An optimal dose-finding technique based on bayesian decision theory for oncology phase I/II clinical trials

Loke, Yee Chong

2008

Loke, Y. C. (2008). An optimal dose-finding technique based on bayesian decision theory for oncology phase I/II clinical trials. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/41746>

<https://doi.org/10.32657/10356/41746>

AN OPTIMAL DOSE-FINDING TECHNIQUE BASED ON BAYESIAN DECISION THEORY FOR ONCOLOGY PHASE I/II CLINICAL TRIALS

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A thesis submitted to Nanyang Technological University
in fulfillment of the requirement for the degree of
Doctor of Philosophy

2008

Acknowledgements_____

I would like to express my appreciation to many of the staff at the National Cancer Centre Singapore (NCCS) for their assistance and support. The three years I have spent as a full time research student in NCCS could not have been made more enjoyable or comfortable.

To all (both past and present) who have passed through the Department of Clinical Trials & Epidemiological Sciences (NCCS), I express my gratitude for the friendship and the tremendous amount of help I received throughout the course of my studentship.

I am most grateful to my parents for their unconditional support and great patience with my impatience. A special thank you goes out to my Wife, Linda Koh, for just listening and for bringing the much needed calm back into my life.

I wish to express my sincere thanks to Assoc. Prof. Tan Say Beng and Prof. David Machin of NCCS for the advice and support and for giving me the fantastic opportunity of pursuing further studies.

Finally, I am eternally grateful to Assoc. Prof. Cai Yi Yu for his never yielding patience, guidance and generosity. Under his mentorship I realized the importance of humility, honesty and most importantly, kindness.

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Summary

A phase I dose-finding clinical trial has always been a challenge to find a safe dosage, given a very limited sample size and shorter timeframe. This is particularly important for cancer trials as new experimental drugs could be cytotoxic and life threatening if too high a dose is given or an inaccurate estimated dose level is thought to be safe and continues to be used for subsequent Phase II and III trials. In this research work, a new approach is proposed that help to improve on the current Phase I design in obtaining a better reliability of finding a safe dosage and using fewer patients to obtain the results. The proposed design utilizes a Bayesian decision theory to look at either single event of toxicity or a combined event of both toxicity and efficacy to obtain an optimal dose for a Phase I/II clinical trial study. The method assumes binary outcomes for all of these events which give rise to a multinomial likelihood. A decision table is defined with utility values attached to each possible decision. One of the unique attributes of this design is that it has a relationship between these utility values and the target probability associated with a toxicity and efficacy outcomes. By eliciting this target value from the clinical investigator, along with their beliefs on the relative importance of efficacy and toxicity in their trial, appropriate trial specific utility values may be obtained. Due to this interaction between the utility and the target value, the process of finding the optimal dose can be escalated. In addition, the design proposes a stopping criterion based on Bayesian inference to bring the trial to an early completion with a minimum number of patients. The results show promising performance by the proposed design and it has a competitive edge over some of the well-established phase I designs where the comparison is based on simulation run using various clinical scenarios. The design is also tested using actual clinical study data to obtain the optimal dose at the correct dose level using fewer cohorts of patients.

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CHAPTER 1

Introduction

1.1 Overview

Modern medical research demands the highest standard of research methodology and patient ethics. In the area of drug development, the testing of new drugs on human subjects is important to the entire development process. Such studies known as clinical trials need to be carefully planned with regards to the safety and other ethical issues pertaining to the patients' well being. The two main considerations in a clinical trial are to treat the patients in the trial as well as to generate information that may lead to improve treatments for future patients.

In order to achieve the best balance between these two considerations, careful thought needs to be given to the design, conduct and analysis of clinical trials. Medical statistics plays a key role in this.

Bayesian statistical approach has become increasingly popular in many areas of medical research, including clinical trials. This is especially so as the advancement in modern computing power and technique allow many previously very difficult Bayesian computations to be relatively easily implemented. Bayesian methods offer practical, potentially better approach to design, conduct and analyse a clinical trial.

On a global scale, clinical trials are broadly categorised into four different phases. However, one of the most critical, yet important phase is the Phase I clinical trial. This is the first experimentation of a new drug on human subjects. The safety and accuracy of conducting the trial has to be looked upon with deepest scrutiny. The objective of a Phase I trial is to determine an acceptable single drug dosage (i.e. how

much drug can be applied without causing serious side effects). This is usually the highest dose possible of a potential drug that has associated acceptable toxicity. This dose is referred to as the maximum tolerable dose (MTD) and is the dose that will be used in subsequent trials in the development process. Phase I trials are essentially dose-escalation experiments, whereby cohorts of typically 1 to 6 patients are subjected to increasing doses of the drug according to a predetermined schedule.

Several researchers have discussed the statistical considerations for Phase I clinical trials and have proposed several designs [1 – 5]. However, the majority of trials done in practice still use the classical “3+3” design [6] with the fixed and pre-specified dose options chosen by the design team. This is in spite of the “3+3” design being shown to be inferior to other designs in terms of the reduced number of subjects required, as well as the accuracy of the MTD estimate [4].

The general algorithmic nature of the “3+3” design, which focuses on the presence or absence of toxicity entirely, is as follows. The design begins with a group of three patients treated at a predetermined starting dose level. Escalation of this dose level occurs if no toxicity is observed in all three patients. If two or more of the three patients experience toxicity, the trial will stop. If one toxicity is observed, an additional three patients are treated at the same dose level. If none of these three has toxicity, escalation again continues; otherwise, the trial will stop.

The possibility of using a Bayesian approach for a Phase I design was first proposed with the Continual Reassessment Method (CRM) [5]. This sequential design treats the MTD as a parameter to be estimated. The goal of the CRM is to reduce the number of patients who receive the lower doses of unlikely efficacy, and to obtain a more accurate estimate of the MTD. The presumption here is that although an assessment of efficacy (benefit to the patient) is not the objective of the trial, it is

“unethical” to give trial patients such low doses for which there can be little possibility of gain. CRM is model specific and one of its characteristics is the explicit utilisation of prior information from various sources for quantifying the dose-toxicity relationship before the start of the trial. In addition, an acceptable target probability of toxicity is specified. The MTD is obtained once the estimated model reaches this target probability of toxicity. The relative performance of the CRM as compared with the “3+3” design showed superiority of the CRM in terms of correct dose allocation at the end of the trial. However, it received some criticisms, among which were that the patients included early on in the trial were potentially exposed to a dose level which resulted in excessive toxicity [7,8].

Whitehead and Brunier [9] use a Bayesian model coupled with a decision theoretic procedure for finding the optimal dose level. In their method, the dose is selected at each stage so as to minimise the asymptotic variance of the maximum likelihood estimates. This criterion of minimising the variance can be viewed as a utility (or loss) function that seeks to minimise the distance of the probability of toxicity associated with the next assigned dose to the targeted toxicity probability. Whitehead [10], and Whitehead and Williamson [11] reported that simulation comparisons between the minimum variance loss function and a CRM-type loss function showed that there is a little difference in the operating characteristics of the procedures.

The above designs focus on toxicity as the single endpoint of interest. Thall and Russell [12] proposed a design for dose finding which involves both an evaluation of toxicity and an indication of efficacy. This method involves a binary toxicity outcome (absence or presence of toxicity) and a 3-level ordinal efficacy outcome (adverse effect, inefficacious, efficacious). In this manner the selected dose

takes into account both safety and efficacy. A Bayesian criterion is used to generate decision rules while also relying on frequentist criteria to determine a design parameterisation with good operating characteristics. O'Quigley *et al* [13] also incorporate into CRM information on efficacy in their dose finding studies in patients with HIV. Efficacy in this case is a prespecified reduction in viral load. The optimal dose is chosen when it satisfies a high probability of viral reduction in the absence of any toxic side effect. Braun [14] studies the bivariate case using the CRM concept where MTD is based jointly on both toxicity and disease progression.

In the case of chemotherapy for Oncological trial, most of the dose regimen would consist of combination dose therapy where it consists of multiple drugs for a single treatment. The situation is more complicated as the biochemical and biological phenomena occurring with the combination are generally quite complex and may cause therapeutic effects that are difficult to predict. Thall *et al* [15] introduces a two stage Bayesian procedure in finding an acceptable dose combination of 2 cytotoxic agents. The method requires two dose agents that have been previously studied as a single agent. A parametric model is assumed for the probability of toxicity as a function of the two doses. Korn and Simon [16] propose a method based on the idea of the "total equivalent dose" of the combination agents. Another approach is to limit the search to a sequence of combination such that each level is obtained from the previous one by increasing one or both of the single-agent doses. Since this ensures that the probability of toxicity is monotone in the levels, a single-agent dose-finding algorithm requiring only monotonicity, such as the continual reassessment method (CRM) [5] can be applied. These types of approach severely restrict the domain of possible dose pairs that are considered.

1.2 Objectives

The motivation behind this study is to extend the design of a phase I trial where it will address some of the limitations in historically simplistic Phase I study designs such as the “3+3” method [6]. It is also with interest to further explore the Bayesian Paradigm into the design of a Phase I trial. Bayesian decision theoretic methods which have been advocated for many situations, is especially suitable for “decision-oriented applications”, such as Phase I dose escalation trials.

The main research direction is to focus on the development of a novel Phase I clinical trial design based on Bayesian decision theory. The objective is to find the optimal dose (OD) of an experimental drug to be used for further testing in the development process. The specific context is that of cancer, where typically, only a small number of suitable patients are available for such studies. The proposed design evaluates the optimality of a drug dose on the basis of its associated toxicity as well as indication of its efficacy.

The second direction is to look at the pragmatism of a new proposed design towards an implementation on an actual Phase I clinical trial.

1.3 Organisation of the thesis

Chapter 2 will give an overview of Phase I clinical trial designs, in particular highlighting the general methodology of designs and whether they can be practically used in clinical setting.

Chapter 3 will introduce the general principle of Bayesian statistics and decision theory to build up the foundation of this proposed research.

Chapter 4 introduces a novel Phase I clinical trial design based on the framework of Bayesian decision theoretic approach. It mainly discusses the

theoretical background that provides the functional aspect of the methodology. The implementation of this method is also discussed and is based on some hypothetical data to illustrate the example. To access the performance of this design, comparisons are made between the proposed method and other existing designs in term of its operational characteristic and practicality.

Chapter 5 presents a modification of the proposed design where the performance is further enhanced. This improved method is specifically applied to a combination dose therapy where it involves a dual dose agent. Actual clinical case study is used to access the practicality of the improved method.

Lastly, the report will end with a final conclusion and a few ideas for future work.

CHAPTER 2

Literature Review: Design of Clinical Trials

2.1 What constitutes a Clinical Trial study?

The evaluation of possible improvements in the treatment of diseases has historically been an inefficient and haphazard process. Only in the last few years has it become widely recognised that properly conducted clinical trials provide the only reliable basis for evaluating the efficacy and safety of new treatments. What exactly do we mean by a “clinical trial”? It can be briefly explained as any form of “planned experiment” which involves human subjects and is designed to determine the most appropriate treatment for future patients with a given medical condition.

The majority of clinical trials are concerned with the evaluation of drug therapy. This involves a close collaboration between the pharmaceutical company and hospital where the actual experimentation is carried out. Clinical trials may also involve other forms of treatment such as surgical procedure, radiotherapy for cancer, different forms of medical advice (eg, diet and exercise policy after a heart attack). There are four main phases of experimentation used in clinical trial studies. These four phases are a general guideline as to how the clinical trials research programme for a new treatment in a specific disease might develop. The basic fundamental structure of these phases is sequentially shown as follows:

Phase I trials: Clinical pharmacology and toxicity

These first experiments in human subjects are primarily concerned with drug safety, not efficacy. The first objective of phase I trials is to determine an acceptable

single drug dosage (i.e. how much drug can be given without causing serious side-effect). Such information is often obtained from dose-escalation experiments, whereby an individual is subjected to increasing doses of the drug according to a predetermined schedule. Phase I will also involve studies of drug metabolism and bioavailability and, later, studies of multiple doses will be undertaken to determine appropriate dose schedules for use in Phase II. Typically, Phase I studies require a sample size of around 20 – 80 subjects and patients.

Phase II trials: Initial clinical investigation for treatment effect

These are fairly small-scale investigations into the effectiveness and safety of a drug and require close monitoring of each patient. The main purpose of Phase II trials is to select those relatively few drugs of genuine potential from the larger number of drugs which are inactive or over-toxic, so that the chosen drugs may proceed to Phase III trials. Seldom will Phase II trial go beyond 50 – 100 patients on a drug.

Phase III trials: Full-scale evaluation of treatment

After a drug is shown to be reasonably effective, it is essential to compare it with the current standard treatment(s) for the same condition in a large randomised trial involving a substantial number of patients. To some people, the term “clinical trial” is synonymous with such a full-scale Phase III trial, which is the most rigorous and extensive type of scientific clinical investigation of a new treatment.

Phase IV trials: Post marketing surveillance

After the research programme leading to a drug being approved for marketing, there remain substantial enquiries still to be answered regarding monitoring for adverse effects and additional large-scale, long-term studies of morbidity and mortality. Also the term “Phase IV trials” is sometimes used to describe promotion

exercises aimed at bringing a new drug to the attention of a large number of clinicians, typically in general practice. This latter type of enquiry has limited scientific value and hence should not be considered as part of clinical trial research.

In some situations, there are trials that involve features of Phase I and II trials. They are mainly designed to provide preliminary information on safety and efficacy.

Each phase of the clinical trial study has its unique characteristics and methods in implementation. It is beyond the scope of this thesis to individually discuss the designs relating to each of these clinical trial phases. Instead, the main interest is to look further into Phase I clinical trial design, as they are important in early human studies. The specific area of interest for the Phase I study is in Medical Oncology (i.e. cancer).

2.2 Design of phase I trials in oncology

The initial phase of human experimentation in the development of chemotherapeutic drugs involves finding a dose that produces an acceptable level of toxicity. This dose-toxicity relationship has a fundamental objective of determining the maximum dose of drug that will produce an acceptable level of toxicity. This dose is usually referred to as the maximum tolerable dose (MTD). A typical definition of acceptable toxicity is usually reflected by the side effects that the patient experiences when given a particular dose level. In recent years, the level of toxicity has been standardised by the establishment of the common toxicity criteria (CTC) by the U.S. National Cancer Institute (NCI) (<http://ctep.info.nih.gov/ctc3/ctc.htm>). The following is a list of adverse events (AE) and is categorised into five classes.

1. CTC grade 0, no AE or normal;

2. CTC grade 1, mildly (elevated/reduced);
3. CTC grade 2, moderate;
4. CTC grade 3, serious/severe; and
5. CTC grade 4, very serious or life threatening.

