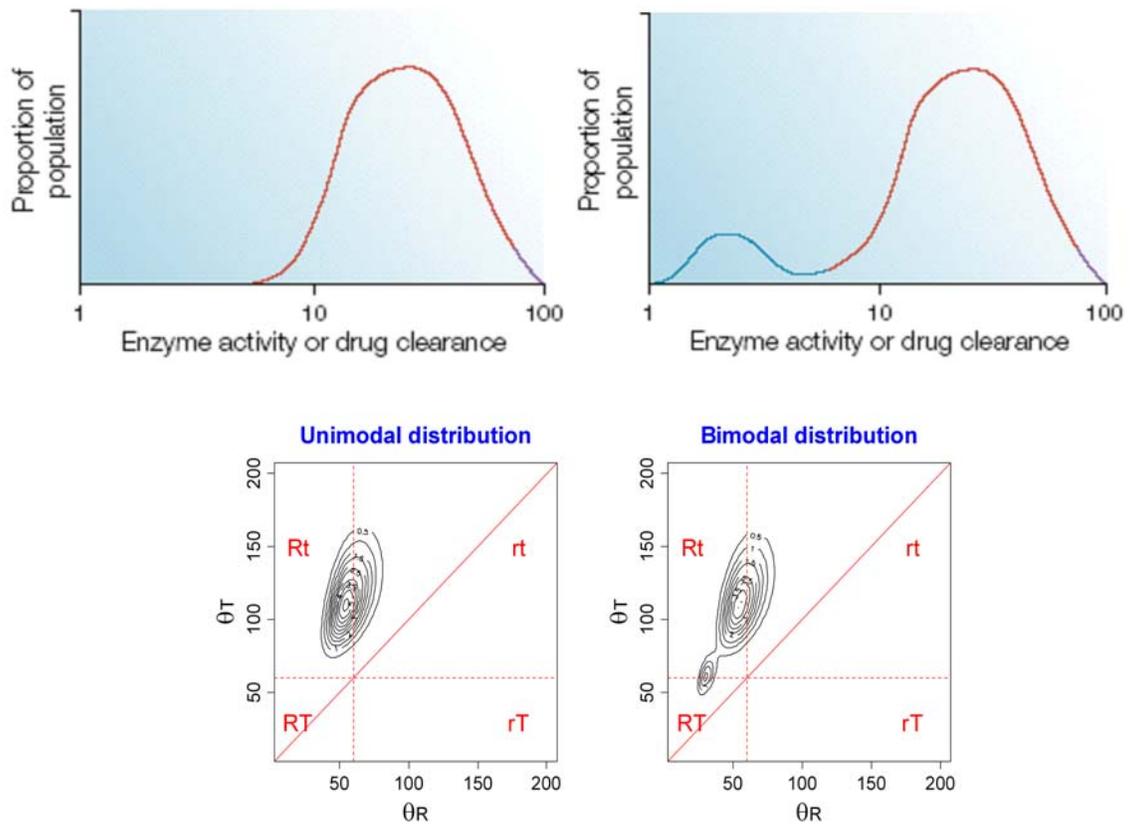


Figure 12: *Population Distribution in the Activity of Drug Metabolism Enzymes and Corresponding Thresholds ( $\theta_R, \theta_T$ )*

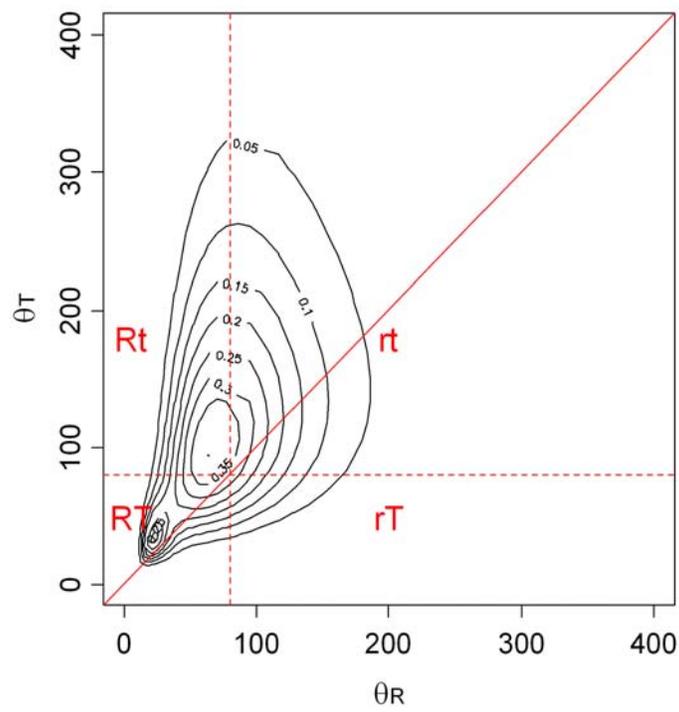


Figure 13: *Distribution of Thresholds ( $\theta_R, \theta_T$ )*

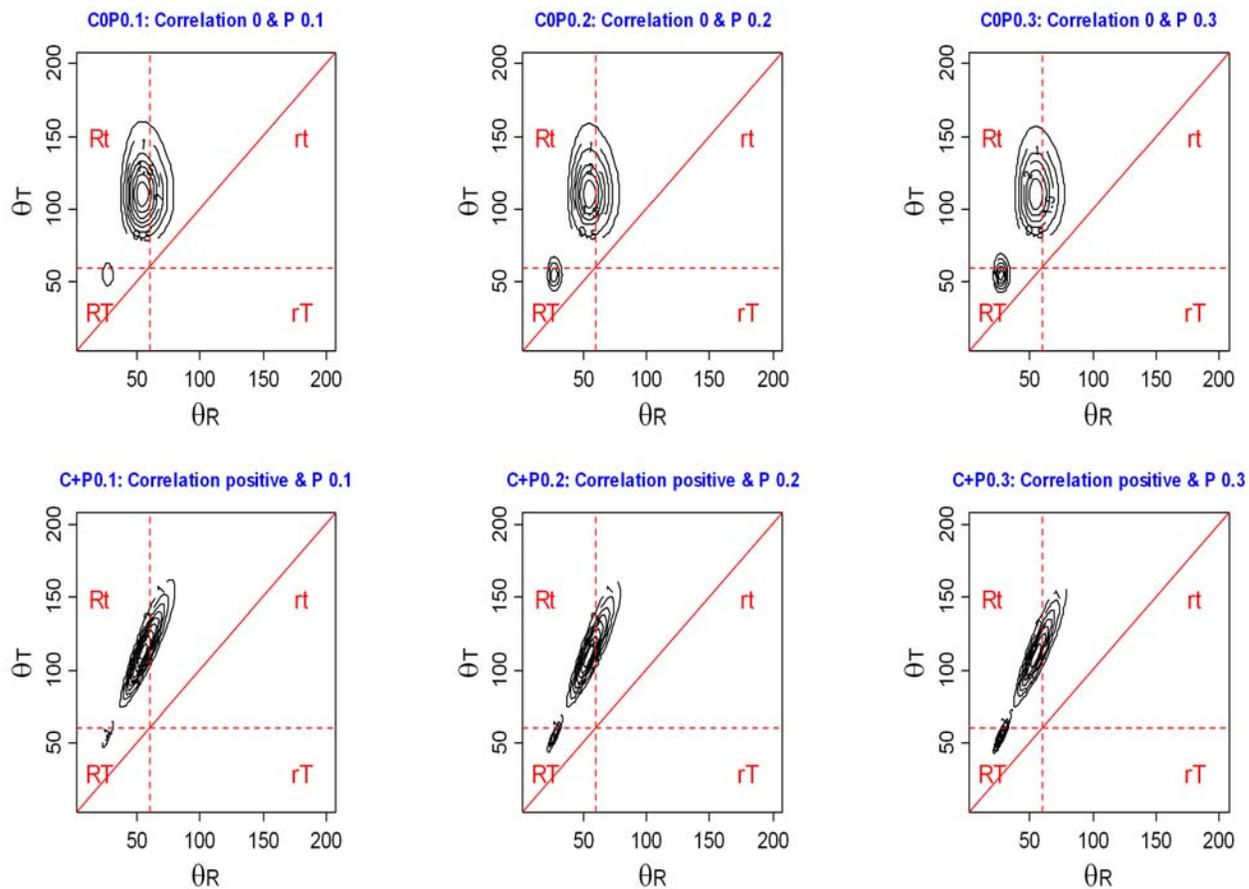


Figure 14: *Scenarios for Robustness Check*

Note: The contour plots of six scenarios, which are combinations of correlation  $\rho$  and proportion  $p$

Table 8: *Different Scenarios and Simulation Results for Mixture Model*

Scenario	$\mu_R$	$\mu_T$	$\sigma_R$	$\sigma_T$	$\rho$	$\mu_{ratio}$	$\sigma_{ratio}$	$p$	OPT	OPT range	$\overline{opt}_{est}(sd)$
C0P0.1	4.0	4.7	0.18	0.18	0	0.8	0.8	0.1	78.89	66.79 ~ 93.95	85.92(4.31)
C0P0.2	4.0	4.7	0.18	0.18	0	0.8	0.8	0.2	78.82	66.00 ~ 94.59	79.95(3.94)
C0P0.3	4.0	4.7	0.18	0.18	0	0.8	0.8	0.3	78.72	64.85 ~ 95.38	85.98(4.47)
C+P0.1	4.0	4.7	0.18	0.18	0.9	0.8	0.8	0.1	78.89	66.79 ~ 93.95	84.61(5.38)
C+P0.2	4.0	4.7	0.18	0.18	0.9	0.8	0.8	0.2	78.82	66.00 ~ 94.59	83.26(4.83)
C+P0.3	4.0	4.7	0.18	0.18	0.9	0.8	0.8	0.3	78.72	64.85 ~ 95.38	81.21(5.86)

Note: The six scenarios are combinations of correlation  $\rho$  and proportion  $p$ . The estimate of OPT has good accuracy(mean close to true OPT and small SD).

## 4.6 APPLICATION

Clinical protocols for cancer vaccines present a case where, based on previous experience, toxicities are usually not expected to be severe, and dose-seeking is often strongly motivated by the need to identify a dose that may plausibly lead to a clinically meaningful benefit in subsequent studies. Under such circumstances, there is a motivation to bypass phase I trials. Since vaccines have occasionally had unexpected severe toxicity, caution needs to be built into the experimental design. Previous studies indicate that clinical response is associated with "determinant spreading" (Ribas 2003)[74], providing a potential indication of clinical potential with higher frequency than clinical response. The approach here, based on expected utility, can help guide dosage choices by taking into account such a biological measurement. Another area of application is the study of agents whose clinical benefits may not be associated with traditional clinical responses at all: agents which induce cytostatic behavior over extended time periods. In this case, with no timely clinically observed endpoint, the availability of indicators of biological activity from ancillary laboratory studies

can augment such a trial usefully. For example, apoptosis in post-treatment bone marrow biopsies has been studied in the treatment of patients' myelodysplastic syndromes with the anti-angiogenic agent Thalidomide (Bouscary 2005)[75].