An occurrence of toxicity that is unacceptable is said to be a dose-limiting toxicity (DLT). Usually, a toxicity of grade 3 or 4 is considered dose limiting.

Phase I clinical trials are particularly important in Oncology because of the severity of side effects of cytotoxic drugs that are needed to treat cancers. Therefore, the sample size of the patients is usually small. Ethically, the initial administration of such drugs cannot be investigated in healthy volunteers, but only in cancer patients [17]. A slow dose escalation, during the experimentation stage, may put patients at increased risk of death from the disease. Some of the uncertainties and challenges that need to be considered when determining the required dose level for the patient in a Phase I trial are as follow:

1. At low doses, there might be little effect on the patient;
2. At high doses, it may pose a severe toxic or even life threatening effect on the patient;
3. Little is known about the relationship between dose and probability of toxicity;
4. There is a need to reconcile the risks of toxicity to patients with the potential benefit to these same patients; and
5. The design should be efficient and use no more patients than necessary.

Based on literature survey, the formal definition of the MTD varies with investigators. Schneiderman [18] first delineated it as an estimation of dose yielding a

fixed percent (often 33%) of toxicity but not lower. Some researchers define it as the maximal dose that was administered during trial without eliciting any toxicity [19]. Others define it as the minimal administered dose associated with some toxic response [20]. Storer [1] takes the MTD to mean some percentile of the dose-toxicity relationship (he uses 33% as the probability of target toxicity). In general, it would seem desirable to estimate some arbitrary percentile chosen by the experimenter. This percentile is otherwise known as target probability of toxicity. The target probability of toxicity can also be interpreted as the desired probability of obtaining a DLT at the MTD.

To obtain these target doses to a certain degree of accuracy, several methods have been designed over the years to carry out and analyse Phase I trials in Oncology. The following section will present some of these common methods which have been proposed and implemented in actual Phase I trials.

2.2.1 Initial dose level

The first problem in a Phase I trial is deciding on a safe, but not overly conservative, initial dose for the trial. If the agent is new to clinical testing, this must be based on animal studies. It has been determined that the dose (defined in mg per meters squared of body surface area) associated with 10% lethality in mice ($MELD_{10}$) can be predicted to be roughly equivalent to the human MTD [21]. This approach is derived from the concept of “allometric scaling” [22,23], toxicity as a function of body weight or surface area is assumed to be roughly constant across species. The initial dose for the Phase I trial is taken to be 1/10 the $MELD_{10}$ or, if similar, 1/3 the LD_{10} (associated with 10% Lethality) in the beagle dog [24]. The use of a second species has been shown to be necessary, since in approximately 20% of

approximately 90 reviewed drugs, mouse data alone was insufficient to safely predict the human MTD [25]. American investigators generally use the dog as the second species, while European investigators generally use rat, with equivalent safety [25]. The next problem is to define dose increments for the subsequent dose levels, and it is here where various Phase I trial designs evolved.

2.2.2 Standard design

The “standard” Phase I design utilises a set of decreasing “fibonacci” dose level increments proposed by Schneiderman [18], and currently taken to be 100%, 67%, 50%, 40%, and 33% thereafter [26]. These increments are added to each dose level to give the succeeding level. In other words, the second dose level is 100% greater than the first; the third is 67% greater than the second, and so forth. The purpose is to allow more aggressive dose escalation for the initial levels, which are expected to be sufficiently removed from the MTD for this to be safe. If the MELD₁₀ accurately predicted the human MTD, only 5–6 such dose escalations would be necessary to complete a “standard” phase I design. Unfortunately, this is often not the case.

The “standard” rule governing dose escalation from one level to the next relies on no assumptions concerning the shape of the dose-toxicity curve or the potential for cumulative toxicity, and therefore the decision to escalate to the next dose level is based solely on toxicity results from the first course administration of the current level. This dose escalation rule is often referred to as the “3+3” design which uses a cohorts of 3-6 patients per dose level [6]. At the k dose level three patients are treated. If at least 2 patients are observed to have DLT, the prior dose level ($k-1$) is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the

tentative MTD). If 0 of the 3 patients are observed to have DLT, the dose level is escalated one step ($k+1$) for the next cohort of 3 patients, and the process continues as above. If exactly 1 of the 3 patients treated shows DLT, 3 additional patients are treated at the current dose level. If none of these additional 3 patients show DLT, the dose level is escalated for the next cohort of 3 patients, and the process continues as above; otherwise, the prior dose level is defined as the MTD (unless only 3 patients have been treated at that level, in which case it is the tentative MTD). A tentative MTD becomes final when a total of 6 patients are treated with less than 2 showing DLT.

Figure 2.1 Graphical representation of a “3+3” design algorithm

The actual target probability of the MTD is generally not well defined in the “3+3” method. Lin and Shih [27] have shown that the 3+3 design results in an MTD which is lying somewhere between 0.1 and 0.29.

This design has been criticised in the literature [1,3,4,28] as scientifically vague and the approach is somewhat on a “trial and error” basis which will not truly identify an accurate dose level. This may potentially result in errors being passed on to subsequent Phase II and Phase III trials. Furthermore, it has also been criticised for its tendency to include too many patients at suboptimal dose levels and give poor estimate of the MTD [5]. However, it is still widely used in practice because its algorithmic-based simplicity means that it is very easy for clinical investigators to carry out as compared to a more advanced method which requires complex mathematical calculation [5,29].

Since the “standard” method has become a “norm” for most of clinical investigators, it seems difficult to change their mindset for a better but completely different design. Therefore, a modified “3+3” design was proposed and implemented [6]. This is a more conservative version of the current method whereby escalation of doses is somewhat controlled and stringent to ensure overall safety of the patient. To illustrate further, patients are treated in cohorts of three where each receives the same dose, d_k . If none of the three patients shows a DLT at level d_k , the next cohort of three patients receives the next higher dose level d_{k+1} . If one of the three patients has DLT, then six more patients will be treated at the same dose level d_k . If none of these additional patients has DLT, then the dose will be escalated. If at least one of the six additional patients has DLT, then six more patients are treated at the lower dose level (i.e. dose de-escalation), provided that only three patients are previously treated at that dose level. The MTD is therefore defined on a dose level at which none or one out of

the nine patients (0/9 or 1/9) experiences DLT and that at least two out of three patients (2/3) or two out of nine patients (2/9) treated with the next higher dose have had DLT [4,27].

2.2.3 Storer's Up-and-Down Design (SUDD)

As mentioned in the previous section, the paradigm of the “standard” design is still upheld by many due to its simplicity in application and despite criticisms of its potential inaccurate conclusions. Storer [1], on the other hand, explored a combination of more traditional methods, in order to minimise the number of patients treated at lower dose levels and to focus on sampling around the MTD; these methods also use an explicit dose-response framework to estimate the MTD.

The design has two stages and uses a combination of simple dose-escalation algorithms. In the first stage, a tolerable toxicity of 0.33 is first assigned. He suggested a number of designs: (i) use cohorts of one patient each and escalate or de-escalate depending on whether a toxicity is seen; (ii) use cohorts of one patient and escalate only after two consecutive non-toxic responses are seen, but de-escalate whenever a toxic response is seen; (iii) use cohorts of three patients and escalate if no toxic responses are seen, stay at the same dose if one toxicity is seen, and de-escalate if more than one toxic response is seen. He later suggested a more sophisticated design [2] whereby cohorts of one patient are used for an initial escalation stage until the first toxic response appears, at which point the design proceed to stage II.

In the second stage, a fixed number of cohorts of 3 to 5 patients are entered. If the current cohort is treated at d_k , the next cohort is treated at d_{k+1} , d_k or d_{k-1} depending on whether 0, 1 or >1 patients in the cohort have DLT, respectively. Following a second-stage sample size of 24 patients, the true dose-response follows a standard two

parametric logistic model on the log dose scale, that is that $\text{logit } p(d) = \alpha + \beta \log d$. The dose-response setting is determined by fixing $p(d)$ and the distance to d_{MTD} on the log scale, so that $\beta = (\text{logit } p_{MTD} - \text{logit } p(d_1))/\Delta$, where $\Delta = \log d_{MTD} - \log d_1$, and $\alpha = \text{logit } p(d_1) - \beta \log d_1$. The two standard two-parameter logistic model is fit to the data, whence $\log d_{MTD} = (\text{logit } p_{MTD} - \alpha)/\beta$. If it is not the case that $0 < \beta < \infty$, then the geometric mean of the dose level for the last cohort and the dose level that would have been assigned to the next cohort is used as the MTD. In either case, if that dose is higher than the highest dose at which patients have actually been treated, then the latter is taken as the MTD.

2.2.4 The Continual Reassessment Method (CRM)

The Continual Reassessment Method (CRM) was first proposed by O'Quigley and his team in the 1990 [5] as a new approach for dose finding study in cancer patients, as this method deals with the problem of having a fairly high, acceptable rate of toxic response in effective doses. The aim of CRM is to estimate the dose giving a toxicity with the chosen acceptable probability. CRM has gained increasing popularity among the scientific investigators and also by far the most well written about and simulated alternative to the standard method in Phase I Oncology trials [29,30 – 37]. This method treats one patient at a time and uses accumulated toxicity data to determine the next dose level. In this form, the CRM requires two pieces of information to implement a Bayesian approach to estimation: a parametric model that represents the dose-toxicity relationship, and a prior distribution for each unknown parameter. An acceptable probability of dose-limiting toxicity (DLT) is identified, and the goal is to estimate the dose associated with this target probability θ .

An approximate dose-toxicity relationship is obtained from animal studies, and a model for the probability of DLT given a dose d_i , $\psi(x_i)$, is chosen to represent this relationship. Next, k doses are chosen which are believed to cover an acceptable range of DLT probabilities, including the target probability θ . The first patient is given the dose, d_{θ} , for which the estimated probability of toxicity is closest to θ . Since the parameter to be estimated is considered a random variable, it is given a prior distribution, chosen to reflect all available prior information concerning it. If no reliable prior information is available to the investigator, a vague or non-informative prior distribution can be chosen.

To represent the dose-toxicity relationship, O'Quigley and Chevret [29] suggested one of the following one-parameter models:

$$\text{Power model: } \psi_a(d_i) = [\theta_{i1}(d_i)]^a$$

$$\text{Logistic model: } \psi_a(d_i) = \frac{\exp(a_0 + ad_i)}{1 + \exp(a_0 + ad_i)}$$

$$\text{Hyperbolic tangent model: } \psi_a(d_i) = \{(1 + \tanh d_i) / 2\}^a$$

where d_i is the i th dose, $i=1, \dots, k$, $\theta_{i1}(d_i)$ is an initial estimate of the probability of toxicity at the i th dose, and a_0 is a fixed constant. Chevret [32] conducted simulations which compared estimation results using the exponential, gamma, log-normal, uniform and Weibull prior distributions to determine if the form of the prior distribution was important. The simulations showed that the form of the prior distribution did not considerably affect the results, and no one prior distribution performed consistently better or worse than others.

Just prior to testing the j th patient, the likelihood function is given by

$$L(a; \Omega_j) = \prod_{l=1}^{j-1} \{\psi_a(d_{l(l)})\}^{y_l} \{1 - \psi_a(d_{l(l)})\}^{(1-y_l)} \quad (2.1)$$

where Ω_j represents all accumulated information on the first $(j-1)$ patients, $d_{i(l)}$ is the dose administered to the l th patient, and y_l is the binary toxicity response for the l th patient. As patients are entered into the study and toxicity data are collected, the *posterior* distribution of a is updated using Bayes rule. The posterior distribution is given by

$$f(a|\Omega_j) = \frac{L(a; \Omega_j)g(a)}{\int_0^\infty L(u; \Omega_j)g(u)du}. \quad (2.2)$$

The Bayes estimate of a , the posterior mean, is then

$$\mu(j) = \int_0^\infty af(a|\Omega_j)da. \quad (2.3)$$

An estimate of the probability of toxicity at dose level i given the accumulated information on the first $(j-1)$ patients, θ_{ij} , can be found by substituting the mean of the posterior distribution into the dose-toxicity model $\psi(d_i)$. Thus, after each patient is entered, the probability of toxicity associated with each dose is updated, and the next dose will be that for which the estimated posterior probability is closest to θ , the target probability. This process continues until a pre-specified number of patients have been treated, at which point the final estimate of the recommended Phase II dose is obtained.

2.2.4.1 Modification of the original CRM design

In recent years, some of the literatures on Phase I trials [7,39] have been devoted to simulation comparisons between the conventional “3+3” Phase I designs and the CRM. The CRM has received some criticism, primarily from three aspects:

- (a) Choice of the starting dose level according to the prior $g(a)$ that could results in a dose level in the middle and not in the lower dose region. This is mainly an ethical issue of subjecting the patient to too high a dose level at an initial stage.
- (b) Allowance to jump over parts of the dose region and skipping intermediate levels. This is largely determined by the dose-response model used.
- (c) Lengthening the trial because one needs to know the result from the previous patient before assigning the next patient. Korn *et al* [7] conclude that CRM takes $2\frac{1}{2}$ times longer to complete as the standard design.

Many authors have proposed modification to the original CRM. Each proposed method was aimed at a perceived or specific problem. Farries [40], in his earlier work, proposed a modification of CRM to deal with the problem of skipping dose levels.

Moller [41], on the other hand, proposed an external CRM that uses “up and down” method in an initial state and also allows escalation to the next adjacent dose level only. In his studies where large number of dose levels, 12 or more, are used which will incur the problem of skipping doses.

However, O’Quigley pointed out that had the CRM been correctly implemented many of these problems would not occur, for example, in the case of “skipping” dose level. Some of the investigators [32,39] use logistic regression model. If the parameter of this model is set inappropriately it may oppose the CRM class of model [13]. Strictly speaking, dose “skipping” can be considered as an operating characteristic of CRM. Such operating characteristic depends on the choice of model as well as given design features such as the number of dose levels and the value of

target probability value. However, such problems do not arise when CRM is correctly implemented. In other cases, the criticism about CRM taking up longer operating time to determine the MTD, O’Quigley argues that the literature merely makes this comparison on the basis that the classical design includes three patients at a time whereas the original CRM [5] includes one patient at a time. Therefore, this criticism simply disappeared when the comparison was based on group inclusion whereby the time required to complete the trial was the same as for the standard method.

Piandodasi and Liu [36] proposed incorporating pharmacokinetic data into the dose-response model in order to obtain a better fitting model and thereby improve the chance of finding an accurate dose. This is potentially a very useful idea, but would require much further research from statisticians in collaboration with pharmacologist.

2.2.4.2 Inclusion of stopping rule

The usual CRM design requires that a given sample size be determined in advance. Given the convergence properties of CRM, it may occur in practice that the MTD will be attained before having included the full sample size n of anticipated patients. A properly designed stopping rule may bring the study to an early close thereby enabling the Phase II study to be undertaken more quickly.

Korn *et al* [7] also proposed a stopping rule that ends the CRM algorithm after a certain number of patients (denoted as c) are assigned to the same dose; $c = 6$ has been explored via simulation.

O’Quigley and Reiner [42], and other investigators [43], later explored a stopping rule in detail where it consists of two actions namely, “continue the trial” and “stop the inclusions for non-usefulness of continuation”, when a predetermined suitable estimation of the MTD has been reached. The idea is based on the

convergence of CRM and that, as the dose-response relationship reaches a plateau, the next patient cohort is expected to receive the same dose level. As such, the stopping criterion will be based on the probability that the administered dose remains unchanged for the additional patients, using a decision tree technique [44,45]. When the probability of the administered dose that remains unchanged is high (at least 0.90), the trial will then terminate.

Mathematically, this can be interpreted by a criterion where

$$\begin{cases} \text{stop, if } \tilde{p}\{Z(j+1)=Z(j+2)=\dots=Z(j+c)|\Omega_j\} > \zeta_{01} \\ \text{continue, otherwise} \end{cases}$$

where ζ_{01} is an arbitrary chosen cut-off point ranging from 0 to 1;

$P\{Z(j+1)=Z(j+2)=\dots=Z(j+c)|\Omega_j\}$ is the probability of no change in the administered dose of c additional inclusion, defined by

$$P\{Z(j+1)=Z(j+2)=\dots=Z(j+c)|\Omega_j\} = \sum_{r=0}^c A_r [1-\psi(z_{j+1}, a)]^{c-r} [\psi(z_{j+1}, a)]^r$$

and estimated by

$$\tilde{P}\{Z(j+1)=Z(j+2)=\dots=Z(j+c)|\Omega_j\} = \sum_{r=0}^c A_r (1-\tilde{p})^{c-r} \tilde{p}^r$$

with $\tilde{p} = \psi(z_{j+1}, \bar{a})$ and A_r is the number of paths of decision tree that contain the same number of toxicities (r) from the root to the leaf and $\bar{a}$ is the expected value of parameter “ a ”.

Thall and Russell [12] previously proposed a stopping action to be used in the context of Phase I/II clinical trials. Although this proposed stopping rule is not considered in the context of CRM, it is mentioned as it can be applied in the CRM context. Two stopping rules are applied in this setting. They consist of two actions, that is “continue the trial”, or “stop the inclusion for unsuitability of dose range”. These stopping criteria are based on the posterior probability that the response rate of all doses is either higher (rule 1) or lower (rule 2) than the target response rate (θ_{tox}).

In rule 1, it must satisfy a condition

$$\begin{cases} \text{stop, if } w_1(z_1, \Omega_j) > \zeta_{02} \\ \text{continue, otherwise} \end{cases}$$

and rule 2 satisfies a condition

$$\begin{cases} \text{stop, if } w_1(z_k, \Omega_j) > \zeta_{03} \\ \text{continue, otherwise} \end{cases}$$

where the rule must be applied after j^{th} inclusion of patients; ζ_{02} and ζ_{03} are arbitrary chosen cut-off point ranging from 0 to 1. $w_1(z_1, \Omega_j)$ and $w_2(z_2, \Omega_j)$ can be expressed as follows:

$$w_1(z_1, \Omega_j) = \int_0^{\infty} (\psi(z_1, a) > \theta_{tox}) f(a | \Omega_j) da$$

$$w_2(z_k, \Omega_j) = \int_0^{\infty} (\psi(z_k, a) < \theta_{tox}) f(a | \Omega_j) da$$

where $f(a|\Omega_j)$ is the posterior density for parameter “ a ”.

Since the underlying dose-response relationship is supposed to be monotonically increasing, only the first z_1 or the last z_k has to be considered, respectively. When either of this criteria reaches a fixed level (at least 0.9), termination of inclusion is decided [12].

2.2.5 Bayesian methodology in Phase I design

The advent of CRM design “sparked off” other researchers [9,31,33,46] to consider applying Bayesian method into the design of Phase I clinical trial. It is realised that Bayesian method is particularly suitable for Phase I study in Oncology because it can be applied even if little data is present. Furthermore, Bayesian method is well suited for decision making and it tends to allocate patients at higher doses after nontoxic and at lower doses after toxic responses. The accumulation of information and the tendency for allowing real time decision makes Bayesian design particularly useful when patients are treated one at a time and when toxicity information is available quickly.

Whitehead and Brunier [9] introduced a full Bayesian design for Phase I trial incorporating Bayesian decision theory [44,47], namely actions, which are the set of assignment dose levels, prior and loss functions. Generally, the decision is to be based on a set of data y which has already been collected. The model, $\psi(d,a)$, is chosen for these data expressed as a joint density function $f(y|a)$ of known form

$$f(y|a) = \prod_{j=1}^n \{\psi(d_j, a)\}^{y_j} \{1 - \psi(d_j, a)\}^{1-y_j}$$

where y_j denotes the patient's outcome with the sample size of the total patients at $j=1, \dots, n$. d_i and " a " denote the dose level with $i=1, \dots, k$ and parameter " a " respectively.

The prior density function $g(a)$ is expressed as the uncertainty about parameter " a ". There will be a set of possible actions denoted by $A(d)$ for $d_1, d_2, d_3 \in D$, where d_1, d_2, d_3 represent the current 3 dose levels for that single cohort of three patients. Essentially, a gain function (negative loss) G is needed to characterise the gain information when an action is taken given the true unknown value of parameter " a ". The gain function $G(a)$, represents the gain made if action $A(d)$ is chosen when parameter value " a " is valid. The objective is to choose the action which will maximise the expected gain.

The procedure of this decision problem begins by deriving the posterior density function $h(a|y)$ by Bayes theorem

$$h(a|y) = \frac{\psi(y, a) g(a)}{\int_{\Omega} \psi(y, a) g(a) da} \quad (2.4)$$

where Ω denotes the parameter of space for a ; and then the action $A(d)$ is chosen when the posterior expected gain G is maximised,

$$G_i = E[G_i(a)|y] = \int_{\Omega} G_i(a) h(a|y) da \quad i = 1, 2, \dots, k \quad (2.5)$$

This maximisation of the expected gain is analogous to the CRM procedure where it minimises the distance between the next assigned dose from the target probability. Other researchers [10,11] report simulation comparisons between the

minimum variance loss function and a CRM-type loss function which indicates that there is a little difference in the operating characteristics of the procedures.

The approach outlined by Whitehead [9] draws similarity with the CRM where it involves updating the prior distribution on the parameters and allocating a dose according to a specific loss function. For the CRM this is the dose that is, in some sense, close to the estimated target (or in the terminology of Whitehead the “patient gain”). In fact, the loss function used in the CRM can be formulated such that patients are not allocated to doses higher than the current estimate of the MTD.

2.2.6 Escalation With Overdose Control (EWOC)

More recently, Zack *et al* [48] and Babb *et al* [31] have studied Bayesian dose escalation with overdose control that is essentially a modified CRM. This method approaches the MTD as fast as possible and is subjected to the constraint that the predicted proportion of patients who receive an overdose does not exceed a specified value. Instead of using a dose with toxicity deemed closest to the target toxicity for updating, Babb *et al* [31] suggested using the highest dose d_i such that:

$$p(MTD \leq d_i | \pi_j) < \alpha$$

for the $j^{th} + 1$ cohort, given a tolerance level α and the history up to the j^{th} cohort where π_j denotes the data at the time of treatment for the j^{th} patient and would include for each previously treated patient the dose administered, the highest level of toxicity observed and any relevant covariates measurement. They called $1 - \alpha$ a Bayesian-feasible level and suggested a value of 0.25 in their study.

In general, CRM and EWOC are two examples of Bayesian sequential designs. They are, in some sense, myopic in strategy where it is not always globally optimal. However, to ensure a globally optimal strategy, back calculation (dynamic

programming) is required. It is a computationally intensive determination of all possible strategies that could be taken each time a patient is assigned to a dose level. While back calculation is difficult logistically, it is possible using parallel processing and modern computational facilities. However, avoiding the constraint that patients not being assigned to highly toxic dose levels can lead to globally optimal strategies that have unacceptable toxicity. The EWOC incorporated a feasibility constraint into their myopic strategy which is optimal in the class of these feasibility procedures.

2.2.7 Other Phase I design issues

Other alternatives of phase I design have also been proposed. Among them are the simple “up-and-down” design (UaD), introduced by Dixon and Mood [49], and the stochastic approximation method (SAM), developed by Robbins and Monro [50]. SAM, however, has never been considered seriously for Phase I trials. One reason is that, the use of a continuum of dose levels leading to impracticable differentiation between doses; another reason could be the ambiguity of the adapting parameter sequence $\{a_j\}$ [31].

For UaD, it is a nonparametric design initially introduced as a dose escalation design to estimate median effective dose (MED) which is defined as the dose that elicits a toxic response in 50 per cent of treated patients [49]. The principal advantage of UaD is its simplicity and great ease of application. However, several limitations can be pointed out. Firstly, it samples around the median where in practice, particularly in Oncology, the preferred percentile would be 33rd or lower. Secondly, this design supposes that the tested doses are fixed in advance and equally spaced, although Dixon and Mood initially suggested that the distance between two doses should be chosen approximately equal to the standard deviation of the dose-toxicity curve. Its unavailability will lead investigators to choose the dose level arbitrarily.

Thirdly, this design recommends that sample sizes be restricted to be over 50 observations. Unfortunately, in most Phase I trials in cancer, only a small number of patients are available, often no more than a maximum sample size of 24.

Despite their limitations, UaD rules are recently adapted for medical application by considering grouped entry and Bayesian modifications [51]. Storer [2] developed several types of “up-and-down” designs that target the quartile corresponding to $\theta=0.33$. Random walk rules (RWR), on the other hand, generalise this approach by providing a unifying theory for targeting any quantile of interest. Patients are assigned sequentially to the next higher, same, or next lower dose level according to some probability and the previous patient’s response. The most appropriate random walk rule for Phase I clinical trials is perhaps the following rule [51]:

Figure 2.2 Schematic flow chart of Durham *et al* [51] random walk rule design

Durham and Flourney [38] show that if $b = \theta / (1-\theta)$, the asymptotic frequency distribution of dose assignments for RWR will be unimodally distributed

around an unknown quantile μ . While this is an asymptotic result, small sample studies have shown that the unimodality property holds for values of n acceptable in phase I clinical trials. Thus, RWR creates a unimodal distribution around the target quantile. Consequently, some patients will be assigned above the MTD, in accordance with a mixture of discrete normal distribution [38].

Random walk rules have finite distribution properties that can be derived from results in the literature on finite Markov chains. In fact, much of the literature on RWRs has been devoted to finite properties of the rules. Simple software in MATLAB which gives the finite properties of the design in seconds has also been developed [51]. Such information has previously only been obtained by simulation for the CRM. RWRs have the advantage of being nonparametric, having a workable finite distribution theory; simple to explain and easy to implement.

2.2.8 Phase I design in consideration of dual endpoint

The primary consideration in a phase I trial is finding a dose level that satisfies the safety aspect of the patient which is associated with the toxicity of each dose level. In some situations, a Phase I study will consider the effectiveness of the drug as a secondary consideration of interest. This is usually associated with experimentation in an early Phase I/II trial (as mentioned in Section 2.1). Thall and Russell [12] proposed a Phase I/II design where the goal is to define a dose satisfying both safety and efficacy requirements, to stop early when it was likely that no such dose could be found, and to continue if there remained good chances of finding one. Two toxicity outcomes (absence or presence of toxicity) and three efficacies related outcomes (no effect, desired effect, severe effect) are considered. Toxicity and efficacy outcomes are combined into a comprehensive ternary outcome variable Y with values $Y = 0$ if no effect and no toxicity, $Y = 1$ if desired effect and no toxicity, and $Y = 2$ if severe effect

and toxicity occurred. This results in three dose-dependent outcomes probabilities and a two-dimensional dose-effect endpoint. These two endpoints are defined as two decision criteria in terms of posterior probabilities given the accumulated data at any interim point in the trial. A dose is thus acceptable only when it satisfies the two criteria and unacceptable when it is otherwise. In their design, the number of patients should be large enough to estimate reliably both the toxicity rate and the response rate at the selected dose. O'Quigley *et al* [13] also incorporate into CRM information on efficacy in their dose finding studies in patients with Human Immunodeficiency Virus (HIV). Efficacy in this case is a prespecified reduction in viral load. The optimal dose is chosen when it satisfies a high probability of viral reduction in the absence of any toxic side-effect. Braun [14] studies the bivariate case using the CRM concept where MTD is based jointly on both toxicity and disease progression. Whitehead *et al* [68] developed a Bayesian decision procedure for bivariate observations of undesirable events and signs of therapeutic benefit. In their methods, logistic regression models are used to model the two responses, which are both assumed to take a binary form. Fan and Wang [69] proposed a decision-theoretic framework for designing sequential dose-finding trials with multiple outcomes. Their methods make use of an optimal strategy from the theory of bandit problems [70] and dynamic programming to determine the optimal dose allocation and the optimal time to terminate the trial. Zohar and O'Quigley [71] proposed a design that looks at bivariate response. The method states that it has optimal properties where the current estimates of both probability of toxicity and those for response achieve the Cramér-Rao bound for every dose level. Zhang *et al* [72] recently develop an approach that incorporates both toxicity and efficacy data into the estimation of the biologically optimal dose of an agent in a phase I trial. The approach is based on the flexible continuation-ratio

model, and uses straightforward optimal dose selection criteria. Dose selection is based on all patients treated up until that time point, using continual reassessment method approach. Their dose-outcomes curves consist of a monotonically increasing, monotonically decreasing, and unimodal curve.

2.2.9 Pharmacokinetically guided dose escalation

An entirely different approach to the problem of safely accelerating the dose in Phase I studies was proposed by Collins *et al* [26]. They presented a retrospective analysis of anti-cancer agents which demonstrated that, for the most part, toxicity was not a function of administered drug dosage, but, rather, was a function of AUC, the area ($C \times T$) under the curve of plasma drug concentration (C) measured over time of exposure (T). Therefore, they proposed a “pharmacokinetic guided dose escalation” (PGDE) scheme that involved targeting the AUC associated with the mouse LD_{10} (rather than the $MELD_{10}$ itself).