Gleevec(Imatinib), a relatively specific inhibitor of the BCR-ABL tyrosine kinase, is the first successful cytostatic agent for CML. The initial phase I dose-escalation study showed that Gleevec is well tolerated and has significant antileukemic activity in patients with CML, demonstrating the potential of development of anticancer drugs based on the specific molecular abnormality [77]. The five-year follow-up study showed that Gleevec as initial therapy of treatment of chronic-phase CML, was found to induce a durable response in a high proportion of patients with estimated rates of complete hematologic response 98%, major cytogenetic response 92%, complete cytogenetic response 87%, event-free survival 83%, progression 7%, and overall survival 89% [78]. In the case of Gleevec, there is minimal toxicity, high response and a strong relationship between response and survival. Such a circumstance, which we hope will be increasingly more common in the future, would be the most promising for achieving benefit from the proposed design incorporating both response and toxicity, in comparison to phase I dose-finding trials based solely on adverse effects.

From the published data, the toxicity and hematologic complete response curves were estimated from the bivariate unimodal threshold model, via maximum likelihood (Figure 15 A). Simulations based on this fit and both proposed and standard designs were conducted to investigate the criteria of patient protection and accuracy of the optimal dose estimate. Table 9 shows the comparison among the results of the original paper, the simulation average for the standard MTD design, and the simulation average for the proposed design incorporating both response and toxicity. The latter was repeated with several utility functions (simple, additive, cautious, aggressive). The proportions of outcomes varied across the designs. Because the design used in the original paper was a somewhat modified standard MTD design that did not exactly follow the dose-escalation rules in standard MTD design, the proportions of outcomes from the simulated standard MTD design differed from those of the original paper. The original design and the standard MTD design had more patients with neither response nor toxicity. In the original paper of 83 patients, 19 patients (23%) were undertreated, experiencing  $rt$ , while less than 20% of the patients experienced  $rt$  under

the guidance of proposed design with four different utilities. Excluding the proposed design with aggressive utility function usage, the percentage of overtreated patients did not vary significantly across the designs. Moreover, the final recommended doses based on the proposed design approximate the recommended dosage in the original paper except under the aggressive utility usage. This provides evidence about the importance of the choice of utility function.

It is of interest to know whether or not the larger proportion of "undertreated" patients with the original design is due to appropriate cautiousness which would be beneficial had the drug been more toxic. Therefore, we reran the comparison using a threshold distribution for toxicity centered at a much lower value. Figure 15 B demonstrates the toxicity curve and hematologic complete response curves, and Table 9 shows the simulation results. Compared to the results based on the curve A, the percentages of undertreated and overtreated patients are higher. Furthermore, except under the aggressive utility usage, the percentages of undertreated patients under proposed designs are closer to those from the original paper, lending support to the original design with appropriate cautiousness about the more toxic guess leading to the larger percentage of "undertreated" patients.

The aggressive utility function usage leading to obviously undesirable patient experience and dose recommendation, further support the importance of the choice of utility function with only sensible and ethical utility function leading to more ethical designs. Moreover, the underlying reasons also could be that: When the assigned dose is greater than threshold of response, the patient may not react to the higher assigned dose level due to severe toxicity, withdrawal from the study, death, etc, which exclude response.

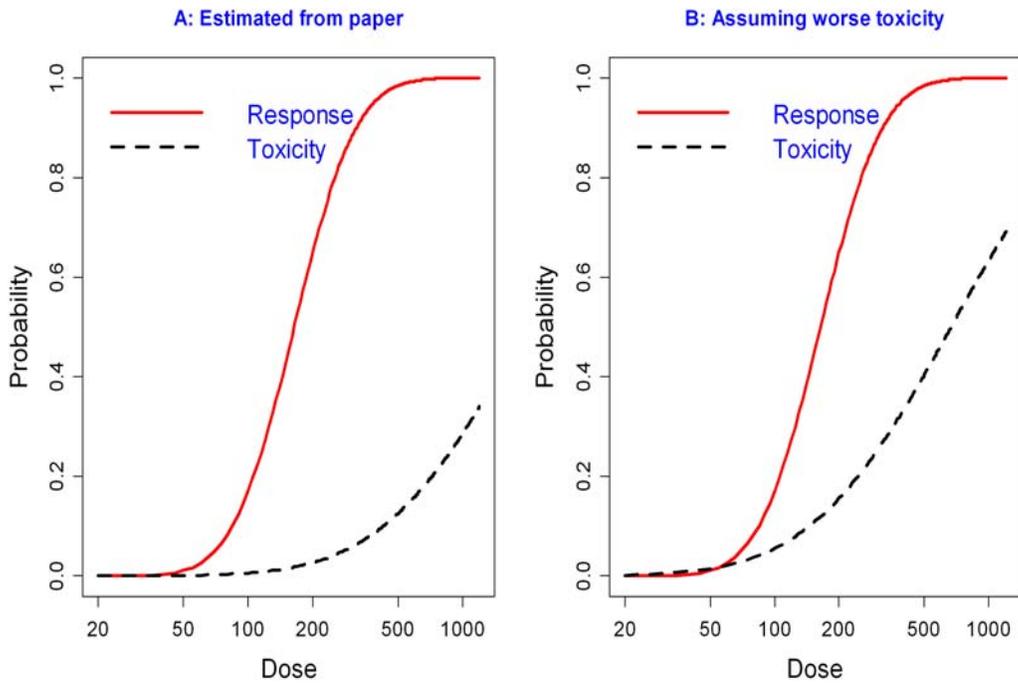


Figure 15: *Assumed Toxicity and Hematologic Response Curves for Gleevec*

Note: Figure A is estimated from the original paper; Figure B assumes worse toxicity.

Table 9: *The Application of Gleevec Data*

Assumed Toxicity Model	Source or Designs	U	Percentage of Patients Outcome				Recommended Dose( $mg/m^2$ )	Patients Enrolled
			$rt$	$rT$	$Rt$	$RT$		
			mean (sd)				mean(sd)	mean
	Original paper	-	23	0	66	11	400	83
Estimated	Standard design	-	33(8)	0(0)	59(10)	8(3)	500(100)	42
	Proposed design	$U_{sim}$	11(5)	0(0)	78(8)	11(6)	390 (80)	30
		$U_{add}$	12(6)	0(0)	76(9)	12(6)	370(67)	30
		$U_{agg}$	0(0)	0(0)	72(10)	28(10)	> 1200(380)	30
		$U_{cau}$	16(7)	0(0)	74(10)	10(4)	340(72)	30
More toxicity	Standard design	-	57(10)	0(0)	30(5)	13(4)	200(40)	27
	Proposed design	$U_{sim}$	15(6)	0(0)	62(10)	23(8)	350(60)	30
		$U_{add}$	22(9)	0(0)	53(12)	25(6)	275(60)	30
		$U_{agg}$	5(5)	0(0)	10(10)	85(15)	> 1200(> 500)	30
		$U_{cau}$	49(12)	0(0)	38(10)	13(7)	185(50)	30

Note: The proportions of outcomes from the simulated standard MTD design differed from those of the original paper because the design used in the original paper did not exactly follow the dose-escalation rules in standard MTD design. The percentages of  $rt$  and  $RT$  are higher under more toxicity assumption(Curve B) compared to those under estimated toxicity model(Curve A).

## 4.7 DISCUSSION

Although the primary goal of phase I trials is to find the maximum tolerated dose to pass to phase II trials for further investigation of efficacy, with the emergence of cytostatic agents and vaccine, in which the toxicity rate may be very low, finding a promising therapeutic dose might be a better goal. Responses are rare in phase I cancer trials. But "biological responses" may be common. Most biomarkers may not provide true surrogate endpoint information, but provide confirmation that the drug has the hoped-for potential. Augmenting toxicity data with biological endpoint data might be important in phase I trials. In phase I cancer clinical trials, the chance of benefit and risk of toxicity are uncertain; this leads to tough ethical problems, especially at the beginning stage of trials and the first-in-human trials. What dose should be assigned to the next patient is the key decision in the implementation of trials.

We have proposed an adaptive Bayesian dose-finding algorithm that incorporates both response and toxicity under the assumption that thresholds of response and toxicity follow a bivariate log-normal distribution. In an ideal decision theory framework, the choice of dose for each successive patient would incorporate what is best for the patient, together with the value of the information to be obtained for the trial. However, to explicitly evaluate the latter would be computationally difficult. For simplicity, we restrict attention to the probability of each outcome for the next patient only. The model assumes that response and toxicity events happen depending on the respective thresholds for response and toxicity, and it provides a framework for incorporating prior information about the population threshold distribution as well as accumulated data. The next dose can be assigned to maximize expected utility, which assigns certain utilities to all possible outcomes. The most impressive advantage of the proposed adaptive Bayesian design is to address ethical considerations through full Bayesian decision analysis, combining utility and Bayesian posterior distribution to take a Bayesian action by maximizing expected utility. Moreover, Bayesian expected utility could be expressed as a function of dose and population threshold parameters; therefore, adaptive Bayesian design has some ability to fully explore dose response and toxicity curves, providing useful information for the future dosage modification in subsequent phase II trials.

In either the standard non-parametric or some parametric dose-finding designs, patients are allocated to the pre-specified doses, thereby posing many problems. Berry discussed this in detail. When the study results become known, the investigators usually regret not having assigned patients in some other fashion. Perhaps the dose-response curve seems to shift to the left or right from the anticipated curve. If so, then assignment of patients on one end or the other of the dose range was wasted. Perhaps the slope of the dose-response seems to be steeper than anticipated in a narrow interval. In this case, the patients assigned to the flat regions of the curve would have been more informative had they been assigned doses in the region with steeper slope[80]. A better strategy to avoid the above results is to proceed adaptively using cumulative information to assign to continuous doses, not pre-fixed doses.

Extensive simulations are conducted to assess the design performance with regard to the accuracy of estimate and patient protection under high response scenarios. The adaptive Bayesian design incorporating both response and toxicity and using continuous adaptive doses based on the maximization of Bayesian expected utility is more effective in identifying the right dose; and it usually identifies the right dose with small sample size in comparison with alternative designs with or without incorporating toxicities and using pre-specified fixed doses. Moreover, the adaptive Bayesian design considering both response and toxicity could lead to more patients experiencing desirable outcome  $Rt$  and fewer patients experiencing undertreated outcome  $rt$  compared to standard MTD design and two other non-parametric designs. This provides evidence incorporating response has potential to improve early clinical trials.

The proposed adaptive Bayesian design, a full Bayesian approach combining utility function and Bayesian posterior probability, provides an opportunity to run more ethical and informative trials by taking into account priors and utilities that balance the value of knowledge with what benefits patients. However, only if Bayesian decision theory is correctly used and the prior distribution and the utility function are sensible will the resulting clinical trial designs be both sensible and ethical; otherwise, the designs may be suboptimal, sometimes leading to wrong conclusions. Four priors and four utility functions address the design performance under different scenarios, combinations of three types of response and two types of correlation with regard to the final recommended OPT, number of patients experiencing four

different outcomes, and the EU at final recommended OPT. In this design,  $\mu_R$  and  $\mu_T$  are assumed to follow normal distributions with prior information, and the variance-covariance matrix  $\Sigma$  is assumed to follow the Inverse-Wishart( $R, \rho$ ) distribution with vague information, which has little effect on the posterior estimate of  $\Sigma$ . When the prior guess about threshold mean is far from true value and the distribution is narrow, cumulative patient information still dominates the final conclusions. The final recommended optimal dose is still closer to the true value, but the distribution of patient outcomes under optimistic or pessimistic prior differs from that under vague prior guesses. We could conclude that when the prior distribution is too optimistic or pessimistic, the designs may be suboptimal. To avoid the suboptimal trials, the best strategy is to use vague prior information when prior information from previous trials or pre-clinical trials is uncertain.

Simple utility function just putting positive utility on co-occurrence of response and non-toxicity, is dangerous especially under the cases where responses are rare. Under the high response scenarios, different utility functions lead to different final OPT recommendations. The OPTs from additive utility function are smaller than those from aggressive utility function, but larger than those from cautious utility function. Under poor response scenarios, the EU curves are flat and irregular depending on the assigned utilities, meaning that given the pre-specified utility, the optimal dose range is broad. Moreover, the introduction of utility could lead to more patients experiencing desirable outcomes corresponding to the specified utilities, therefore protecting patients.

The application of the proposed design to Gleevec data is successful, even though the original Gleevec phase I dose-finding trial focuses solely on toxicity. This provides strong evidence not only for the feasibility of the application of new designs to the future real trials but also for the importance of the choice of utility function.

Before implementing the trials, the relationship of toxicity and response curves is not clear. Figure 16 Case A demonstrates cases where the dose-response curve is suddenly steep around the dose level with  $Pr[T] = 0.33$ , however, the dose-toxicity curve is flat. Raising the dose leads to a significant increase in response; lowering the dose leads to a large decrease in response, but the changes of dosage around MTD have little influence on toxicity. Under these circumstances, good response should cause a trial to push the dose higher based on

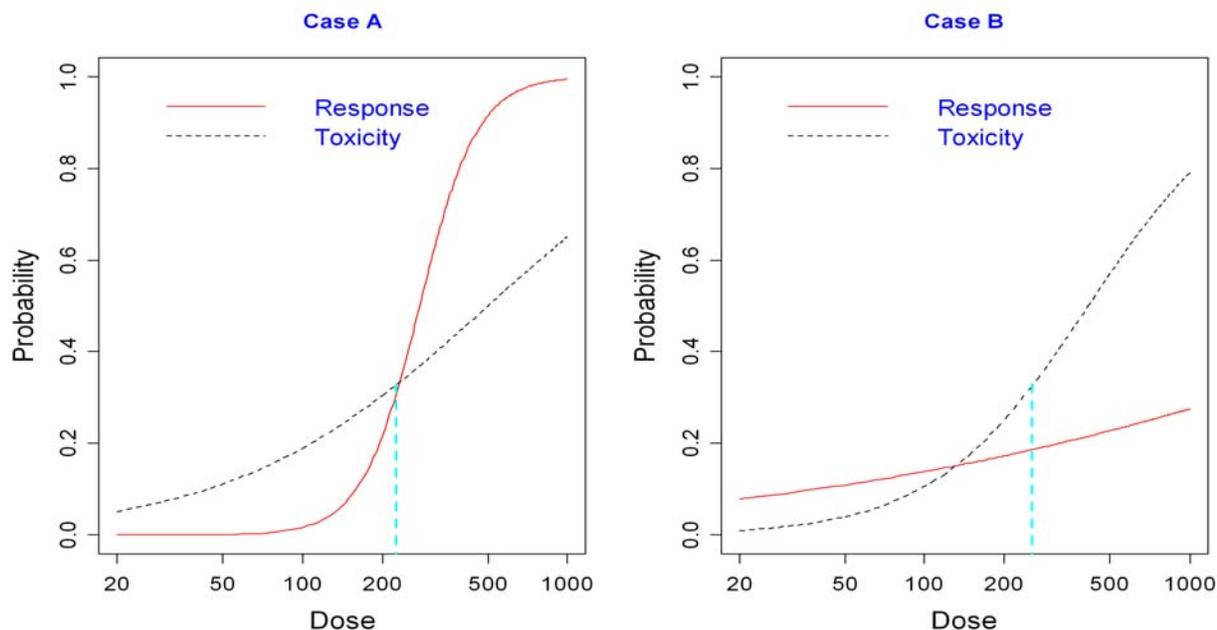


Figure 16: *Possible Relationship of Response and Toxicity Curves*

the great gain on response without significantly jeopardizing toxicity. Moreover, patient preference about the trade-off of response and toxicity must also be incorporated. Under the cases where the dose-response curve is much flatter than the dose-toxicity curve, Figure 16 Case B demonstrates this clearly. The MTD corresponding to the pre-specified target toxicity may lead to poor response. If an agent is safe and well-tolerated but has little effect on response, it may be a counter-indication for phase II commitment. Under these circumstances, low response should cause a trial to stop earlier based on the potential poor benefit on response. This requires the incorporation of both response and toxicity in dose-seeking process. An expected utility curve that is flat or irregular signals that the optimal dose range is wide and the investigator could decide the optimal dose and the termination of the trials.

Although the proposed dose-finding algorithm is involved with more complicated modeling and computation than regular dose-finding algorithms, it still has several advantages:

- 1) It introduces a new concept that dose-finding could be solved in term of thresholds for re-

sponse and toxicity determining the occurrence of response and toxicity; and 2) Full Bayesian decision-analytic approach is used, therefore taking into account both scientific and ethical concerns with the goals to identify the right dose as effectively as possible and to treat more patients as ethically as possible.

The proposed model assumes that patients experience response and toxicity according to their specific thresholds following a bivariate log-normal distribution. However, some potential drawbacks exist. First, our model assumes that if threshold is less than or equal to the assigned dose, event occurs; this means only if the assigned dose is equal to or greater than the patients' specific threshold dose event occur. This is not true for agents. When the assigned dose is greater than threshold of response, the patient may not react to the higher assigned dose level due to severe toxicity, withdrawal from the study, death, etc. We could use "response-limiting event" to denote these possible reasons. In addition, some patients are refractory to specific agents, meaning that their threshold of response is closer to infinity. To eliminate the above two drawbacks, the model should be modified by introducing response-limiting toxicity threshold and probability of refractory. TKRLOT has explored some properties about the model incorporating the above two factors. The results seem encouraging, but given the relatively small size of phase I study, it is not feasible to apply the fully developed model to real trials.

## 5.0 KNOWLEDGE-DIRECTED BAYESIAN ADAPTIVE DESIGN IN PHASE I TRIALS

### 5.1 INTRODUCTION

Pharmacogenetics and pharmacogenomics gained much popularity to elucidate the genetic basis for interindividual difference in drug efficacy and toxicity commonly observed in all therapeutic areas. Pharmacogenetics (PG) is the study of the relationship between an individual's genetic makeup and the response to drugs, whereas pharmacogenomics investigates a large number of clinically important genes and their expressions that underlie the response to the drugs. PG variations lead to the changes of drug absorption, distribution, metabolism, excretion, drug-target interaction, and finally have an important impact on the drug response through pharmacokinetics(PK) and pharmacodynamics(PD). PK effects are due to the inter-individual differences in absorption, distribution, metabolism, or excretion of the drug, which influence the final drug concentration at intended sites. For example, PK genetic variation resulting in loss or increase of drug metabolizing enzyme (DME) activity, and then the change of clearance rate can have profound effects on the relationship between drug dosage and observed plasma concentrations[69, 70, 91, 92]. PD effects are due to the functional difference of receptor or serum binding proteins. For example, the polymorphisms of genes encoding transporters or receptors are likely to affect the efficacy of cancer treatment, either by directly affecting antitumor efficacy or by influencing the likelihood of unacceptable adverse effects[82, 83, 84, 85, 86].

PK/PD modeling, which considers the dose-exposure-effect relationship, gained much attention in drug development in the past decades. Exposure can be the drug concentration vs time profile, or a summary measure such as area under the concentration curve(AUC)

or maximum concentration( $C_{max}$ ). Effect may be a pharmacological marker, a measure of efficacy or safety. The introduction of PK/PD modeling to the drug development process has provided a vital tool that facilitates the drug approval process by providing individualized dose-exposure-effect predictions. To date, however, the potential of this tool has not been widely used in practice. In 1986, Collins et al[93] proposed the "Pharmacokinetically guided dose-escalation(PGDE)". This approach assumes that interspecies variability in toxicity is largely due to interspecies differences in drug metabolism, elimination and binding. The difference between  $LD_{10}$  in mice and the MTD in humans was huge, but the AUC at the  $LD_{10}$  in mice was of the same order of magnitude as the AUC at the MTD in men. Therefore, it was suggested that AUC be used as a target of dose-escalation in phase I studies.

Genetic variations related with changes drug concentration at intended sites or response targets which finally have an influence on the drug response have been widely explored, and some of them have already been used in clinical practice. For example, three genotypes of TPMT have dramatically different effects on AUC through the PK process, while no evidence supports the effects on PD process. Patients who carry TPMT mutations are at risk for severe hematologic toxicities when treated with 6-MP because these mutations lead to a decrease in the rate of 6-MP metabolism [67, 68]. Appropriate 6-MP dose reductions for TPMT-deficient patients have allowed for similar toxicity and survival outcomes as patients with normal TPMT levels[69, 70]. TPMT testing is now being used for dose optimization in children with ALL before 6-MP is initiated[72]. Irinotecan, an anticancer drug, metabolized by UGT1A1, is associated with severe diarrhea and neutropenia. In vivo research demonstrated an association between UGT1A1\*28 and toxicity with Irinotecan treatment [91, 94, 95, 96, 97, 98, 99]. One of the most important studies related with the labeling change for Irinotecan is a prospective study of 66 patients with advanced malignancies refractory to other treatments receiving Irinotecan  $300mg/m^2$  every three weeks[91]. The prevalence of grade 4 neutropenia was 9.5%. Of the six homozygous (7/7) patients, three developed grade 4 neutropenia with prevalence of 50%. In contrast, only three of twenty-four patients with 6/7 genotype and none of twenty-eight patients with 6/6 genotype developed grade 4 neutropenia, respectively with prevalence of 12.5% and 0%. Patients with 7/7 genotype had a 9.3-fold higher risk of developing grade 4 neutropenia than patients with 6/6 and 6/7 genotypes. FDA updated

the Irinotecan label in 2005 to provide pharmacogenetic information, recommending a dose reduction of Irinotecan for patients known to be homozygous for the UGT1A1\*28 allele because of the increased risk of neutropenia[100]. In addition, the labeling cautions that patients who are UGT1A1\*28 heterozygous may also have an increased risk of developing neutropenia, although no dosage reduction is required.