The PGDE scheme of Collins *et al* [26] involved escalating to an MTD by targeting a maximal tolerated AUC, and proceeded as follows:

- (1) Determine the mouse LD_{10} , and the associated mouse AUC, of the new agent.
- (2) Treat the initial cohort of three patients at $1/10$ $MELD_{10}$, as is standard, measure the average (human) AUC over this cohort of patients.
- (3) Escalate the doses for subsequent cohorts of three patients according to the distance to the target AUC (that which is associated with the $MELD_{10}$), according to one of the following two rules:
 - (i) First escalation step increases the initial dose by a factor equal to the square root of the ratio of the target AUC associated with the

initial dose, and subsequent escalation steps follow the Fibonacci scheme.

- (ii) Escalation steps are by a factor of two until the AUC is 40% of the target AUC, and subsequent escalation steps follow the Fibonacci scheme.

Retrospective analyses by Collins *et al* [26] indicated that the sample sizes of Phase I trials could be reduced by 20% – 50% by utilizing this pharmacokinetically guided dose escalation (PGDE) scheme.

The efficiency of PGDE relies on the assumption that drug toxicity is really a function of drug AUC, and that equivalent AUC for human and mouse will result in equivalent toxicity. Furthermore, the underlying assumption is that the mouse LD₁₀ roughly equals the human MTD, other doses measured as a function of body surface area (in mg/m²) because, in general, the two doses yield roughly equivalent AUC levels for the two species. However, as noted by Collins *et al* [26], there are important exceptions to this rule. For example, the MTD of doxorubicin in humans is five-fold higher than the MELD₁₀ because the clearance rate of doxorubicin is much higher in human than in the mouse, leading to a much smaller AUC in man for the equivalent dose. This sort of situation leads to a striking advantage for PGDE, since the smaller than expected AUC for the first dose will result in escalation of the initial dose step(s). Other situations, also noted by Collins *et al* [26], on the other hand, may lead to problems for PGDE. For some drugs, there is a drug concentration threshold for action and a necessary minimum exposure time above the threshold. For such drugs, the relation between mouse toxicity and human toxicity is complicated by the fact that, in general, the smaller species experiences a higher initial drug concentration and a shorter half-life [22]. Thus, if the threshold is high and the necessary exposure time

short, the mouse may experience much more serious toxicity for equivalent AUC (or equivalent dose). Likewise, if the threshold is low and the necessary exposure time long, the human may experience much more serious toxicity. For other drugs, there is a marked difference between the two species in target cell sensitivity, again rendering mouse dose or AUC non-predictive of the human MTD.

2.2.10 Further consideration

Several other alternative Phase I designs have been proposed for special situations. For drugs with variable dose effect based on a patient baseline characteristic (initial white blood count, in particular), Mick and Ratain [34] suggested using a dose-toxicity model, incorporating this additional variable, to define both the MTD and the dose escalation schema. For Phase I studies of drug combinations, Korn and Simon [16] point out that there may be a wide variety of combined MTD's, involving different drug proportions. They provide guidance in arriving at a favourable combination, from a dose-intensity perspective, as well in designing the combined dose-escalation schema. Thall *et al* [15], on the other hand, introduce a two stage Bayesian adaptive method for determining several acceptable dose pairs of two agents used together in a phase I cancer chemotherapy trial. The method requires two dose agents that have previously been studied as a single agent. A parametric model is assumed for the probability of toxicity as a function of the two doses. Despite the fact that the method is computationally intensive, the algorithm is rooted in actual clinical practice.

Phase I studies in children are generally performed after an adult MTD has been established, and dose escalation begins at 80% of the adult dose, to minimise under-treatment [52]. In the past, Phase I studies have routinely excluded elderly

patients due to the assumption that they are inherently more susceptible to toxicity. Cascinu *et al* [53] review the results of a comparison of toxicity seen in 120 elderly patients, compared with that seen in 120 non-elderly patients with similar clinical features and receiving the same chemotherapeutic regimens. They report that the chemotherapeutic regimens, for both groups, yield similar benefits and similar toxicities. They conclude that chronologic age is a weak predictor of either toxicity or failure to respond

Except for phase I studies of non-toxic therapeutics, which we have discussed at length, there is usually little attempt to assess the efficacy of the therapy in the phase I trial. Sometimes the MTD cohort is expanded to approximately 10 patients, to further assess toxicity. In these cases, care should be taken to not over-interpret any responses seen, or, more importantly, lack of response. Phase II trials of efficacy are significantly larger than 10 patients, and still give only crude indications of response rate. Moreover, 10 patients' immunity to toxicity is generally insufficient evidence upon which to reject the potential efficacy of an agent. Most importantly, the patient population of phase I trials is generally not as favourable as that of Phase II trials with respect to the likelihood of seeing tumour response.

The last decade has witnessed a dramatic change in the design and practice of Phase I trials. A study of the Phase I trials conducted at M.D. Anderson Cancer Centre between 1991 and 1993 [52] concluded that all used standard designs, with 23% of the patients treated at less than 50% of the determined MTD. In contrast, all participants in a 1998 colloquium on new Phase I designs [54] agreed that they no longer used standard Phase I designs routinely, that dose escalation with one-patient cohorts in the initial stages of Phase I trials has become frequent and was apparently

safe, and that all of the commonly used newer methods are generally preferable to the standard Phase I design.

CHAPTER 3

Bayesian Theory

In the subsequent chapters, most of the mathematical formulation and discussion will be based on Bayesian theory. Therefore, in this chapter a general framework for Bayesian statistical inference [44] will be discussed. In the beginning, Bayes theorem for discrete parameters will be shown and followed by Bayes theorem for continuous parameters. This will be followed by a discussion of Bayesian estimation in a decision-theoretic context. Bayesian theory is a very large and general field and a full discussion of all its aspects is well beyond the scope of this report. Therefore, only the basic principles will be highlighted.

3.1 Bayes theorem for discrete parameter

Let $x_1, \dots, x_n \in \mathbf{x}$ denote independent and identically distributed random vector variables, each with probability density function $f(\mathbf{x} | \theta)$ conditional upon θ . θ is assigned to be unobservable and unknown quantities. Assume θ is discrete and let $g(\theta)$ denote its probability density function. Then, Bayes theorem asserts that the probability density function of θ , a given $(x_1, \dots, x_n)$, is expressed by :

$$h(\theta | x_1, \dots, x_n) = \frac{f(x_1 | \theta) \dots f(x_n | \theta) g(\theta)}{\sum_{\theta} f(x_1 | \theta) \dots f(x_n | \theta) g(\theta)} \quad (3.1)$$

It can be written as $h(\theta|x_1, \dots, x_n) \propto L(x_1, \dots, x_n)g(\theta)$, where $\propto$ denotes proportionality and where $L(x_1, \dots, x_n|\theta) \equiv f(x_1|\theta) \dots f(x_n|\theta)$ is the likelihood of the data given the parameter θ , assuming $x_1, \dots, x_n$ are independent. Note that when viewed as a function of θ , the likelihood function is unique only up to a multiplication constant. The constant makes no difference in Bayes theorem since it is absorbed into the proportionality constant. $g(\theta)$ is called the prior probability density function, since it is determined prior to observing $\mathbf{x}$ in the current experiment; that is, $g(\theta)$ is based upon previous practical experience and understanding or external information. For example, if θ denotes the mean value of a population, then $g(\theta)$ represents your prior belief about this average value, based upon earlier experience with populations and other external source of information. $h(\theta|x_1, \dots, x_n)$ is called the posterior probability density function of θ , given the current data, since it is determined posterior to, or after, observing the current set of data. In summary, Bayes theorem can be expressed as

$$\text{Posterior} \propto \text{Likelihood} \times \text{Prior}$$

The general implication of Bayesian theorem is that if there are no current observations to draw upon, then one can pass judgement on θ based on previous experience; that is, to use the prior probability density function, $g(\theta)$ only. On the other hand, if there are both previous experience and current perceptions based upon observational data, one revises $g(\theta)$ according to Bayes theorem and obtain inference about θ on $h(\theta|x_1, \dots, x_n)$, the posterior probability density function.

3.2 Bayes theorem for continuous parameter

Let $x_1, \dots, x_n$ denote as sample from a distribution with likelihood function L indexed by a continuous parameter θ , with the prior density $g(\theta)$. Then, the posterior density for θ is given by

$$h(\theta|x_1, \dots, x_n) = \frac{L(x_1, \dots, x_n|\theta)g(\theta)}{\int_{\Omega} L(x_1, \dots, x_n|\theta)g(\theta)d\theta} \quad (3.2)$$

where Ω denotes the parameter space of θ . Analogous to the discrete case, one can express (3.2) by a proportionality factor, $h(\theta|x_1, \dots, x_n) \propto L(x_1, \dots, x_n|\theta)g(\theta)$.

$\int_{\Omega} L(x_1, \dots, x_n|\theta)g(\theta)d\theta$, the normalising constant of the probability distribution of $L(x_1, \dots, x_n|\theta)$, is often called the marginal distribution of the data or the prior predictive distribution. Most of the density functions used in the later chapters concern continuous random samples. Therefore the general equation of (3.2) will be applied frequently.

Till now, the Bayesian paradigm is conceptually simple, intuitively plausible and probabilistically elegant. However, the main challenge from now on is the numerical implementation which is often complex and not straightforward.

In most models and applications, the marginal distribution $\int_{\Omega} L(x_1, \dots, x_n|\theta)g(\theta)d\theta$, does not have an analytic closed form, and therefore the posterior probability distribution will not have a resulting closed form as well. This dilemma has resulted in much research on the computational methods for sampling from the posterior probability as well as method for estimating the marginal distribution. Perhaps one of the most popular computational methods for sampling

from the posterior probability is the Gibbs sampler. This method is one of the best known Markov Chain Monte Carlo (MCMC) sampling algorithms. It generally allows sampling for posterior probability without knowing the normalising constant. (further details see Chen, Shao and Ibrahim, 2000 [55]; Gilks, Richardson and Spiegelhalter, 1998 [56]).

Alternatively, mathematical and numerical convenience in sampling the posterior distribution can be achieved when there is the presence of a natural conjugate prior (or natural conjugate family). This is interpreted as having a posterior in the same form as a prior such that the overall posterior distribution function remains in the same family of the prior.

To illustrate, suppose the likelihood function is binomial, so that

$$L(\theta) = \theta^y (1 - \theta)^{n-y}.$$

where y and n are sampled data.

The family of natural conjugate priors is first developed by interchanging the roles of the random variable and the parameter in the likelihood function and then “enriching” the parameters, that is, making their values perfectly general and not dependent upon the current data set. Thus, if θ is the random variable, $L(\theta)$ would look like a beta distribution. But one would not want the beta prior family to depend upon sample data (y and n), so the arbitrary parameters (α , β) are used to normalise the density, to make it proper, so as to get the beta prior density

$$g(\theta) = \frac{1}{B(\alpha, \beta)} \theta^{\alpha-1} (1 - \theta)^{\beta-1}, \quad \alpha > 1, \quad \beta > 0$$

Now, the prior belief to assess the hyperparameters α and β is used; that is, having fixed the family of priors as the beta distribution, only (α, β) remain unknown.

An additional mathematical convenience arises in computing the posterior. Since the posterior density is proportional to the likelihood times the prior, in the case of a beta prior, the posterior density is given by

$$h(\theta|y) \propto \left[\theta^y (1-\theta)^{n-y} \right] \left[\theta^{\alpha-1} (1-\theta)^{\beta-1} \right], \text{ or}$$
$$h(\theta|y) \propto \theta^{y+\alpha-1} (1-\theta)^{n-y+\beta-1},$$

which is a beta posterior. Conjugate prior distributions have the advantage that the posterior distributions have the same form (distributional family) as the prior distributions. This “closure property” for some distribution of the natural conjugate family holds for all sampling distribution members of the exponential family, that is, the family of distributions with sufficient statistics. Table 3.1 provides sampling distributions in the exponential family, along with their corresponding natural conjugate priors

Table 3.1 Some natural conjugate prior distributions	
Sampling Distribution	Natural Conjugate Prior Distribution
1. Binomial	Success probability is beta
2. Negative binomial	Success probability is beta
3. Poisson	Mean is gamma
4. Exponential with mean λ^{-1}	λ is gamma
5. Normal with known variance but unknown mean	Mean is normal
6. Normal with known mean but unknown variance	Variance is inverted gamma

3.3 Decision theory

Suppose a particular decision D is selected and the uncertain event, θ , occurs. The occurrence of the event will remove all uncertainty from the problem and the action, D , will produce a definite result which can be seen with certainty. In other words, the combination of D with θ will result in a consequence. This consequence will be written as C_{mn} or equally (D_m, θ_n) where the subscripts m, n represent the location in the row and column in a decision table as shown in the following

A decision problem, in general, can be presented in the form of a table (as shown in Table 3.2) containing lists of the decisions as rows and the uncertain events as columns. In the table, the intersection of any row with any column bears a number corresponding to the utility of the consequence associated with the decision of that row, and the event of that column where it contains decision D_m , events θ_n , and consequences C_{mn} . Suppose that any pair of consequences can be compared in the sense that one of them is preferred to the other or alternatively that they are equally desirable. Suppose further that this comparison is coherent if a consequence C_1 is preferred to C_2 and C_2 is preferred to C_3 , then C_1 is preferred to C_3 . Associated with any consequence C_{mn} is a unique number u which is denoted as $u(C_{mn})$, rather than just u , and will be called the *utility* of C_{mn} . Because of the coherence required in the comparison of the consequences, it is clear that C_{mn} if preferred to C_{kl} , then $u(C_{mn})$ will be larger than $u(C_{kl})$ where C_{kl} refers to any consequence other than C_{mn} ; if C_{mn} and C_{kl} are equally desirable then $u(C_{mn})$ will be equal to $u(C_{kl})$; finally if C_{mn} is worse than C_{kl} , then $u(C_{mn})$ will be less than $u(C_{kl})$. This explicit numerical measure of the desirability of any of the consequences in the decision table is called a utility of the consequence. Lindley (1985) propounded that this utility by itself is a probability and therefore should obey the laws of probability. It therefore follows that u is the

probability of obtaining the most desirable consequence C . Alternatively, this utility can be expressed as any form of reasonable value where the ranking of the respective consequence can take place.

Table 3.2 Decision table displaying the utility of consequence

	θ_1	θ_2	θ_3	θ_4
D_1	$u(c_{11})$	$u(c_{12})$	$u(c_{13})$	$u(c_{14})$
D_2	$u(c_{21})$	$u(c_{22})$	$u(c_{23})$	$u(c_{24})$
D_3	$u(c_{31})$	$u(c_{32})$	$u(c_{33})$	$u(c_{34})$

Combining the utility value with the probabilities of specific event produces a set of numbers for the decision. The best decision is thus the one with the highest number. In other words, this combination can be expressed as the expected utility of D_m and we write it as $U(D_m)$. Hence with $C_{mn} = (D_m, \theta_n)$, the consequence of taking D_m and θ_m obtains [45],

$$U(D_i) = \sum_{j=1}^n u(D_i, \theta_j) p(\theta_j) \tag{3.3}$$

where $p(\theta_j)$ is the probability of event θ_j .

The conclusion from all the arguments presented up to now can be simply stated as follows. A decision problem can be formulated as lists of decisions and of uncertain events. On the assumptions of coherent comparisons of events, and of consequences, probabilities can be assigned to the events and utilities to the consequences. Each decision can then be assigned a value given by equation (3.3). The decision problem is solved when the decision associated with the expected utility is maximised.

Introducing the Bayesian context, the initial probabilities of $p(\theta_1)$, $p(\theta_2), \dots$, $p(\theta_n)$, which reflect the uncertainties can be replaced by a posterior probability of $p(\theta_j | X)$ where X denotes the data or information. Equation (3.3) can finally be written as (Lindley, 1985)

$$U(D_i) = \sum_{j=1}^n u(D_i, \theta_j) p(\theta_j | X). \quad (3.4)$$

In a continuous case, θ will be expressed by some parameter space where it encompasses within the set Ω of all possible values θ . Thus

$$U(D_i) = \int_{\Omega} u(D_i, \theta_j) p(\theta_j | X) d\theta. \quad (3.5)$$

CHAPTER 4

Dose-finding weighted design in Dual endpoint Phase I Clinical Trial

4.1 Introduction

The development of an alternative Phase I clinical trial design based on Bayesian decision theory is discussed. The objective is to find the optimal dose of an experimental drug to be used for further testing in the development process. The proposed design evaluates the optimality of a drug dose on the basis of its associated toxicity as well as indication of its efficacy. In this manner, it differs from the design proposed by Whitehead and Brunier [9] although they also adopt a Bayesian decision theoretic approach. Their focus is on the single endpoint of interest that is toxicity. Thall and Russell [12] also proposed a two endpoint design. However, their design typically requires a relatively large number of patients to be used. This limits the design's practical value, especially in the area of Oncology.

Since the principal purpose of a Phase I clinical trial is to determine the “best” dose of a new compound to be used in subsequent trials, both toxicity and efficacy are important criteria in obtaining the OD in a Phase I trial. Unlike the conventional design where the focus is on toxicity as the single endpoint of interest, the proposed design makes use of a decision theoretic method to incorporate both toxicity as well as efficacy in determining the optimal dose level of a drug in a Phase I trial.

The Bayesian decision theoretic approach is adopted where it involves the specification of a utility function, which represents preferences over the consequences of possible actions to be taken.

4.2 Design

4.2.1 Overview

Figure 4.1 presents a schematic tree-diagram for the operating procedure of the proposed trial design. The design commences after the starting dose level has been defined. This can be based on the target probability of some outcome that is pre-specified by the investigator. Alternatively, the starting dose level can be determined by the first stage of the Storer's two-stage design [2].

The key objective of the design is to make the optimal decision from the set of possible actions comprising de-escalating the dose (Action A_{-1}), keeping the same dose (A_0) or escalating the dose to the next higher dose level (A_1) after the data from each patient is obtained. The action taken affects the dose to be used for the next patient in the trial.

As with most phase I dose-finding designs, the approach is based on a "single-step look-ahead" methodology. It makes use of previous and current data to estimate the best or "optimal" action in dose finding which is beneficial for patient's well being. The main aim, at the end of the trial, is to locate a dose level that achieves a tolerable target probability (TP).

A total of k fixed dose levels (denoted by d_l , $l=1,\dots,k$) have been chosen for the design. Corresponding to each of these dose levels is the probability of toxicity, PT_l , and efficacy, PE_l . There are four possible outcomes for each patient in the study (T_0, E_0), (T_0, E_1), (T_1, E_0) and (T_1, E_1) where T_0 and T_1 are outcomes of non-toxicity and toxicity respectively; E_0 and E_1 are outcomes of non-efficacy and efficacy. These four combinations reflect the patient's response at a particular dose level. Following O'Quigley's bivariate dose finding studies in HIV, it is assumed that the probability of toxicity is independent from its efficacy counterpart [13]. Although, toxicity and

efficacy can be correlated biologically but it will be too profound to mathematically quantify the two parameters together. Therefore, a more plausible and simplified way is to assume the independence between toxicity and its efficacy effect. The consequence is a resulting four possible probabilities of combination outcomes for each DL. These can be expressed as

$$\begin{aligned}
 \theta_{1l} &= p(T_0, E_0) = (1 - PT_l) \times (1 - PE_l) , \\
 \theta_{2l} &= p(T_0, E_1) = (1 - PT_l) \times (PE_l) , \\
 \theta_{3l} &= p(T_1, E_0) = (PT_l) \times (1 - PE_l), \\
 \theta_{4l} &= p(T_1, E_1) = (PT_l) \times (PE_l) .
 \end{aligned}
 \tag{4.1}$$

The final optimal dose is determined when the design meets the condition of a stopping criterion. Further illustration will be shown in the next few sections.

Figure 4.1 Schematic tree diagram of the proposed phase I design

4.2.2 The model

The data from each patient consists of both toxicity and efficacy effects. This can be expressed in one of the following four possible combinations of outcomes (Table 4.1).

Table 4.1 Four combinations of outcomes of patient’s effect on a particular therapeutic treatment.

Events	Data outcomes	Probability outcomes
Non toxic – non efficacious (T ₀ E ₀)	y ₁	θ ₁
Non toxic – efficacious (T ₀ E ₁)	y ₂	θ ₂
Toxic – non efficacious (T ₁ E ₀)	y ₃	θ ₃
Toxic – efficacious (T ₁ E ₁)	y ₄	θ ₄

The combination of outcomes are represented by $y = (y_1, y_2, y_3, y_4)$; where $y_1, y_2, y_3, y_4 \in \{0,1\}$, with a “1” representing the occurrence of the outcome combination and a “0” otherwise. Note that $\sum_{i=1}^4 y_i = 1$ for each patient.

The following model is chosen as it allows for multiple binary outcomes in the data. It is also mathematically and computationally convenient. The design process begins by eliciting from the clinical investigators, the prior probability of outcome values for each dose level.

The prior is assumed to have a Dirichlet distribution with random variable $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$, where $(0 \leq \theta_i \leq 1)$ and $\sum_{i=1}^4 \theta_i = 1$, of the form

$$p(\theta) = \frac{\Gamma\left(\sum_{i=1}^4 \rho_i\right)}{\prod_{i=1}^4 \Gamma(\rho_i)} \prod_{i=1}^4 \theta_i^{\rho_i-1}, \tag{4.2}$$

where $\Gamma(.)$ is the Gamma function and a parametric vector $\rho = (\rho_1, \dots, \rho_4)$ with $\rho_i > 0$ ($i = 1, \dots, 4$).

Although values of ρ_i should reflect clinical opinion, this is more likely to be obtained indirectly via eliciting from the investigator the likely values of the mean of each θ_i and in discussing with the trial statistician, the variance, $Var[\theta_i]$, of the vague priors. The latter is required in order to obtain the necessary unique solutions for ρ_i form,

$$E[\theta_i] = \frac{\rho_i}{\sum_{i=1}^4 \rho_i} \quad (4.3)$$

and

$$Var[\theta_i] = \frac{E[\theta_i](1 - E[\theta_i])}{1 + \sum_{i=1}^4 \rho_i}. \quad (4.4)$$

Without loss of generality, the constraint $\sum_{i=1}^4 \rho_i = 1$ is chosen, although this represents a desirable high variance which is necessarily associated with a vague prior.

The multiple outcomes in the trial have a multinomial likelihood of the form

$$p(y | \theta) = \frac{\left(\sum_{i=1}^4 y_i\right)!}{\prod_{i=1}^4 y_i!} \prod_{i=1}^4 \theta_i^{y_i} \quad (4.5)$$

where the vector y is the data from the patients. Since the posterior density is proportional to the likelihood times the prior (Dirichlet prior), this leads to the following Dirichlet posterior distribution

$$p(\theta|y) \propto [p(\theta)][p(y|\theta)]$$

which implies $p(\theta|y) \propto \left[\prod_{i=1}^4 \theta_i^{\rho_i-1} \right] \left[\prod_{i=1}^4 \theta_i^{y_i} \right]$ (from Equations 4.2 and 4.5)

$$p(\theta|y) \propto \left[\prod_{i=1}^4 \theta_i^{\rho_i+y_i-1} \right]$$

thus, the posterior distribution of θ given vector y is a Dirichlet distribution with parametric vector $\rho^* = (\rho_1 + y_1, \dots, \rho_4 + y_4)$. Formally, the Dirichlet distribution is said to be “conjugate” [44] to the multinomial. Hence, the overall expression is therefore expressed as

$$p(\theta|y) = \frac{\Gamma\left(\sum_{i=1}^4 (\rho_i + y_i)\right)}{\prod_{i=1}^4 \Gamma(\rho_i + y_i)} \prod_{i=1}^4 \theta_i^{\rho_i+y_i-1}. \quad (4.6)$$

4.2.3 The utility weights

The utility weight to be used is defined in Table 4.2. This decision table contains the actions (A_{-1} , A_0 , and A_1) as rows and the outcome combinations (y_1 , y_2 , y_3 and y_4) as columns. For clarity, the table will indicate the toxicity/efficacy combination that each y_i refers to (e.g. T_0E_1 means no toxicity but efficacy presents). The intersection of any row with any column bears the utility u_{vi} ($v=1,2,3$ and

$i=1,2,3,4$) of the consequence associated with the action of that row, and the event of that column.

Table 4.2 Decision table for utility weight value of four different toxicity/efficacy combinations

	$y_1(T_0, E_0)$	$y_2(T_0, E_1)$	$y_3(T_1, E_0)$	$y_4(T_1, E_1)$
A_1	$u_{11} = 2$	$u_{12} = 1$	$u_{13} = 0$	$u_{14} = 0$
A_0	$u_{21} = 1$	$u_{22} = 2$	$u_{23} = 2$	$u_{24} = 1$
A_{-1}	$u_{31} = 0$	$u_{32} = 0$	$u_{33} = 1$	$u_{34} = 2$

For each outcome combination, each of the actions A_{-1} , A_0 and A_1 , takes one of 3 possible ordered (but arbitrary) values 0, 1 and 2. The utility weight to be used is defined in Table 4.2. The weight values reflect the relative optimality of each action in relation to the outcome combination. Thus, for example, for outcome combination (T_0, E_0) , the “best” action to take would be to escalate the dose (A_1). This is because there is neither toxicity nor efficacy at the current dose level. At the same time, action A_0 , while not as good as action A_1 , is a better alternative to action A_{-1} . Therefore action A_1 , has utility weight of 2, A_0 has utility weight of 1, while A_{-1} has utility weight of 0.

For the outcome combinations (T_0, E_1) and (T_1, E_0) , the choice of utility weight also reflects the added influence given to toxicity over efficacy. The optimal decision in both cases is to retain the same dose (A_0). This reflects the trade-off between the toxicity and efficacy aspects. However the next best action for (T_0, E_1) is to escalate (A_1), whereas it is to de-escalate (A_{-1}) for (T_1, E_0) . This is because toxicity (or the lack of it) is felt to be a more important criterion than efficacy, all else being the same. This is a choice which will depend on the clinical context. Should toxicity and efficacy be felt to be equally important, for example, then the utility values for

outcomes (T_0, E_1) and (T_1, E_0) could both have equal values 0, 2 and 0 corresponding to actions A_1 , A_0 and A_{-1} .

In general, the value given to a particular action in relation to the outcome combination and action does not have to be restricted to just three different utility values. Two actions may for example share the same utility if they are equally optimal. Furthermore, the ranking of the values does not have to be restricted to values between 0 and 2.

It will be illustrated in the next section that the utility value has an implicit relation with the target probability of the outcome combinations. The choice of utility value could thus also depend on this target probability.

4.2.4 Utility weights relative to target probability of outcome combinations

In many phase I trial designs, the objective is to obtain the MTD, which is the dose level with probability of toxicity closest to the pre-specified target probability. This is done by updating the probabilities of toxicity associated with each dose level and finally choosing the one which is closest to the target probability. Decision theory uses a utility value to prioritise the possible actions taken in response to an outcome. The utility is related to the selected target probability value. Thus the choice of a utility weight implicitly corresponds to a choice of a target probability and vice versa. This section explores the relationship between the utility weight and the target probability.

The nature of the relationship between the utility and the target probability has to satisfy certain criteria and constraints. When the outcome probability estimate is equal (or at least very close) to the target probability value, the optimal decision should maintain at the same dose level. This relationship can be expressed by:

$$U(A_0) > U(A_1) = U(A_{-1}) \quad (4.7)$$

which implies $U(A_0) - \varepsilon = U(A_1) = U(A_{-1})$

where $U(A_1)$, $U(A_0)$ and $U(A_{-1})$ are the expected utility value for the corresponding actions and, $\varepsilon > 0$ is some arbitrary positive value. Other possible occurrence of the relationship can also happen such as: $U(A_0) > U(A_1) \geq U(A_{-1})$ or $U(A_0) > U(A_{-1}) \geq U(A_1)$. The expected utility value of $U(A_0)$ will always take precedence over other actions which therefore make $U(A_1)$ and $U(A_{-1})$ trivial. To simplify the mathematical relationship between target probability and utility weight, Equation 4.7 is thus adopted.

The rationale behind this is that, at the target probability value, the decision to escalate and de-escalate the dose level should share the same expected utility which has to be less than the decision to maintain the same dose level. This is because at this juncture, the dose level has converged to an optimal dose. Thus the optimal decision should remain at the same dose level.

The relationship between the utility and the target probability is now being discussed. For simplicity, the case of a single outcome of interest – toxicity will first be considered. This is then followed by dual outcomes – toxicity and efficacy.

4.2.4.1 Theorem I: Single outcome (toxicity)

Given a target probability of toxicity θ_{tox} , if the corresponding utility is represented by a decision table as shown in Table 4.3, then

Table 4.3 Decision table of utilities for a single (toxicity) event.