Ramchandani et al[101] conducted the regression analysis of the combined data from Innocenti et al[91] and Iyer et al[95] with the goal to more reliably estimate the influence of UGT1A1\*28 polymorphism on toxicity. Variations of UGT1A1 have been linked with elevated and prolonged levels of SN-38 AUC. An increase of both SN-38 AUC and UGT1A1 7/7 genotype were significantly associated with a lower absolute neutrophil count nadir. The effect of UGT1A1 7/7 genotype was found to be significant in addition to the effect of SN-38 exposure, suggesting that the impact of genotype extended beyond the increased exposure. This lends support to the conclusion that genotypes of UGT1A1 have significant effects on PD process in addition to the PK process.

Single agents currently cure few cancers. Because most cancer chemotherapies are combinations of multiple drugs, drug co-administration raises a lot of attention. Gleevec is a good case in point. Response is strongly related with drug exposure, proportional to the assigned dose[88]. However, when EIAED or other CYP3A4 substrate or inducer drug is concomitant with Gleevec, exposure to Gleevec decreases by 70%, unable to reach the thresholds of response[89, 90]. Cytochrome P450 enzymes might be responsible for activation or inactivation of antitumor drugs, and the CYP3A P450s account for approximately half of the metabolism carried out by cytochrome P450 enzymes. Drug co-administrations motivate researchers to recognize the necessity of incorporating known information which may have effects on the PK/PD process.

Since genetic variations or drug co-administrations can lead to huge inter-individual differences in drug efficacy and toxicity, it is desirable to individualize chemotherapy. Before patient enrollment or dosage assignment, some patient specific characteristics may have already been identified to have influence on the PK or PD process. These characteristics may not lead to dramatic difference in response or toxicity, but at least they indicate that this known information has some hoped-for potential to protect patient if incorporated in

the dose-finding process. So without consideration of known patient information may not be enough for dose-finding in phase I clinical trials. Those affecting drug metabolism are expected to affect all PD processes downstream, including both efficacy and toxicity, while other genetic variations or drug co-administrations may affect only one PD process. This suggests that a hierarchical model could help in designing an improved phase I trial incorporating specific suspicious information and prior belief. On the other hand, phase I trials are small and may not contain enough information to support a highly adaptive design. The question is whether such a design could be helpful.

We propose an adaptive Bayesian design based on a hierarchical PK/PD model incorporating patient response, toxicity, genotype/co-administration information and prior belief. Moreover, we compare this design with those without incorporating known information with regard to patient protection and accuracy of final estimates with the following two goals: 1) Determine if incorporating specific information and prior belief has potential to improve early clinical trials; 2) Provide further information about this specific information in order to early identify subset to individualize dosage according to specific characteristics.

## 5.2 METHODS

The PK/PD model, used to address the dose-exposure-effect relationship, consists two separate sub-models: a PK model for drug concentration as a function of drug metabolism constant, dose, genetic makeup, and individual random error; a PD model for drug effect as a function of concentration, genetic makeup, and individual random error. The hierarchical model approach has gained much popularity among PK/PD models by conditioning on individual-specific covariates, dosage, and parameters. The following presents the detailed interpretation for the hierarchical model in mathematical notation:

Stage I: PD model is used to describe the relationship between drug concentration ( $C$ ) and effect(response and toxicity) through the comparison of  $C$  and individual thresholds ( $\theta_R^c, \theta_T^c$ ), which are assumed to follow a bivariate log-normal distribution conditional on

specific characteristic  $\gamma$ :

$$(\log\theta_R^c, \log\theta_T^c)|\gamma \sim N \left[ \begin{pmatrix} \mu_R^c + \beta_R^c \gamma \\ \mu_T^c + \beta_T^c \gamma \end{pmatrix}, \begin{pmatrix} \sigma_R^{c^2} & \sigma_R^c \sigma_T^c \rho \\ \sigma_R^c \sigma_T^c \rho & \sigma_T^{c^2} \end{pmatrix} \right] \quad (5.1)$$

where  $\gamma$  denotes patient specific covariate,  $\beta_R^c$  and  $\beta_T^c$  are the coefficients of  $\gamma$ , representing the effects of  $\gamma$  on  $\theta_R^c$  and  $\theta_T^c$ ,  $\mu_R^c$  and  $\mu_T^c$  are the means of  $\theta_R^c$  and  $\theta_T^c$  without specific characteristic,  $\sigma_R^c$  and  $\sigma_T^c$  are standard deviations of  $\theta_R^c$  and  $\theta_T^c$ , and  $\rho^c$  is correlation.

For patient  $i$  with specific  $\gamma$  there exist four probabilities,

$$P_{irt} = Pr[\theta_R^c > C_i, \theta_T^c > C_i] \quad (5.2)$$

$$P_{irT} = Pr[\theta_R^c > C_i, \theta_T^c \leq C_i] \quad (5.3)$$

$$P_{iRt} = Pr[\theta_R^c \leq C_i, \theta_T^c > C_i] \quad (5.4)$$

$$P_{iRT} = Pr[\theta_R^c \leq C_i, \theta_T^c \leq C_i] \quad (5.5)$$

Stage II: PK model is used to describe the relationship between dosage and drug concentration  $C$ :

$$\log(C|\gamma) = \alpha + \beta\gamma + \log(dose) + \epsilon \quad (5.6)$$

where  $\alpha$  is the constant for PK model,  $\beta$  is the coefficient of  $\gamma$ , describing the effect of  $\gamma$  on  $C$ , and  $\epsilon$  is the random error.

Stage III: Assume  $\gamma$  follows a Bernoulli distribution and random error  $\epsilon$  follows a normal distribution.

$$\gamma \sim \text{Bernoulli}(P_\gamma) \quad (5.7)$$

$$\epsilon \sim N(0, \sigma^2) \quad (5.8)$$

Stage IV: Prior distributions on  $\mu_R^c$ ,  $\mu_T^c$ ,  $\sigma_R^c$ ,  $\sigma_T^c$ ,  $\rho^c$ ,  $\beta_R^c$ ,  $\beta_T^c$ ,  $\alpha$ ,  $\beta$ ,  $\sigma^2$  and  $P_\gamma$  are specified with their own hyperparameters. Let  $\Sigma$  denote the var-cov of  $(\theta_R, \theta_T)$ , and  $\mu^c$  denote  $(\mu_R^c, \mu_T^c)$ , the detailed information for priors is listed as follows:

$$\Sigma \sim W^{-1} \left[ \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, 2 \right] \quad (5.9)$$

$$\mu^c \sim N(\mu_0, \Sigma/n_0) \quad (5.10)$$

$$\beta_R^c \sim U(\beta_{R_l}^c, \beta_{R_u}^c) \quad (5.11)$$

$$\beta_T^c \sim U(\beta_{T_l}^c, \beta_{T_u}^c) \quad (5.12)$$

$$\alpha \sim U(\alpha_l, \alpha_u) \quad (5.13)$$

$$\beta \sim U(\beta_l, \beta_u) \quad (5.14)$$

$$\sigma^2 \sim Inv - \chi^2(s_0, \nu_0) \quad (5.15)$$

$$P_\gamma \sim Beta(P_\alpha, P_\beta) \quad (5.16)$$

The above is general mathematical notations for the hierarchical PK/PD modeling when we suspect PK/PD process, for example, the possible existence of bimodality, but  $\gamma$  and  $P_\gamma$  are unknown. Given the availability of data, the above general modeling could be reduced to the following three cases:

1) Scenario 1: Some preclinical data support that a particular gene plays an influence on PK/PD process. The frequency of genotype  $\gamma$  is known; but patient specific  $\gamma$  is not measured.

2) Scenario 2:  $P_\gamma$  is known; moreover, patient specific  $\gamma$  is measured.

3) Scenario 3:  $\gamma$  is a vector of multiple genes instead of single genotype, and many genotypes are determined.

For now, we restrict our attention to scenario 2 to illustrate the implementation of this hierarchical modeling in phase I clinical trials, including the cumulative data, posterior distribution, calculation of OPT, and independent draws from posterior distribution. For simplicity,  $\gamma$  is assumed to only have effect on PK process.

After observing the results of  $n$  patients, there exist assigned dosages, response and toxicity outcomes as well as specific patient covariate. Given data  $\mathcal{D}_n = \{(Dose_m, R_m, T_m, \gamma_m),$

$m = 1, 2, \dots, n\}$ , the joint likelihood function of  $\varphi$  for  $(\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, \alpha, \beta, \sigma^2, C)$  is

$$\begin{aligned}
L(\varphi|\mathcal{D}_n) &= L(\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, \alpha, \beta, \sigma^2, C|\mathcal{D}_n) \\
&= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T [P_{ijk} | (\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, C_i)]^{n_{ijk}} \\
&\quad \prod_{i=1}^n f(C_i | \alpha, \beta, \sigma^2)
\end{aligned} \tag{5.17}$$

We incorporate prior information about  $\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, \alpha, \beta,$  and  $\sigma^2$  through prior density function  $\pi(\varphi)$  defined by

$$\begin{aligned}
\pi(\varphi) &= \pi(\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, \alpha, \beta, \sigma^2) \\
&= \pi(\mu_R^c, \mu_T^c) \pi(\sigma_R^c, \sigma_T^c, \rho^c) \pi(\alpha) \pi(\beta) \pi(\sigma^2)
\end{aligned} \tag{5.18}$$

Through the application of Bayesian theorem, the joint posterior distribution of  $\varphi$  given  $\mathcal{D}_n$  is :

$$\begin{aligned}
\pi^*(\varphi) &\propto L(\varphi|\mathcal{D}_n) \pi(\varphi) \\
&= \prod_{i=1}^n \prod_{j=r}^R \prod_{k=t}^T [P_{ijk} | (\mu_R^c, \mu_T^c, \sigma_R^c, \sigma_T^c, \rho^c, \beta_R^c, \beta_T^c, C_i)]^{n_{ijk}} \\
&\quad \prod_{i=1}^n f(C_i | \alpha, \beta, \sigma^2) \pi(\mu_R^c, \mu_T^c) \pi(\sigma_R^c, \sigma_T^c, \rho^c) \pi(\alpha) \pi(\beta) \pi(\sigma^2)
\end{aligned} \tag{5.19}$$

The proposed adaptive Bayesian method for dose-finding uses a full Bayesian decision-analytic approach. Upon completion of updating cumulative patient outcome information, we can estimate the optimal dose by maximizing the Bayesian expected utility with the choice of utility function  $U$ , determined by the investigators and patients based on the drugs and goals of the trials. The proposed adaptive Bayesian design defines the utility function as before:

$$U(\theta_R^c, \theta_T^c, C) = \begin{cases} U_{rt} & \text{if } \theta_R^c > C, \theta_T^c > C \\ U_{rT} & \text{if } \theta_R^c > C, \theta_T^c \leq C \\ U_{Rt} & \text{if } \theta_R^c \leq C, \theta_T^c > C \\ U_{RT} & \text{if } \theta_R^c \leq C, \theta_T^c \leq C \end{cases}$$

As a result, Bayesian expected utility for the next patient is:

$$\begin{aligned}
E(U|Dose) &= E_\varphi[E_{\theta|\varphi}[U(\theta_R^c, \theta_T^c, C)]] \\
&= \int_\varphi \int_{\theta_R^c} \int_{\theta_T^c} U(\theta_R^c, \theta_T^c, C) f(\theta_R^c, \theta_T^c | C) \\
&\quad \pi^*(\varphi | \mathcal{D}_n) d\theta_R^c d\theta_T^c d\varphi \\
&= \int_\varphi \sum_{j=r}^R \sum_{k=t}^T U_{jk} P_{jk}(C | \varphi) \pi^*(\varphi | \mathcal{D}_n) d\varphi \\
&= \int_\varphi \sum_{j=r}^R \sum_{k=t}^T U_{jk} P_{jk}(h(Dose) | \varphi) \pi^*(\varphi | \mathcal{D}_n) d\varphi \\
&= E_\varphi \left[ \sum_{j=r}^R \sum_{k=t}^T U_{jk} P_{jk}(h(Dose) | \varphi) \right] \\
&= \sum_{j=r}^R \sum_{k=t}^T U_{jk} E_\varphi [P_{jk}(h(Dose) | \varphi)] \tag{5.20}
\end{aligned}$$

where  $h(Dose) = \exp(\alpha + \beta\gamma + \log(Dose) + \epsilon)$ .