	T_0	T_1
Escalate, A_1	$u_{11} = a_1$	$u_{12} = b_1$
Maintain, A_0	$u_{21} = a_2$	$u_{22} = b_2$
De-escalate, A_{-1}	$u_{31} = a_3$	$u_{32} = b_3$

$$(b_3 - b_1) = \left(\frac{1 - \theta_{tox}}{\theta_{tox}} \right) (a_1 - a_3) \quad (4.8)$$

$$(b_3 - b_2) = \left(\frac{1 - \theta_{tox}}{\theta_{tox}} \right) (a_2 - a_3) - \frac{\varepsilon}{\theta_{tox}} .$$

Conversely, given any utility as expressed in (4.8), the corresponding θ_{tox} must satisfy both

$$\theta_{tox} = \frac{a_1 - a_3}{b_3 - b_1 + a_1 - a_3} \quad (4.9)$$

$$\text{and } \theta_{tox} = \frac{a_2 - a_3 - \varepsilon}{b_3 - b_2 + a_2 - a_3} .$$

For a unique solution of θ_{tox} , it must satisfy

$$\frac{(a_1 - a_3)(a_3 - a_2 + b_2 - b_3)}{b_3 - b_1 + a_1 - a_3} + a_2 - a_3 > 0 . \quad (4.10)$$

Proof of Theorem I:

At the MTD, the expected utility values of the three actions will be expected to be

$$U(A_1) = U(A_{.1}) = U(A_0) - \varepsilon, \quad \varepsilon > 0,$$

where

$$U(A_1) = a_1 \theta_1 + b_1 \theta_2,$$

$$U(A_0) = a_2 \theta_1 + b_2 \theta_2,$$

$$U(A_{.1}) = a_3 \theta_1 + b_3 \theta_2.$$

From

$$U(A_1) = U(A_{.1}),$$

one obtains

$$a_1 = \frac{a_3 \theta_1 + b_3 \theta_2 - b_1 \theta_2}{\theta_1}. \quad (4.11)$$

From

$$U(A_{.1}) = U(A_0) - \varepsilon,$$

one obtains

$$a_3 = \frac{a_2 \theta_1 + b_2 \theta_2 - b_3 \theta_2}{\theta_1} - \frac{\varepsilon}{\theta_1}. \quad (4.12)$$

But $\theta_{tox} = \theta_2 = 1 - \theta_1$

Therefore (4.11) becomes

$$a_1 = \frac{a_3(1 - \theta_{tox}) + (b_3 - b_1)\theta_{tox}}{(1 - \theta_{tox})} \quad (4.13)$$

and (4.12) becomes

$$a_3 = \frac{a_2(1 - \theta_{tox}) + (b_2 - b_3)\theta_{tox}}{(1 - \theta_{tox})} - \frac{\varepsilon}{(1 - \theta_{tox})}. \quad (4.14)$$

From (4.13)

$$(a_1 - a_3) = \frac{(b_3 - b_1)\theta_{tox}}{(1 - \theta_{tox})},$$

resulting in

$$(b_3 - b_1) = \left(\frac{1 - \theta_{tox}}{\theta_{tox}} \right) (a_1 - a_3). \quad (4.15)$$

From (4.14)

$$a_3 - a_2 = \frac{(b_2 - b_3)\theta_{tox}}{(1 - \theta_{tox})} - \frac{\varepsilon}{(1 - \theta_{tox})},$$

resulting in

$$b_3 - b_2 = \left(\frac{1 - \theta_{tox}}{\theta_{tox}} \right) (a_2 - a_3) - \frac{\varepsilon}{\theta_{tox}} \quad (4.16)$$

as required.

Now rewriting (4.15) gives

$$\theta_{tox} = \frac{a_1 - a_3}{b_3 - b_1 + a_1 - a_3}$$

and rewriting (4.16) gives

$$\theta_{tox} = \frac{a_2 - a_3 - \varepsilon}{b_3 - b_2 + a_2 - a_3}.$$

For a unique θ_{tox} , it must satisfy

$$\frac{a_1 - a_3}{b_3 - b_1 + a_1 - a_3} = \frac{a_3 - a_2 + \varepsilon}{a_3 - a_2 + b_2 - b_3}$$

rewriting this gives

$$\frac{(a_1 - a_3)(a_3 - a_2 + b_2 - b_3)}{b_3 - b_1 + a_1 - a_3} + a_2 - a_3 = \varepsilon > 0.$$

The first part of Theorem I implies that to find the utility corresponding to θ_{tox} , one can choose any value of a_1 , a_2 , a_3 and b_3 and find the corresponding b_1 and b_2 values as defined in (4.8). The second part of Theorem I states that given any utility of the same general form, the corresponding θ_{tox} value can be obtained. The condition for this value has to be unique.

In the situation whereby the utility value of action A_0 is midway between A_1 and A_{-1} then $a_2 = (a_1 + a_3) / 2$, $b_2 = (b_1 + b_3) / 2$ and it can be shown that

$$\frac{(a_1 - a_3)(a_3 - a_2 + b_2 - b_3)}{b_3 - b_1 + a_1 - a_3} + a_2 - a_3 = 0. \quad (4.17)$$

This is exactly equal to and not greater than zero which implies that there is no unique solution for θ_{tox} in this case.

4.2.4.2 Theorem II: Dual outcome (toxicity & efficacy)

Given a target probability vector $\theta_r = (\theta_{1r}, \theta_{2r}, \theta_{3r}, \theta_{4r})$, if the corresponding utility is represented by Table 4.4, then with $\sum_{i=1}^4 \theta_{ir} = 1$,

Table 4.4. Decision table for dual outcomes of utility variables

	T_0, E_0	T_0, E_1	T_1, E_0	T_1, E_1
Escalate, A_1	$u_{11} = a_1$	$u_{12} = b_1$	$u_{13} = c_1$	$u_{14} = d_1$
Maintain, A_0	$u_{21} = a_2$	$u_{22} = b_2$	$u_{23} = c_2$	$u_{24} = d_2$
De-escalate, A_{-1}	$u_{31} = a_3$	$u_{32} = b_3$	$u_{33} = c_3$	$u_{34} = d_3$

$$\begin{aligned} (a_1 - a_3) &= (c_3 - c_1) \frac{\theta_{3r}}{\theta_{1r}} + (d_3 - d_1) \frac{\theta_{4r}}{\theta_{1r}} - (b_1 - b_3) \frac{\theta_{2r}}{\theta_{1r}} \\ (a_3 - a_2) &= (c_2 - c_3) \frac{\theta_{3r}}{\theta_{1r}} - (d_3 - d_2) \frac{\theta_{4r}}{\theta_{1r}} + (b_2 - b_3) \frac{\theta_{2r}}{\theta_{1r}} - \frac{\varepsilon}{\theta_{1r}}. \end{aligned} \quad (4.18)$$

Conversely, given the utility value, one can obtain the corresponding value of θ_r . However, unlike the case of a single outcome, the final expression is now much more complicated. This is probable if one of the target probability outcomes is treated as a constant, resulting in non-uniqueness of the solution for θ_r . The implication of this is that each utility corresponds to a set of possible values of θ_r . Detail of the

expression for θ_r corresponding to a pre-specified utility expression will be given. It also gives the proof of Theorem II.

Proof of theorem II:

For a multiple outcome, at the optimal dose level, the expected utilities of the three actions are expressed as

$$U(A_1) = U(A_{.1}) = U(A_0) - \varepsilon, \varepsilon > 0,$$

where

$$U(A_1) = a_1 \theta_{1r} + b_1 \theta_{2r} + c_1 \theta_{3r} + d_1 \theta_{4r},$$

$$U(A_0) = a_2 \theta_{1r} + b_2 \theta_{2r} + c_2 \theta_{3r} + d_2 \theta_{4r},$$

$$U(A_{.1}) = a_3 \theta_{1r} + b_3 \theta_{2r} + c_3 \theta_{3r} + d_3 \theta_{4r}.$$

From $U(A_1) = U(A_{.1}),$

it yields $a_1 \theta_{1r} + b_1 \theta_{2r} + c_1 \theta_{3r} + d_1 \theta_{4r} = a_3 \theta_{1r} + b_3 \theta_{2r} + c_3 \theta_{3r} + d_3 \theta_{4r},$

which eventually gives

$$(a_1 - a_3) = (c_3 - c_1) \frac{\theta_{3r}}{\theta_{1r}} + (d_3 - d_1) \frac{\theta_{4r}}{\theta_{1r}} - (b_1 - b_3) \frac{\theta_{2r}}{\theta_{1r}}. \quad (4.19)$$

From $U(A_{.1}) = U(A_0) - \varepsilon,$

it yields $a_3 \theta_{1r} + b_3 \theta_{2r} + c_3 \theta_{3r} + d_3 \theta_{4r} = a_2 \theta_{1r} + b_2 \theta_{2r} + c_2 \theta_{3r} + d_2 \theta_{4r} - \varepsilon,$

which eventually gives

$$(a_3 - a_2) = (c_2 - c_3) \frac{\theta_{3r}}{\theta_{1r}} - (d_3 - d_2) \frac{\theta_{4r}}{\theta_{1r}} + (b_2 - b_3) \frac{\theta_{2r}}{\theta_{1r}} - \frac{\varepsilon}{\theta_{1r}}. \quad (4.20)$$

To obtain the corresponding target probability value from a given utility value, equations (4.19) and (4.20) can be solved together with

$$\theta_{1\tau} = 1 - \theta_{2\tau} - \theta_{3\tau} - \theta_{4\tau}. \quad (4.21)$$

Fixing $\theta_{4\tau}$ as a constant, and substituting (4.21) in (4.19) and (4.20), one eventually obtains

$$(a_3 - a_1 + b_1 - b_3)\theta_{2\tau} = (c_3 - c_1 + a_1 - a_3)\theta_{3\tau} + (d_3 - d_1 + a_1 - a_3)\theta_{4\tau} + (a_3 - a_1). \quad (4.22)$$

and

$$(a_2 - a_3 - b_2 + b_3)\theta_{2\tau} = (c_2 - c_3 + a_3 - a_2)\theta_{3\tau} + (d_2 - d_3 + a_3 - a_2)\theta_{4\tau} + (a_2 - a_3) - \varepsilon. \quad (4.23)$$

Subtracting Equation (4.22) from (4.23) to obtain

$$(a_2 - 2a_3 + a_1 - b_2 + 2b_3 - b_1)\theta_{2\tau} = (c_2 - 2c_3 + c_1 + 2a_3 - a_2 - a_1)\theta_{3\tau} + (d_2 - 2d_3 + d_1 + 2a_3 - a_2 - a_1)\theta_{4\tau} + (a_2 - 2a_3 + a_1) - \varepsilon$$

thus

$$\theta_{2\tau} = \frac{(c_2 - 2c_3 + c_1 + 2a_3 - a_2 - a_1)\theta_{3\tau} + (d_2 - 2d_3 + d_1 + 2a_3 - a_2 - a_1)\theta_{4\tau} + (a_2 - 2a_3 + a_1) - \varepsilon}{(a_2 - 2a_3 + a_1 - b_2 + 2b_3 - b_1)} \quad (4.24)$$

For a clearer representation of the above (4.24) and to ease the complexity of further derivation for $\theta_{1\tau}$, $\theta_{2\tau}$ and $\theta_{3\tau}$, let

$$A = c_2 - 2c_3 + c_1 + 2a_3 - a_2 - a_1 \quad E = a_3 - a_1 + b_1 - b_3$$

$$B = d_2 - 2d_3 + d_1 + 2a_3 - a_2 - a_1 \quad F = c_3 - c_1 + a_1 - a_3$$

$$C = a_2 - 2a_3 + a_1 \quad G = d_3 - d_1 + a_1 - a_3$$

$$D = a_2 - 2a_3 + a_1 - b_2 + 2b_3 - b_1 \quad H = a_3 - a_1$$

Thus equation (4.24) can then be rewritten as

$$\theta_{2\tau} = \frac{A\theta_{3\tau} + B\theta_{4\tau} + C - \varepsilon}{D},$$

and (4.22) can be expressed as

$$E\theta_{2\tau} = F\theta_{3\tau} + G\theta_{4\tau} + H.$$

By substituting (4.24) into (4.22), one obtain

$$\left(\frac{A\theta_{3\tau} + B\theta_{4\tau} + C - \varepsilon}{D} \right) E = F\theta_{3\tau} + G\theta_{4\tau} + H$$

$$\left(\frac{AE}{D} - F \right) \theta_{3\tau} = \left(\frac{GD - BE}{D} \right) \theta_{4\tau} + \frac{HD - CE + E\varepsilon}{D}$$

and finally

$$\theta_{3\tau} = \frac{(GD - BE)\theta_{4\tau} + HD - CE + E\varepsilon}{AE - FD}. \quad (4.25)$$

Substituting (4.25) into (4.24) leads to

$$\theta_{2\tau} = \frac{A((GD - BE)\theta_{4\tau} + HD - CE + E\varepsilon)}{D(AE - FD)} + \frac{B\theta_{4\tau} + C - \varepsilon}{D}$$

and eventually
$$\theta_{2r} = \frac{((GDA - BFD)\theta_{4r} + AHD - FDC + FD\varepsilon)}{D(AE - FD)}. \quad (4.26)$$

Substituting (4.25) and (4.26) into (4.21)

to give
$$\theta_{1r} = 1 - \frac{(AGD - BFD)\theta_{4r} + AHD - FDC + FD\varepsilon}{D(AE - FD)} - \frac{((GD - BE)\theta_{4r} + (HD - CE + E\varepsilon))}{(AE - FD)} - \theta_{4r}$$

or
$$\theta_{1r} = \frac{\left(\left[D^2(F - G) + D(BF - AG + BE - EA) \right] \theta_{4r} - D^2(F + H) \right)}{D(AE - FD)}. \quad (4.27)$$

The implication of Theorem II is that given a specified target probability vector θ_r , one can choose any value of $a_3, b_1, b_2, b_3, c_1, c_2, c_3, d_1, d_2, d_3$, and find the corresponding a_1 and a_2 values as defined in (4.18). This is therefore one of the characteristics of this design whereby the clinical investigator will be given certain degree of freedom in setting a utility value that is specific in each clinical context.

4.2.5 Boundary conditions for proper elicitation of the utility weight value

Depending on the situation at hand, decision makers may feel uncomfortable with the direct application of expected utility as basis for decision ranking. There are principally two reasons for this; the decision maker is uncertain about either the assessment of the consequences entering the utility weight or the probabilistic modelling of the associated uncertainties. In order to account for the possible misjudgements of eliciting utility weight, sensitivity analysis was done on section 4.7

to study the fundamental variation of this design. The boundary condition that ensures the design is operating in the correct path of obtaining good estimate of the optimal dose is given in Table 4.5. These boundary conditions are guideline such that clinical investigator will not be too biased in the parameter setting that make the design go ‘off-course’.

Table 4.5 Boundary condition of Utility table

Single Outcome				
	(T ₀)		(T ₁)	
A ₁	x		0	
A ₀	x / 2		Equation 4.8	
A ₋₁	0		Equation 4.8	

Dual Outcomes				
	(T ₀ E ₀)	(T ₀ E ₁)	(T ₁ E ₀)	(T ₁ E ₁)
A ₁	x	x / 2 or Equation 4.18	0	0
A ₀	x / 2	x or Equation 4.18	x or Equation 4.18	x / 2
A ₋₁	0	0	x / 2 or Equation 4.18	x

In all cases: $0 < x < 10$ and $0.05 < \varepsilon < 0.1$.

The utility weight value is represented by a variable x and ranges from 0 to 10 for optimised results. Table 4.5 shows how a single outcome can be achieved, when eliciting the weight value is first bounded by the expression of variable x for the nontoxicity event and thereafter these values will be applied to Equation 4.8 to obtain the rest of the weight value under the event of toxicity. For the case of dual outcomes, the investigator is given a choice of either adopting Equation 4.18 or using an alternative expression x and $x/2$ for either of the outcome combination (T_0E_1) or (T_1E_0) . In a typical situation where the trial study preferred efficacy to be more important than toxicity, the eliciting of the weight values is first given via the expression of variable x for the two most obvious outcomes of T_0E_0 and T_1E_1 . Next, Equation 4.18 is recommended for the outcome of (T_0E_1) where it has an implicit

relationship with the target probability while the remaining outcome of T_1E_0 will adopt the expression of variable x .

4.3 Stopping criterion

The process of finding the action that corresponds to the maximum expected utility allows for the identification of the appropriate dose to be used for the next patient. An efficient stopping criterion has to be put in place so as to bring the trial to an immediate close once a firm decision on the OD is made. The next phase of drug development is to be initiated more rapidly thereby leading to benefits for the patients.

The proposed stopping criterion works as follows. Primarily, the trial will stop when the posterior probability of a patient being assigned (p_a) to any of the predefined dose levels is higher or equal than some pre-specified trial-termination target value (TTV). In addition, the trial will also stop if the maximum number of patients is reached or if the trial de-escalates to the lowest dose level with the next recommended action being to de-escalate further or if the trial escalates to the highest dose level with the next action being to escalate further. From the sensitivity analysis (see Section 4.7.3), a suitable value of TTV can be set in the range of 0.7–0.9. The p_a for each dose level is represented by, γ_l ($l=1, \dots, k$), $0 \leq \gamma_l \leq 1$.

Before the start of a trial, there are some uncertainties about the outcomes of the different doses and the p_a values in each specific dose level. Intuitively, all γ_l are treated as of equal footing: γ_l can take any value between 0 and 1, and this can be assumed that all these values are *a priori* equally likely. Although this is not the only plausible way to define “equal footing”, it is simple to interpret and to justify. Let’s assume that the prior distribution for the p_a values for each respective dose level is uniform. An interesting justification of the use of uniform priors is provided, among

others, by Edwards *et al* [57], who discuss the so-called *principle of stable estimation*.

In their words:

“To ignore the departures from uniformity it suffices that your actual prior density changes gently in the region favoured by the data and not itself too strongly favour some other region. But what is meant by “gently”, by “region favoured by the data”, by “region favoured by the prior distribution”, and by two distributions being approximately the same? Such questions do not have ultimate answers ...”

Their paper discusses in more detail a proposal for formal conditions for proceeding as though the prior were uniform. The uniform prior distribution is thus expressed as,

$$p(\gamma) = \begin{cases} 1, & \text{if } 0 < \gamma_l < 1 \\ 0, & \text{otherwise} \end{cases} \quad (4.28)$$

As there are infinitely many possible values for γ_l , namely all values in the interval (0, 1), γ_l is no longer a list of probabilities, but a probability density function [58] .

For patient j , the p_a values that have been obtained from the previous observation, $j-1, j-2, \dots, 1$, $p(\gamma_l \mid \xi_{j1}, \dots, \xi_{j,j-1})$ will provide the updated prior probability distribution for the current observation. Here ξ_{jl} represents the data in term of “occurrence” for a particular dose level given the current observation of the j^{th} patient. The likelihood function is expressed as,

$$\begin{aligned}
 p(\xi_{lj} | \gamma_l) &= \gamma_l^{\xi_{lj}} (1 - \gamma_l)^{1 - \xi_{lj}}, \\
 &\vdots \\
 p(\xi_{kj} | \gamma_k) &= \gamma_k^{\xi_{kj}} (1 - \gamma_k)^{1 - \xi_{kj}}.
 \end{aligned} \tag{4.29}$$

Using $p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1})$ and $p(\xi_{lj} | \gamma_l)$, Bayes theorem then updates the knowledge about the probability distribution of p_a for each DL,

$$\begin{aligned}
 p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}, \xi_{lj}) &= \frac{p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}) \cdot p(\xi_{lj} | \gamma_l)}{\int p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}) \cdot p(\xi_{lj} | \gamma_l) d\gamma_l} \\
 &\vdots \\
 p(\gamma_k | \xi_{k1}, \dots, \xi_{kj-1}, \xi_{kj}) &= \frac{p(\gamma_k | \xi_{k1}, \dots, \xi_{kj-1}) \cdot p(\xi_{kj} | \gamma_k)}{\int p(\gamma_k | \xi_{k1}, \dots, \xi_{kj-1}) \cdot p(\xi_{kj} | \gamma_k) d\gamma_k}
 \end{aligned} \tag{4.30}$$

since ξ_{lj} is independent of $\xi_{l1}, \dots, \xi_{lj-1}$. The calculation in the denominator is useful for expressing the marginal distribution of the observed sample in terms of the two available distributions $p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1})$ and $p(\xi_{lj} | \gamma_l)$.

To estimate the current p_a for each dose level after observing patient j , the expectation over the posterior distribution of γ_l is expressed as

$$\begin{aligned}
 \hat{\gamma}_l &= E[\gamma_l | \xi_{l1}, \dots, \xi_{lj}] = \int_0^1 \gamma_l \cdot p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}, \xi_{lj}) d\gamma_l \\
 &= \frac{\int_0^1 \gamma_l \cdot p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}) \cdot p(\xi_{lj} | \gamma_l) d\gamma_l}{\int_0^1 p(\gamma_l | \xi_{l1}, \dots, \xi_{lj-1}) \cdot p(\xi_{lj} | \gamma_l) d\gamma_l}
 \end{aligned} \tag{4.31}$$

The stopping criterion is satisfied when the optimal value from the posterior expectations, $E[\gamma | \text{data}]$ from any of the respective dose level is greater than or equal to TTV. The implication of this is that when the probability of the administered dose level reaches a target level, the trial then terminates.

$$\arg \max | E[\gamma | \text{data}] | \geq \text{TTV} \quad (4.32)$$

4.4 Implementation

4.4.1 Practical constraints

Some initial conditions and constraints will be specified in order to illustrate the design in a more pragmatic sense. The maximum sample size for this design is set to 24. This sample size is chosen based on practical consideration and is also close to those used by Storer [1], O'Quigley *et al* [5] and Babb *et al* [31]. Other maximum sample size values can be set if desired.

As mentioned in Section 4.2.2, the choice of the Dirichlet parameter, ρ should reflect past clinical experience. On the other hand, if historical data are available these may also be used to help in the specification of ρ . In the case of a single outcome (toxicity only), Beta (binary Dirichlet) distribution will be used.

4.4.2 Establishing the starting dose level

A starting dose can be established in two different ways. Firstly, the investigator may specify, at the planning stage of the trial, an acceptable target probability value. This represents the desired probability of the combinations of outcomes associated with the OD. The starting dose level of the design is then the one which has an expected prior probability of outcomes (as determined from the value of the prior parameters, ρ_i) closest to that of the target probability. It is noted that, as

discussed in Section 4.2.4, specifying a target probability implies imposing some constraints on the form of utility used.

The alternative, involves an unpredictable number of extra patients, is to conduct a preliminary trial. For example, one option would be to use the first stage of the design suggested by Storer [2]. In this design, a single patient enters at some dose level and if this patient does not experience dose-limiting toxicity (DLT), dose escalation continues patient by patient until the first case of DLT is seen. At this point the design proper will take over but using the dose in the sequence below that induced the DLT. An analogous strategy of de-escalating doses occurs if the first patient experiences DLT.

4.4.3 Computational implementation

A key step in the Bayesian decision approach is the computation of the expected utility value. Out of the three decisions, the optimal decision would then be the one which has the highest expected utility. This expected utility can be considered as the governing equation for the overall computational work. The general expression that defines the expected utility for action $A_{(-1,0,1)}$ is

$$U(A_{(-1,0,1)}) = \int_{\theta} (\text{utility}) p(\theta|y) d\theta. \quad (4.33)$$

To compute the governing equation of the expected utility, G samples from the posterior Dirichlet distribution is generated follow by the average of all the utility values corresponding to these samples, i.e.

$$U(A_1) = \frac{\sum_{s=1}^G \left(\sum_{i=1}^4 u_{1i} \theta_{is} \right)}{G} \quad (4.34)$$

$$U(A_0) = \frac{\sum_{s=1}^G \left(\sum_{i=1}^4 u_{2i} \theta_{is} \right)}{G} \quad (4.35)$$

$$U(A_{-1}) = \frac{\sum_{s=1}^G \left(\sum_{i=1}^4 u_{3i} \theta_{is} \right)}{G} \quad (4.36)$$

where u_{1i} , u_{2i} and u_{3i} as mentioned in Section 4.2.3, are the individual utility values for each action in response to a particular outcome and θ_{is} are samples from the posterior distribution for θ_i . The variable G is the total number of samples from the distribution (for this example, it uses $G = 100\ 000$). From the results of the three expected utilities, the one which has the highest value will correspond to the optimal decision to be made. If one wishes to work with the single outcome case (i.e. only the toxicity aspect), the appropriate Beta distribution is adopted rather than the Dirichlet as above.

The computational procedure in determining the final decision of finding the appropriate dose uses a Fortran source code under a High Performance Computing (HPC) Fortran90 compiler. The coding of Dirichlet samples run on a random sample seed, using a gamma distribution, $\text{Ga}(x | \alpha, \beta)$ and setting $\beta = 1$ [59]. Four sets of gamma variates which are scaled by their sum, so that they will sum to unity will result in a Dirichlet distribution. The entire code of the Dirichlet distribution can be found in appendix I.

To test the coding, result from the Dirichlet distribution must fall within the range of zero to one, i.e. $\theta \in (0,1)$, and the probability of the four outcomes must

sum to unity i.e. $\sum_{i=1}^4 \theta_i = 1$. Figure 4.2 displays the results from the Dirichlet source code, showing a few samples from the Dirichlet distribution, generated means and variances and the Dirichlet mean value.

Figure 4.2 Results from the Fortran coding for Dirichlet distribution

To improve the convergence of the program, different sample trial runs are tested. The trial run is set in such a way that from the random data generated, the generated mean value is compared with the theoretical Dirichlet mean value. This convergence test determined the acceptable number of sample runs for generating the Dirichlet sample. Figure 4.3 shows four plots for the probability outcomes of θ_1 , θ_2 , θ_3 and θ_4 displaying its convergence. Using the Dirichlet expected value of each respective probability outcome as a line of reference, the variation in the generated mean vs sample size stabilises as the sample size increases. From the four plots, a

total sample size of 100, 000 runs meet the condition of stabilisation and will be used for all the simulations.

The overall algorithm to compute the final decision in the dose finding comes in two sections. The generation of the Dirichlet samples requires several sub-routines that use gamma distributions and setting one of its beta parameters to a unity value. The setting of the Dirichlet parameters is estimated under the constraint from the Dirichlet mean and variance value. The final section of the algorithm is to compute the final expected utility as shown in Equations 4.34, 4.35 and 4.36. The decision is then made when the highest values from the expected utility is chosen.

Figure 4.3a Convergence plot of Dirichlet distribution for Outcome θ_1 .

Figure 4.3b Convergence plot of Dirichlet distribution for Outcome θ_2 .

Figure 4.3c Convergence plot of Dirichlet distribution for Outcome θ_3 .

Figure 4.3d Convergence plot of Dirichlet distribution for Outcome θ_4 .

The computation for the Bayes Equations of 4.30 and 4.31 requires numerical integration as there is no finite close form where γ_i is in the interval of 0 and 1. Some of the well-known basic numerical integration methods are trapezoidal rule, Simpson’s 1/3 rule and 3/8 rule, Taylor expansions, Newton Rapson and Gaussian Quadrature method. The latter method was adopted due to its precise and numerical simplicity. When the posterior distribution, γ_i , of Equation 4.30 is substituted into the Expectation of γ_i , the general equation will consist of two integral in the numerator and denominator as shown in Equation 4.31.

4.4.3.1 Gaussian Quadrature

This section briefly illustrates the necessary steps needed for a numerical implementation in approximating any integral solution.

Given $W(x)$, and an integer U , to find a set of weights w_j such that the approximation

$$\int_a^b W(x) f(x) dx \approx \sum_{j=1}^U w_j f(x_j). \quad (4.37)$$

Define

$$g(x) \equiv W(x) f(x) \quad (4.38)$$

and

$$v_j \equiv w_j / W(x_j) \quad (4.39)$$

Equation 4.37 becomes

$$\int_a^b g(x) dx \approx \sum_{j=1}^U v_j g(x_j). \quad (4.40)$$

The function $W(x)$ can be chosen to remove integral singularities from the desired integral to make the solution exact. The weight function is chosen as one of the most commonly used Gauss-Laguerre formulas.

$$W(x) = x^y e^{-x} \quad (4.41)$$

where $y = 0$, $x = \alpha$ and $0 < x < \infty$. The Gauss-Laguerre formula also requires the integration interval to be scale from $[a, b]$ to $[-1, 1]$. Coordinate transformation from $[a, b]$ to $[-1, 1]$ is:

$$t = \frac{b-a}{2} x + \frac{b+a}{2} \quad \begin{cases} x = -1 \Rightarrow t = a \\ x = 1 \Rightarrow t = b \end{cases} \quad (4.42)$$

One can easily apply the Gaussian Quadrature method without the understanding of the theory behind. The tabulated weights and abscissas can be easily

obtained from the reference text [60]. However, the theory will come in handy for the construction of own tabulation of weights and abscissas for an unusual choice of $W(x)$.