$\widehat{OPT}_{n+1}$  is estimated by maximizing  $E(U|Dose)$ , hence the  $(n+1)th$  patient with  $\gamma$  ( $\forall n = 1, 2, \dots, N$ ) receives the dose

$$\begin{aligned}
\widehat{OPT}_{n+1} &= \arg \max_{dose} E(U|Dose) \\
&= \arg \max_{dose} \sum_{j=r}^R \sum_{k=t}^T U_{jk} E_\varphi [P_{jk}(h(Dose) | \varphi)] \tag{5.21}
\end{aligned}$$

It is very complicated to calculate the multiple integration  $E_\varphi [P_{jk}(h(Dose) | \varphi)]$  over  $\varphi$ . A practical approach is available to deal with multiple integrations over  $\varphi$ : substitute the posterior mean  $\hat{\varphi}$  from MCMC sample for  $\varphi$ .

$$\begin{aligned}
\hat{E}_\varphi [P_{jk}(h(Dose) | \varphi)] &= P_{jk}(h(Dose) | \hat{\varphi}) \\
&= P_{jk}(h(Dose) | \sum_{z=1}^Z \varphi_z / Z) \tag{5.22}
\end{aligned}$$

where  $\varphi_1, \varphi_2, \dots, \varphi_Z$  are i.i.d samples from the posterior distribution of  $\pi^*(\varphi | \mathcal{D}_n)$ . Because this posterior distribution has no closed form, MCMC sample draws are used instead of the exact samples.

After each patient's outcomes are observed, we use a MCMC algorithm to update the posterior distributions of unknown parameters. At the  $n$ th stage, the full conditional distributions of the  $\log \theta_R^c$ ,  $\log \theta_T^c$ , and  $\varphi$  are given as follows:

1. Conditional on  $\mathcal{D}_n$ , generate  $(\log \theta_R^c, \log \theta_T^c)$  using truncated normal distributions. For individual  $i$ , if event occurs, the right truncated normal distribution with the point of truncation of assigned  $OPT_i$  is used; otherwise, the left truncated normal distribution with the point of truncation of assigned  $OPT_i$  is used.
2. Conditional on  $\mathcal{D}_n$  and  $\log \theta^c$ , generate  $\Sigma$  and  $\mu$  using Inverse-Wishart and normal distributions.

$$\Sigma | \mathcal{D}_n, \Sigma^{(-)} \sim W^{-1}(I + nS + (nn_0/(n + n_0))(\overline{\log \theta^c} - \mu_0)(\overline{\log \theta^c} - \mu_0)', n + 2) \quad (5.23)$$

$$\mu | \mathcal{D}_n, \mu^{(-)} \sim N((n\overline{\log \theta^c} + n_0\mu_0)/(n + n_0), \Sigma/(n + n_0)) \quad (5.24)$$

where  $\log \theta^c$  denotes  $(\log \theta_R^c, \log \theta_T^c)$ ,  $\overline{\log \theta^c}$  denotes the mean of  $\log \theta^c$ ,  $I$  denotes the identity matrix,  $nS$  denotes the variance-covariance of  $\log \theta^c$ ,  $n_0$  and  $\mu_0$  denotes the prior belief for  $\log \theta^c$ .

3. Conditional on  $\mathcal{D}_n$ , generate  $\sigma^2$ ,  $\alpha$ , and  $\beta$  using inverse-chi-square and normal distributions.

$$\sigma^2 | \mathcal{D}_n, \sigma^{2(-)} \sim Inv - \chi^2((n - 2)S + s_0, \nu_0 + (n - 2)) \quad (5.25)$$

$$\alpha, \beta | \mathcal{D}_n, (\alpha, \beta)^{(-)} \sim N((\hat{\alpha}, \hat{\beta}), \sigma^2 V_{\alpha, \beta}) \quad (5.26)$$

where  $S$ , the residual sum of squares, is equal to  $\sum_{i=1}^n (\log C_i - \log dose_i - (\alpha + \beta\gamma))^2$ ,  $\hat{\alpha}$  and  $\hat{\beta}$  are least square estimates, and  $V_{\alpha, \beta}$  is the variance of estimates.

4. Based on the hierarchical modeling the full conditional distribution of  $C$  is straightforward as shown below:

$$\log C | \mathcal{D}_n, C^{(-)} \sim N(\alpha + \log(dose) + \beta\gamma, \sigma^2)$$

The above proposed adaptive Bayesian design based on hierarchical *PK/PD* modeling, incorporating response, toxicity, patient specific covariate, and prior belief, provides opportunities to improve phase I dose-finding trials, identify subset early, and develop an individualized dosing strategy. Under the circumstances where  $\beta_R^c$ ,  $\beta_T^c$ , and  $\beta$  are equal to 0, the design is reduced to an adaptive design based on a PK/PD model without patient specific covariate, while it will be reduced to an adaptive design based on a simple PD model without patient specific covariate under the cases of  $\beta_R^c$ ,  $\beta_T^c$ ,  $\alpha$ ,  $\beta$ , and  $\sigma$  equal to 0.

For PD modeling, threshold in terms of dose ( $\theta^d$ ) follows a log-normal distribution, while for PK/PD modeling with or without incorporating  $\gamma$ ,  $\theta^d$  also follow a log-normal distribution under the transformation of  $\theta^d$ ,  $\theta^c$ , and  $C$ . Appendix B shows the detailed mathematical interpretation.

### 5.3 APPLICATIONS AND SIMULATIONS

The adaptive Bayesian designs incorporating both response and toxicity in phase I trials assume that thresholds of response and toxicity follow a bivariate log-normal distribution. Patients outcomes are determined by the comparison of individual specific thresholds with assigned dosage or drug exposure depending on the underlying model. The model which takes into account thresholds of response and toxicity, assigned dose, and patient outcome, without considering the underlying algorithm of drug concentration, is a simple PD modeling. This PD modeling is reasonable, especially when the underlying drug-metabolism is unknown. However, it is not ideal because it ignores individual variability in drug concentrations, which play a more important and direct role in determining drug response/toxicity than assigned doses. The model taking into account thresholds based on drug exposure through PK/PD processes may provide a more reasonable way to address dose-seeking process. Incorporating known information into phase I trials through hierarchical PK/PD modeling may have the potential to improve early stage trials and identify subset early.

To ensure the appropriateness of the adaptive designs through the PK/PD processes, simulation studies should be conducted before implementing trials to check the operating

characteristics. Only after simulations show satisfactory results should the proposed design be applied to real trials.

To make simulation results closer to real studies the underlying parameters are roughly generated from the published data of real trials based on the three-level hierarchical model. Gleevec(Imatinib) is the first successful cytostatic agent for CML. Plasma drug exposure was directly related to hematologic response; concomitant administration of drugs inducing CYP3A4 could lead to low and ineffective levels of Imatinib[88]. In the case of chemotherapy for cancer treatment, few single agents could be a cure, making multiple drug coadministrations very common. Moreover, cytostatic agents, such as Gleevec, may become more widespread. Such circumstances would be the most promising for achieving benefit from the proposed design incorporating response, toxicity, and known drug coadministration information, in comparison to phase I dose-finding trials ignoring response and patient specific information. Irinotecan, metabolized by UGT1A1, genotypes of which have significant effects on PD process in addition to the PK process, is another good case in point that emphasizes the importance of incorporating PG into the PK/PD modeling process.

The published data of Gleevec and Irinotecan estimated the underlying parameters for response and toxicity thresholds in terms of dose and drug exposure from a bivariate unimodal model via maximum likelihood; the relationship between dose and C was also explored using a power model. Figure 17 shows the contour plots of thresholds and the relationship between dose and C with/without CYP3A4 inducer. Figure 18 demonstrates the relationship between dose and C and the contour plot in terms of C based on the Irinotecan.

The proposed adaptive Bayesian design uses a full Bayesian decision analysis by combining utility function and Bayesian posterior probability to form Expected Utility and by taking Bayesian action to maximize EU. Four different types of utility functions address ethical considerations:  $U_{simple}$ ,  $U_{additive}$ ,  $U_{aggressive}$  and  $U_{cautious}$ . Different utility functions and designs conduct 100 simulations to reliably assess the design performance. The length of MCMC chain is 10000, the burn-in is 5000, and the thinning is 10 for every patient in this adaptive process. The burn-in is chosen as 5000 because the chain appears to reach equivalence before this point. For the design simulations considered here, sample size is fixed as 30 given the relatively small size of phase I studies.

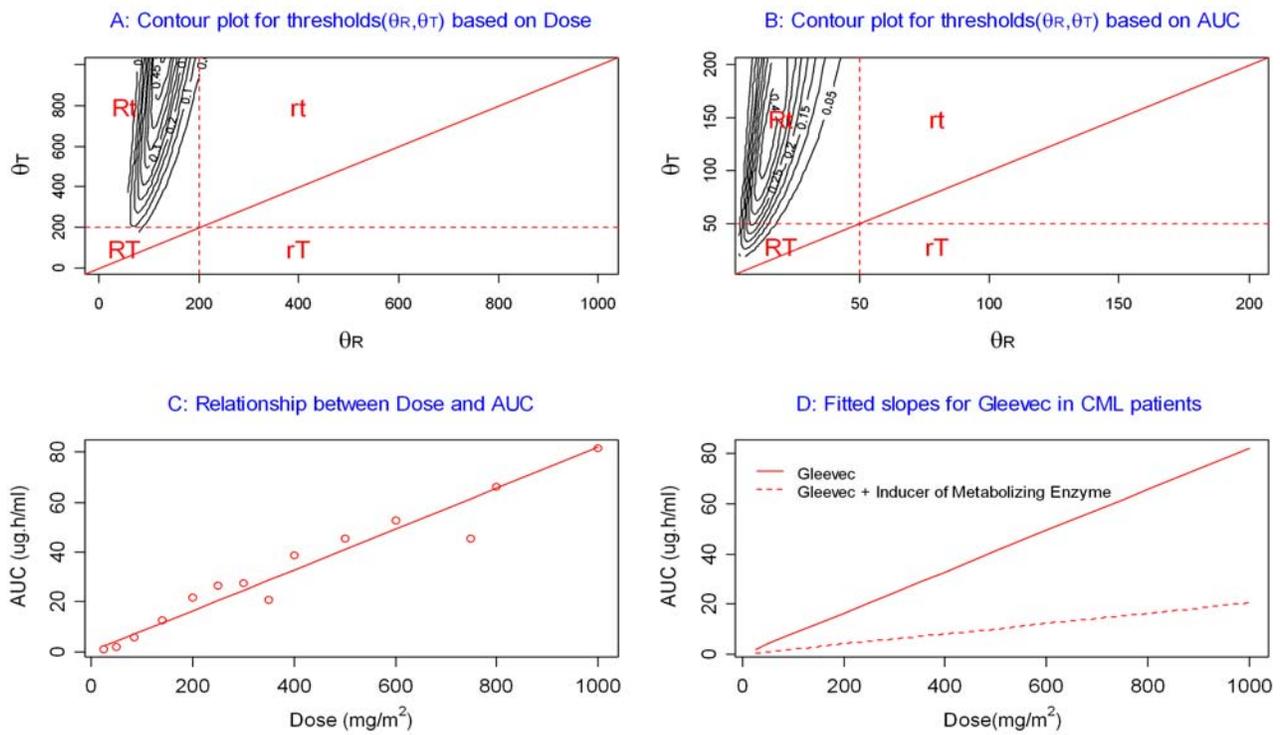


Figure 17: *Contour Plots of Thresholds and Relationship between Dose and AUC Based on Gleevec Data*

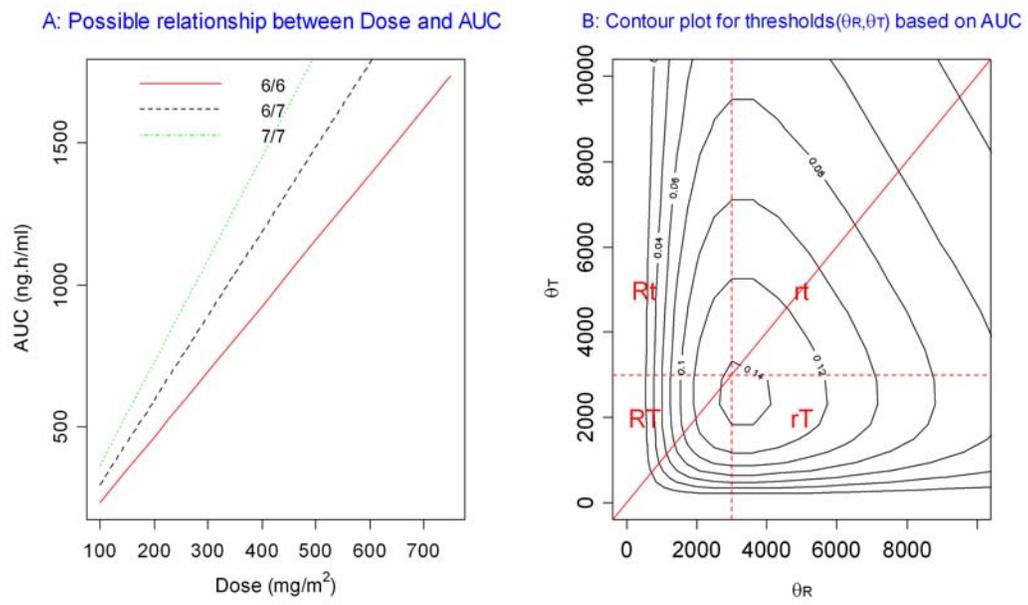


Figure 18: *Relationship between Dose and AUC and Contour Plot of Thresholds Based on Irinotecan Data*

### 5.3.1 Comparison of PK/PD Modeling with PD Modeling

The adaptive Bayesian design could be modeled through PK/PD modeling or just PD modeling. The design based on PD modeling focuses on the relationship between dose and outcome. The design based on PK/PD modeling could address the relationship of dose, exposure, and outcome, while it also introduces more variability. It is necessary to evaluate both models with regard to patient protection and accuracy of estimates under the circumstances of genotype or other patient characteristics unknown before patient enrollment.

Figure 19 shows the comparison of PK/PD modeling with PD modeling with regard to accuracy of estimate and patient protection based on the Gleevec data. The left panel demonstrates the accuracy of estimates between the two designs under four utility functions. These plots, showing that the CDF curves always cross true OPT lines and curves from PD models are steeper than those from PK/PD models, imply that the final recommended OPTs are always closer to the true OPTs, but the variations from PK/PD models are larger. In addition, the recommended OPTs from PK/PD models are greater than those from PD models. For PK/PD modeling, pre-specified utility function plays an important role in the final dose recommendations. For example, aggressive utility function could lead to wrong dose recommendation, such as an extremely high dose recommendation. The right panel demonstrates patient protection between the two designs. The bars corresponding to  $R_t$ , the desirable outcome, are always higher among PD models, while the bars corresponding to  $rt$  and  $RT$ , the undesirable outcomes, undertreated or overtreated, are always higher among PK/PD models. Moreover, under the aggressive utility function usage, more patients experience  $RT$  because of extremely high dose recommendation. These simulation results show that PD modeling is helpful in protecting patients compared to PK/PD modeling when genotype or other patient characteristics is unknown before patient enrollment. The underlying reason is that AUC is proportional to dose, with both strongly related to response; Therefore, the introduction of two more parameters to explain the relationship of AUC and dose could not help the design.

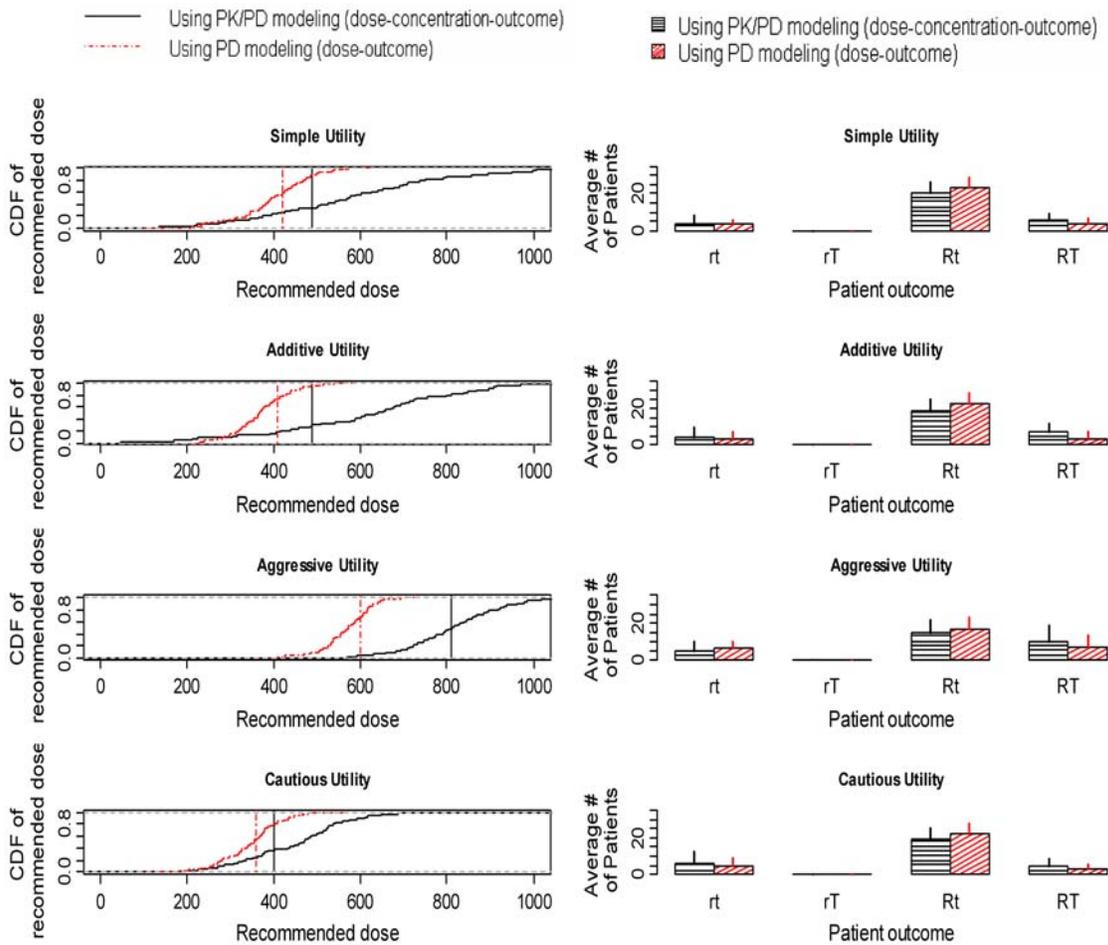


Figure 19: *Comparison of PK/PD Modeling with PD Modeling with Regard to Accuracy of Estimate and Patient Protection*

Note: The vertical lines represent the true optimal doses given models. The CDF curves always cross true OPT lines and curves from PD models are steeper than those from PK/PD models, implying the final recommended OPTs are always closer to the true OPTs, but the variations from PK/PD models are larger. The bars corresponding to Rt, the desirable outcome, are always higher among PD models, while the bars corresponding to rt and RT, the undesirable outcomes, are always higher among PK/PD models. Moreover, under the aggressive utility function usage, more patients experience RT because of extremely high dose recommendation.

### 5.3.2 Comparison of Designs Utilizing Three Model Assumptions under the Case of Known Determinant Having Influence on PK Process

The huge availability of PG information and routine practice of multiple drug combinations for cancer chemotherapy provide a opportunity to improve early stage trials by incorporating known information which may have influence on drug concentration into the phase I dose-finding process through PK/PD modeling. A comparison was made with regard to patient protection for three designs: PK/PD model incorporating known information, PK/PD model ignoring known information, and PD model. The most important part of the PK/PD model incorporating known information is that posterior belief about this known information could be provided to guide the future trials.

Figure 20 demonstrates patient protection for three types of designs under the circumstance that 50% of the enrolled patients are on another CPY3A4 inducer, which dramatically decreases drug exposure by 70%, while another 50% are on a single agent. The bars corresponding to  $R_t$ , the desirable outcome, are always highest among PK/PD models incorporating known information, while the bars corresponding to  $rt$  and  $RT$ , the undesirable outcomes, undertreated or overtreated, are always lowest. These simulation results suggest that PK/PD model incorporating known information is helpful in protecting patients compared to those models without considering genotype or other patient characteristics. Moreover, for PK/PD modeling, pre-specified utility function plays an important role in the final dose recommendations and patient experience. For example, aggressive utility function could lead to extremely high dose recommendations, therefore causing more patients experiencing  $RT$ . Figure 21 demonstrates the posterior distribution of the coefficient  $\beta$  under additive utility function usage. The underlying true parameter  $\beta$  is  $-1.2$ , and the posterior distribution of  $\beta$  based on simulation results is bell-shaped with a posterior mean  $-1.17$ , standard error  $0.145$ , and 95% credibility interval  $-0.87 \sim -1.45$ . This suggests that  $\gamma$  is a statistically significant factor in predicting drug concentration, therefore further confirming the correctness of the incorporation of known  $\gamma$  into the phase I trials. In addition, this also provides evidence that patient covariate  $\gamma$  could be used to guide the dose recommendation for future trials in order to maximize benefit.

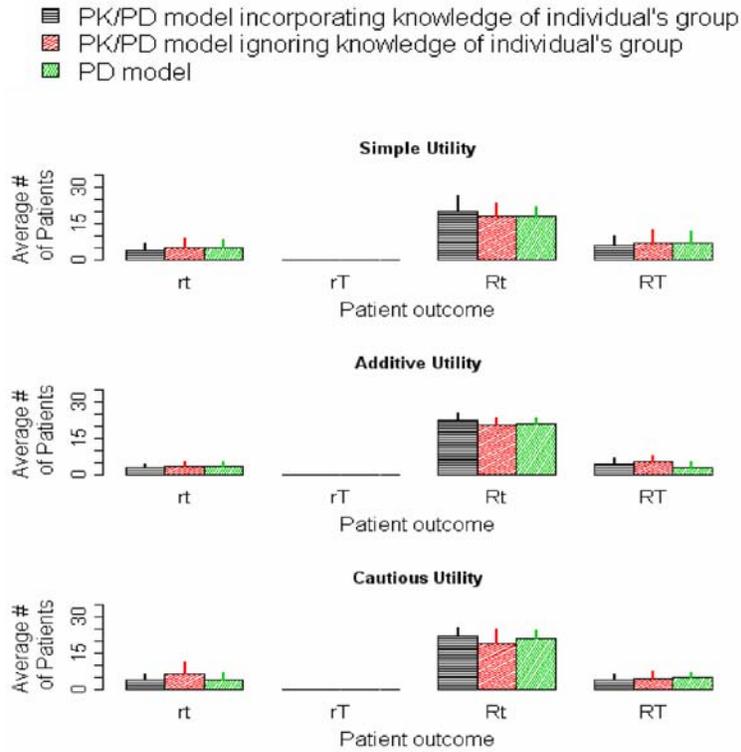


Figure 20: *Comparison of Designs with Regard to Patient Protection*

Note: More patients experience desirable outcome (Rt) and less patients experience undesirable outcomes (rt, RT) in the PK/PD model incorporating known information.

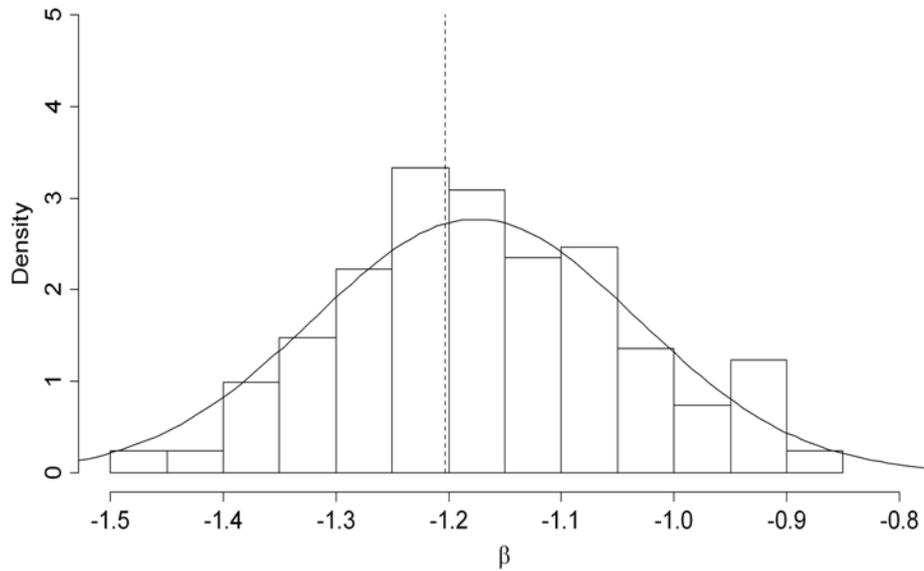


Figure 21: *Posterior Distribution of the Coefficient  $\beta$*

Note:  $\beta$  is the log of concentration ratio ( $\gamma=1$  vs.  $\gamma=0$ ). The underlying true parameter  $\beta$  is  $-1.2$ , and the posterior distribution of  $\beta$  based on simulation results is bell-shaped with a posterior mean  $-1.17$ , standard error  $0.145$ , and 95% credibility interval  $-0.87 \sim -1.45$ .

### **5.3.3 Comparison of Designs Utilizing Three Model Assumptions under the Case of Known Determinant Having Influence on Both PK and PD Processes**

Some pre-identified characteristics have influence on both PK and PD processes; Irinotecan is a case in point. Comparison was also made with regard to patient protection for three approaches: PK/PD modeling with and without incorporating known information and PD modeling. The simulation results were similar to the cases of known determinant having effects only on PK process. More patients experience desirable outcomes. Posterior belief about this known determinant is provided, serving as a guide for future trials.

## 5.4 DISCUSSION

Genetic variations or drug co-administration can lead to huge inter-individual differences in drug efficacy and toxicity, making it desirable to individualize therapy. Those affecting drug metabolism are expected to affect all pharmacodynamic (PD) processes downstream, including both efficacy and toxicity, while other genetic variations or drug-coadministration may affect only one PD process. This suggests that a hierarchical model could help in designing an improved phase I trial incorporating specific information and prior belief. On the other hand, phase I trials are small and may not contain enough information to support a highly adaptive design. The question is whether or not such a design could be helpful. We propose an adaptive Bayesian design based on a hierarchical PK/PD model, incorporating patient response, toxicity, genotype or drug co-administration, and prior belief.

The model assumes that response and toxicity events happen depending on the respective thresholds and the drug exposure determined by the underlying drug metabolism. This model provides a framework for incorporating prior information about the population threshold distribution, suspicious patient characteristics which may have influence on drug exposure, and accumulated data. The next dose can be assigned to maximize expected utility, which assigns certain utilities to all possible outcomes. The proposed design provides an opportunity to improve phase I clinical trials by incorporating known information which may have influence on drug exposure. One of the most impressive advantages of the proposed adaptive Bayesian design is to address ethical considerations through a full Bayesian decision analysis, combining utility and Bayesian posterior distribution to take a Bayesian action by maximizing expected utility.

Extensive simulations based on Gleevec and Irinotecan data were conducted to assess the design performance with regard to the accuracy of estimate and patient protection when genotype or drug co-administration is known before patient enrollment. Moreover, four utility functions are used to address the ethical concern and its influence on the design performance. Under the cases of patient specific PG or other information unknown before implementation of trials, the adaptive Bayesian design could be modeled through PK/PD modeling or just PD modeling. The final recommended optimal dosage is always close to

the true optimal dosage, but the variation from PK/PD modeling is greater than that from PD modeling. In addition, PD modeling leads to more patients experiencing  $R_t$ , the desirable outcome, and fewer patients experiencing  $rt$  and  $RT$ , the undertreated or overtreated outcomes. This suggests that PD modeling is helpful in protecting patients compared to PK/PD modeling when genotype or other patient characteristics is unknown before patient enrollment. Under the cases of patient specific determinant having effects on PK/PD process known before implementation of trials, PK/PD modeling with the incorporation of information has the potential to improve phase I trials compared to PK/PD modeling and PD modeling ignoring this known information, with more patients experiencing desirable outcomes and smaller variations of recommended dose. In addition, posterior belief about patient specific covariate is also provided, serving to subset identification for future phase II trials. For PK/PD modeling, pre-specified utility function plays an important role in the final dose recommendations. For example, aggressive utility function could lead to wrong dose recommendation, an extremely high dose recommendation, therefore creating more patients experiencing response and toxicity.

Although the proposed dose-finding algorithm involves more complicated modeling and computation than regular dose-finding algorithms, it still has two advantages. First, the incorporation of pharmacogenetic information or other known patient characteristics which may have influence on drug metabolism into phase I dose-finding trials has the potential to improve phase I trials and provide further confirmation about the belief of known information, useful for the subset identification. In addition, using a full Bayesian decision-analytic approach takes into account both scientific and ethical concerns with the goals to identify the right dose as effectively as possible and to treat more patients as ethically as possible.

## 6.0 CONCLUSION

According to the ethical principles governing clinical research, in phase I clinical trials decisions about dose assignment should be based on patients' values, preferences, and first and foremost the principle of doing what is best for patients.

We develop a "dose-choice control panel" (DCCP) computer program to explore how the population parameters and utilities affect the dose recommendation. The models and utilities were critiqued, resulting in a richer, more realistic framework. The resulting enhancements include new parameters added to address bimodality, treatment refractoriness, and response-limiting event, as well as broader utility functions.

We present a new adaptive Bayesian method for dose-finding in phase I clinical trials based on both response and toxicity under the assumption that the thresholds of response and toxicity jointly follow a bivariate log-normal distribution. The model assumes that response and toxicity events happen depending on the respective dose thresholds for the individual, and provides a framework for incorporating prior information about the population threshold distribution, as well as accumulated data. The next dose can be assigned to maximize expected utility. We conducted extensive simulations to assess the design performance with regard to the accuracy of estimate and patient protection under different scenarios, priors, and utility functions. The adaptive Bayesian design incorporating both response and toxicity and using continuous adaptive doses based on the maximization of Bayesian expected utility is more effective in identifying the right dose in comparison with alternative designs that consider only toxicity and use pre-specified fixed doses. Moreover, the adaptive Bayesian design combining ethical considerations through the introduction of ethical utility function could lead to more patients experiencing desirable outcomes corresponding to the specified utilities, therefore protecting patients. We could conclude that

incorporating response has the potential to improve phase I trials, especially under the high response cases. Moreover, the introduction of utility function and prior information provide an opportunity to run more sensible and ethical trials. Simple utility function just putting positive utility on co-occurrence of response and non-toxicity, is dangerous especially under the cases where responses are rare. The application of Gleevec data to the proposed design is very encouraging. These provide evidence for the feasibility of the application of new designs to the future real trials.

Those affecting drug metabolism are expected to affect all PD processes downstream, including both efficacy and toxicity, while other genetic variations or drug-coadministration may affect only one PD process. We propose an adaptive Bayesian design based on a hierarchical PK/PD model, incorporating patient response, toxicity, genotype or drug co-administration information, and prior belief. The proposed design provides opportunity to improve phase I clinical trials by incorporating known information which may have influence on drug exposure. We conducted extensive simulations based on Gleevec and Irinotecan data to assess the design performance with regard to the accuracy of estimate and patient protection. Simulation results show that PK/PD modeling with incorporation of known information has the potential to improve phase I trials compared to PK/PD modeling and simple PD modeling without incorporating it, with more patients experiencing desirable outcomes, smaller variations of recommended dose. In addition, posterior belief about patient specific covariate is also provided, helpful to subset identification for future phase II trials. For PK/PD modeling pre-specified utility function plays an important role in the final dose recommendations.

This work attempts to improve beneficence in early stage clinical trials and could improve public health by providing more accurate answers quickly, and by encouraging accrual through explicit consideration of what is best for each individual patient.

## 7.0 APPENDIX A: THE UNIMODAL AND BIMODAL DISTRIBUTION

A): The distribution of thresholds  $(\theta_R, \theta_T)$  based on the unimodal Gaussian assumption is:

$$(\log\theta_R, \log\theta_T) \sim N \left[ \begin{pmatrix} \mu_R \\ \mu_T \end{pmatrix}, \begin{pmatrix} \sigma_R^2 & \sigma_R\sigma_T\rho \\ \sigma_R\sigma_T\rho & \sigma_T^2 \end{pmatrix} \right]$$

Letting  $\theta_J$  represent either  $\theta_R$  or  $\theta_T$  for event  $J \in (R, T)$ ,

$$\begin{aligned} \log\theta_J &= \mu_J + \delta_J \\ \delta_J &\sim N(0, \sigma_J^2) \\ f(\log\theta_J) &= f_N(\log\theta_J - \mu_J, 0, \sigma_J^2) \\ E(\log\theta_J) &= \mu_J \\ var(\log\theta_J) &= \sigma_J^2 \\ cov(\log\theta_R, \log\theta_T) &= \sigma_R\sigma_T\rho \\ Pr[event J] &= Pr[\theta_J \leq dose] = \Phi((\log(dose) - \mu_J)/\sigma_J) \end{aligned}$$

B): The distribution of thresholds  $(\theta_R, \theta_T)$  based on the mixture assumption is:

$$\begin{aligned} (\log\theta_R, \log\theta_T) \sim & pN_1 \left[ \begin{pmatrix} \mu_{R1} \\ \mu_{T1} \end{pmatrix}, \begin{pmatrix} \sigma_{R1}^2 & \sigma_{R1}\sigma_{T1}\rho_1 \\ \sigma_{R1}\sigma_{T1}\rho_1 & \sigma_{T1}^2 \end{pmatrix} \right] + \\ & (1-p)N_2 \left[ \begin{pmatrix} \mu_{R2} \\ \mu_{T2} \end{pmatrix}, \begin{pmatrix} \sigma_{R2}^2 & \sigma_{R2}\sigma_{T2}\rho_2 \\ \sigma_{R2}\sigma_{T2}\rho_2 & \sigma_{T2}^2 \end{pmatrix} \right] \end{aligned}$$

where  $p$  is the proportion of the first density function.

Letting  $\theta_J$  represent either  $\theta_R$  or  $\theta_T$  as above,

$$\begin{aligned}
f(\log \theta_J) &= pf_{N_1}(\log \theta_J - \mu_{J1}, 0, \sigma_{J1}^2) + (1-p)f_{N_2}(\log \theta_J - \mu_{J2}, 0, \sigma_{J2}^2) \\
E(\log \theta_J) &= p\mu_{J1} + (1-p)\mu_{J2} \\
var(\log \theta_J) &= p\sigma_{J1}^2 + (1-p)\sigma_{J2}^2 + p(1-p)(\mu_{J1} - \mu_{J2})^2 \\
cov(\log \theta_R, \log \theta_T) &= p\sigma_{R1}\sigma_{T1}\rho_1 + (1-p)\sigma_{R2}\sigma_{T2}\rho_2 + p(1-p)(\mu_{R1} - \mu_{R2})(\mu_{T1} - \mu_{T2}) \\
Pr[event J] &= Pr[\theta_J \leq dose] \\
&= p\Phi((\log(dose) - \mu_{J1})/\sigma_{J1}) + (1-p)\Phi((\log(dose) - \mu_{J2})/\sigma_{J2})
\end{aligned}$$

## 8.0 APPENDIX B : PK/PD MODELING

A): The model which incorporates PD directly is:

$$(\log\theta_R^d, \log\theta_T^d) \sim N \left[ \begin{pmatrix} \mu_R^d \\ \mu_T^d \end{pmatrix}, \begin{pmatrix} \sigma_R^{d^2} & \sigma_R^d \sigma_T^d \rho^d \\ \sigma_R^d \sigma_T^d \rho^d & \sigma_T^{d^2} \end{pmatrix} \right]$$

where  $(\theta_R^d, \theta_T^d)$  denote the thresholds in terms of dose.

Letting  $\theta_J^d$  represent either  $\theta_R^d$  or  $\theta_T^d$  for event  $J \in (R, T)$ ,

$$\begin{aligned} \log \theta_J^d &= \mu_J^d + \delta_J^d \\ \delta_J^d &\sim N(0, \sigma_J^{d^2}) \\ Pr[event J] &= Pr[\theta_J^d \leq dose] = \Phi(\log(dose) - \mu_J^d) / \sigma_J^d \\ f(\log \theta_J^d) &= f_N(\log \theta_J^d - \mu_J^d, 0, \sigma_J^{d^2}) \\ E(\log \theta_J^d) &= \mu_J^d \\ var(\log \theta_J^d) &= \sigma_J^{d^2} \\ cov(\log \theta_R^d, \log \theta_T^d) &= \sigma_R^d \sigma_T^d \rho^d \end{aligned}$$

B): The model which incorporates both PD and PK hierarchically is:

$$\begin{aligned} PD \quad (\log\theta_R^c, \log\theta_T^c) | \gamma &\sim N \left[ \begin{pmatrix} \mu_R^c + \beta_R^c \gamma \\ \mu_T^c + \beta_T^c \gamma \end{pmatrix}, \begin{pmatrix} \sigma_R^{c^2} & \sigma_R^c \sigma_T^c \rho^c \\ \sigma_R^c \sigma_T^c \rho^c & \sigma_T^{c^2} \end{pmatrix} \right] \\ PK \quad \log(C) | \gamma &\sim N[\alpha + \beta \gamma + \log(dose), \sigma^2] \\ \gamma &\sim Bernoulli(P_\gamma) \end{aligned}$$

where  $(\theta_R^c, \theta_T^c)$  denote the thresholds in terms of a summary of drug concentration  $C$ , such as AUC, and  $\gamma$  is a binary indicator for a genetic variant.

Letting  $\theta_J^c$  represent either  $\theta_R^c$  or  $\theta_T^c$  as above,

$$\begin{aligned}\log \theta_J^c &= \mu_J^c + \beta_J^c \gamma + \delta_J^c \\ \delta_J^c &\sim N(0, \sigma_J^{c^2}) \\ \log C &= \alpha + \beta \gamma + \log(dose) + \epsilon \\ \epsilon &\sim N(0, \sigma^2)\end{aligned}$$

Assume  $C \perp \theta_J^c$ ,

$$\begin{aligned}& Pr[event J] \\ &= Pr[\log \theta_J^c \leq \log C] \\ &= Pr[((\log \theta_J^c - \mu_J^c - \beta_J^c \gamma) / \sigma_J^c) \sigma_J^c - ((\log C - \alpha - \beta \gamma - \log(dose)) / \sigma) \sigma \\ &\leq \log(dose) - \mu_J^c - \beta_J^c \gamma + \alpha + \beta \gamma] \\ &= \Phi\left(\frac{\log(dose) - \mu_J^c - \beta_J^c \gamma + \alpha + \beta \gamma}{\sqrt{\sigma_J^{c^2} + \sigma^2}}\right)\end{aligned}$$

The probability of event could be expressed in another way,

$$\begin{aligned}& Pr[event J] \\ &= Pr[\theta_J^c \leq C] \\ &= Pr[\exp(\mu_J^c + \beta_J^c \gamma + \delta_J^c) \leq dose \exp(\alpha + \beta \gamma + \epsilon)] \\ &= Pr[\exp(\mu_J^c + \beta_J^c \gamma + \delta_J^c - \alpha - \beta \gamma - \epsilon) \leq dose]\end{aligned}$$

Let probability of event using both models be equal, the following equation exists:

$$\theta_J^d = \exp(\mu_J^c + \beta_J^c \gamma + \delta_J^c - \alpha - \beta \gamma - \epsilon)$$

In other mathematical notation,

$$\log \theta_J^d = \mu_J^c + \beta_J^c \gamma + \delta_J^c - \alpha - \beta \gamma - \epsilon$$

As a result, the marginal distribution of  $\log \theta_J^d$  is:

$$f(\log \theta_J^d) = P_\gamma f_N(\log \theta_J^d - \mu_J^c - \beta_J^c + \alpha + \beta, 0, (\sigma^2 + \sigma_J^{c^2})) \\ + (1 - P_\gamma) f_N(\log \theta_J^d - \mu_J^c + \alpha, 0, (\sigma^2 + \sigma_J^{c^2}))$$

with the mean, variance, and covariance of the  $\theta^d$  as following:

$$E(\log \theta_J^d) = \mu_J^c - \alpha + P_\gamma(\beta_J^c - \beta) \\ \text{var}(\log \theta_J^d) = \sigma_J^{c^2} + \sigma^2 + P_\gamma(1 - P_\gamma)(\beta_J^c - \beta)^2 \\ \text{cov}(\log \theta_R^d, \log \theta_T^d) = \sigma_R^c \sigma_T^c \rho^c + \sigma^2 + P_\gamma(1 - P_\gamma)(\beta_R^c - \beta)(\beta_T^c - \beta)$$

For the PK/PD modeling without incorporating  $\gamma$ ,  $\theta^d$  would be reduced to

$$\log \theta_J^d = \mu_J^c + \delta_J^c - \alpha - \epsilon$$

with the following marginal distribution, mean, variance, and covariance:

$$f(\log \theta_J^d) = f_N(\log \theta_J^d - \mu_J^c + \alpha, 0, (\sigma^2 + \sigma_J^{c^2})) \\ E(\log \theta_J^d) = \mu_J^c - \alpha \\ \text{var}(\log \theta_J^d) = \sigma_J^{c^2} + \sigma^2 \\ \text{cov}(\log \theta_R^d, \log \theta_T^d) = \sigma_R^c \sigma_T^c \rho^c + \sigma^2$$

From the above three marginal distributions of  $\theta^d$ , we can conclude the following: 1)  $\theta^d$  follows a mixture distribution based on PK/PD modeling with the incorporation of patient covariate  $\gamma$ ; 2)  $\theta^d$  follows a log-normal distribution based on PK/PD modeling without incorporating patient covariate  $\gamma$ ; 3)  $\theta^d$  follows a log-normal distribution based on PD modeling; and 4) When  $\gamma$  is unknown and unmeasured, the PK/PD modeling and simple PD modeling are same under certain transformation.

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