4.5 Simulated case study

It is beyond the scope of this work to study all possible potential situations. On the other hand, the focus is on setting of the scenario to some broad situations which will be illustrated in the comparison section. Some situation may not seem to represent the design in general but it helps in gaining insight as to the kind of characteristics to anticipate in practice. The whole section, in general, illustrates the operational characteristic and capability in handling different Phase I scenario.

In this section, two simulated examples will be used to illustrate the operational characteristics of the design. The first example will focus on the case where toxicity is the only criteria. This is the situation in most Phase I clinical trial designs. The second example considers the case where both toxicity and efficacy are involved. It parallels with the HIV studies done by O'Quigley [13] for his bivariate version of the CRM.

In each case, the data is simulated according to the “true” probability of outcome for each respective dose level. The “true” probability in this case refers to a hypothetical scenario whereby each dose level will have a given number of responses on each event. For a single toxicity outcome the responses will be simply a binary occurrence. For dual outcome, it will involve four outcome combinations as explained in Section 4.2.2. Tables 4.6 and 4.7 show two sets of hypothetical data that will be used for the following simulation examples. There will be a total of 10 data line up for each dose level. In a real life situation, these data will be in the form of

actual responses from the patient but occurring in a sequential manner as the data can only be obtained from the patient once they have taken the drug and show certain level of effect from it. In a single toxicity outcome, the response is dichotomous with “1” representing toxicity and “0” otherwise. For dual outcomes, the response consists of y_1, y_2, y_3 and y_4 . To illustrate, suppose the starting dose level for a single toxicity event is Dose 3, from Table 4.6, the first data of that specific dose level is “1” (i.e. toxicity response), this will then generate a necessary decision from the simulation. If the optimal decision in this case is to de-escalate the dose level, the next data should be obtained from dose level 2 where it shows “0” (i.e. non-toxicity). The subsequent data is then retrieved in such a manner until the full stopping criterion is satisfied.

Table 4.6 Hypothetical data for single toxicity outcome.

Dose 1 $p_{TrueTox} = 0.0$	Dose 2 $p_{TrueTox} = 0.1$	Dose 3 $p_{TrueTox} = 0.3$	Dose 4 $p_{TrueTox} = 0.6$	Dose 5 $p_{TrueTox} = 0.7$	Dose 6 $p_{TrueTox} = 0.8$
0	0	1	1	1	1
0	0	1	1	1	1
0	1	0	1	1	1
0	0	0	0	0	1
0	0	0	1	1	0
0	0	0	1	1	1
0	0	1	0	0	1
0	0	0	0	1	0
0	0	0	1	0	1
0	0	0	0	1	1

$p_{TrueTox}$ is referred to as the “true” probability of toxicity

Table 4.7 Hypothetical data for dual outcomes.

Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
$p_{TrueTox1}=0.9$	$p_{TrueTox1}=0.5$	$p_{TrueTox1}=0.3$	$p_{TrueTox1}=0.1$	$p_{TrueTox1}=0.0$	$p_{TrueTox1}=0.0$
$p_{TrueTox2}=0.1$	$p_{TrueTox2}=0.4$	$p_{TrueTox2}=0.4$	$p_{TrueTox2}=0.3$	$p_{TrueTox2}=0.4$	$p_{TrueTox2}=0.0$
$p_{TrueTox3}=0.0$	$p_{TrueTox3}=0.1$	$p_{TrueTox3}=0.1$	$p_{TrueTox3}=0.3$	$p_{TrueTox3}=0.1$	$p_{TrueTox3}=0.3$
$p_{TrueTox4}=0.0$	$p_{TrueTox4}=0.0$	$p_{TrueTox4}=0.2$	$p_{TrueTox4}=0.3$	$p_{TrueTox4}=0.5$	$p_{TrueTox4}=0.7$
y_1	y_1	y_4	y_4	y_4	y_4
y_1	y_3	y_4	y_4	y_4	y_4
y_1	y_1	y_2	y_2	y_4	y_3
y_1	y_1	y_1	y_4	y_2	y_4
y_2	y_1	y_1	y_3	y_4	y_3
y_1	y_2	y_3	y_1	y_3	y_4
y_1	y_1	y_2	y_3	y_2	y_4
y_1	y_2	y_2	y_2	y_4	y_3
y_2	y_2	y_1	y_3	y_2	y_4
y_1	y_2	y_2	y_2	y_2	y_4

$p_{TrueTox1}$ is referred to as the “true” probability of outcome combination y_1
 $p_{TrueTox2}$ is referred to as the “true” probability of outcome combination y_2
 $p_{TrueTox3}$ is referred to as the “true” probability of outcome combination y_3
 $p_{TrueTox4}$ is referred to as the “true” probability of outcome combination y_4

4.5.1 Example 1: Single outcome (Toxicity)

Suppose that in a single-outcome design, there are 6 dose levels with the target probability set at $\theta_{tox} = 0.33$ and with the prior clinical information having Beta parameter values of $\rho_2 (= 1 - \rho_1)$ of Table 4.8. These imply starting at dose level 4 as this has a target closest to 0.33 ($\rho_2 = 0.35$). The nature of this example is that of the typical Phase I trial with a single target of toxicity. In such circumstances the OD is usually referred to as the MTD. The stopping criterion of TTV is set at 0.9 for Example 1 where intuitively this value is sufficient to conclude the stabilising dose level and possibly end the trial early. The decision table and its corresponding results for this example are shown in Table 4.9 and 4.10 respectively. In the decision table, the conditions and constraints of the utility setting are set according to those described in Section 4.2.4. It is noticed that a utility value of $u_{22} = 6.7$ is given to action $A_{.1}$ under an event of toxicity compared to a value of $u_{11} = 3.3$ for action A_1 under an event of non-toxicity. This reflects the situation whereby one will be more

reluctant to increase the dose in the event of non-toxicity as compared to decreasing the dose when experiencing toxicity.

The data from the first patient shows toxicity. Thus the optimal decision is to de-escalate to a lower dose level. The second patient also experiences toxicity at dose level 3, resulting in the next optimal action being to de-escalate further to dose level 2. The dose finding process then proceeds in an “up and down” fashion. The maximum tolerable dose level is finally obtained when the dose escalation procedure satisfies stopping criterion $\hat{\gamma}_3 = 0.90$ which is on par with the TTV value and the total number of patients tested being 14.

Table 4.8 The *a priori* Beta parameters ρ for Examples 1

Dose level		1	2	3	4	5	6
Beta	ρ_1	0.95	0.90	0.75	0.65	0.50	0.30
	ρ_2	0.05	0.10	0.25	0.35	0.50	0.70

N.B. The bold values represent the nearest value associated to the corresponding target probability values.

Table 4.9. Decision table for a single outcome design

	$y_1(T_0)$	$y_2(T_1)$
Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$
Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 3.75$
De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$

Table 4.10. Result summary for single outcome

Patient No.	Patient outcome	$U(A_1)$	$U(A_0)$	$U(A_{-1})$	Dose Level	Resulting action	$\hat{\gamma}_1$
1	1	1.0693	2.9877	4.5289	4	A_{-1}	0.25,0.25,0.25, 0.50 ,0.25,0.25
2	1	1.2374	2.8832	4.1877	3	A_{-1}	0.19,0.19, 0.40 ,0.40,0.19,0.19
3	0	3.1342	1.7027	0.3368	2	A_1	0.16, 0.33 ,0.33,0.33,0.16,0.16
4	1	0.6224	3.2658	5.4357	3	A_{-1}	0.16,0.33, 0.50 ,0.33,0.16,0.16
5	1	1.5662	2.6786	3.5201	2	A_{-1}	0.12, 0.43 ,0.43,0.25,0.12,0.12
6	0	3.2160	1.6520	0.1712	1	A_1	0.20 ,0.40,0.40,0.20,0.11,0.11
7	0	2.4381	2.1361	1.7498	2	A_1	0.20, 0.50 ,0.43,0.20,0.10,0.10
8	0	1.9577	2.4350	2.7251	3	A_{-1}	0.14,0.48, 0.48 ,0.14,0.09,0.09
9	0	2.8672	1.8688	0.8784	2	A_1	0.11, 0.50 ,0.44,0.11,0.08,0.08
10	0	2.6271	2.0184	1.3660	3	A_1	0.10,0.49, 0.49 ,0.10,0.07,0.07
11	1	0.5337	3.3400	5.6157	4	A_{-1}	0.09,0.48,0.48, 0.18 ,0.07,0.07
12	0	2.9613	1.8102	0.6875	3	A_1	0.09,0.44, 0.78 ,0.15,0.06,0.06
13	1	0.2699	3.4857	6.1497	4	A_{-1}	0.08,0.40,0.75, 0.25 ,0.06,0.06
14	0	3.1316	1.7043	0.3620	3	terminate	0.08,0.37, 0.90 ,0.20,0.06,0.06

4.5.2 Example 2: Dual outcomes (Toxicity and Efficacy)

This example is based on reference from O’Quigley [13] simulated example in HIV study. The aim is to design a clinical trial to evaluate new antiretroviral treatments for children infected with HIV. The initial activity of a drug, in terms of reducing levels of HIV in a child’s plasma, can be evaluated rapidly, typically within a week or so. This time frame is similar to that for the onset of early side effects. Furthermore, inadequate suppression of HIV might be considered as bad an outcome, if not worse one, than a drug-related side effect. This is because most side effects, while severe enough to result in treatment discontinuation, dissappear once treatment has been effectively discontinued. Furthermore, inadequate suppression can lead to the development of viral resistance to the treatment. Such viral resistance can render the treatment under study ineffective even if higher doses are given. Thus, both inadequate viral suppression and the occurrence of side effects negate the potential

long-term value of a treatment. The aim is therefore to achieve adequate viral load reduction without side effects in a high proportion of patients. The basic set up of the study starts with six pre-defined dose levels. Among these available levels, there is one having a probability of success higher than at any other level. The term “success” corresponds to achieving absolute non-toxicity and a satisfactory reduction in viral load in which in this case is efficacy. The design begins by specifying the (marginal) prior probabilities of toxicity and efficacy for each dose level. The prior toxicity and efficacy information are assumed to follow a monotonic ordering with:

$$PT_1 = 0.05, PT_2 = 0.10, PT_3 = 0.15, PT_4 = 0.35, PT_5 = 0.50, PT_6 = 0.7;$$
$$PE_1 = 0.30, PE_2 = 0.50, PE_3 = 0.80, PE_4 = 0.85, PE_5 = 0.90, PE_6 = 0.95.$$

The Dirichlet prior parameters (ρ) are then obtained (Table 4.11) by combining the information from toxicity and efficacy as shown in Equation (4.1). The recommended dose, in this case, is chosen based on the outcome where the probability of non-toxicity and efficacy has the highest value. The target value for the probability of toxicity is 0.2 and the corresponding efficacy value is 0.84. The resulting TP vector is $\theta_{1\tau} = 0.13$, $\theta_{2\tau} = 0.67$, $\theta_{3\tau} = 0.03$ and $\theta_{4\tau} = 0.17$. The starting dose level is selected primarily on the basis that the prior expected value (as shown in Table 4.10) is nearest to the target value of “success”, where this is defined as the outcome of non-toxicity with efficacy ($\theta_{2\tau}$). On this basis, dose 3 is chosen as the starting dose level since 0.68 is nearest to 0.67.

Table 4.11. The *a priori* Dirichlet parameters, ρ .

		Dose level					
		1	2	3	4	5	6
Dirichlet	ρ_1	0.66	0.45	0.17	0.10	0.05	0.02
	ρ_2	0.28	0.45	0.68	0.55	0.45	0.28
	ρ_3	0.03	0.05	0.03	0.05	0.05	0.04
	ρ_4	0.03	0.05	0.12	0.30	0.45	0.66

The choice of utility weight for this example (Table 4.12) is based on Equation (4.18). These selected utility weight values satisfy the conditions related to the specified TP vector.

The results of this case study is summarised in Table 4.13, where the data had been simulated from a multinomial distribution with parameter equal to the prior estimate.

The first patient is accrued at dose level 3 with a treatment effect of “ y_4 ”, that is toxic and efficacious, the design then recommends de-escalating to dose level 2. For the initial few patients, the design recommends a decision that depend heavily on the patient’s response. This is due to the relative lack of prior information. As the number of accrued patients increase, the prior information is updated and built-up. The design is then less influenced by individual outcomes. For example, when the 15th patient experiences “ y_4 ” effect, instead of de-escalating to a next lower dose due to its toxic side-effect, the design decides to keep the dose for the next accrued patient. For the last 9 patients (12 – 20), there are a total of 9 “successes”, and this is enough to bring the trial to a halt as $\hat{\gamma}_3 = 0.93$ which exceeds TTV = 0.9.

Table 4.12 Decision table for dual outcomes.

	$y_1(T_0, E_0)$	$y_2(T_0, E_1)$	$y_3(T_1, E_0)$	$y_4(T_1, E_1)$
Escalate, A_1	$u_{11} = 2$	$u_{12} = 0.1642$	$u_{13} = 0$	$u_{14} = 0$
Maintain, A_0	$u_{21} = 1$	$u_{22} = 1.5075$	$u_{23} = 2$	$u_{24} = 1$
De-escalate, A_{-1}	$u_{31} = 0$	$u_{32} = 0$	$u_{33} = 1$	$u_{34} = 2$

Table 4.13 Result summary for dual outcomes.

Patient No.	Patient outcome	$U(A_1)$	$U(A_0)$	$U(A_{-1})$	Dose Level	Resulting action	$\hat{\gamma}_i$
1	y_4	0.3018	1.1332	1.2789	3	A_{-1}	0.25,0.25, 0.50 ,0.25,0.25,0.25
2	y_1	0.8768	0.5077	0.2019	2	A_1	0.19, 0.40 ,0.40,0.19,0.19,0.19
3	y_4	0.1510	1.0656	1.6395	3	A_{-1}	0.16,0.25, 0.33 ,0.16,0.16,0.16
4	y_2	0.4384	1.2544	0.6007	2	A_0	0.16, 0.28 ,0.28,0.16,0.16,0.16
5	y_1	0.7395	0.6613	0.2991	2	A_1	0.12, 0.40 ,0.25,0.12,0.12,0.12
6	y_2	0.5742	1.5323	0.8221	3	A_0	0.11,0.38, 0.38 ,0.11,0.11,0.11
7	y_1	0.8069	0.8033	0.4093	3	A_1	0.10,0.33, 0.48 ,0.10,0.10,0.10
8	y_4	0.2088	1.2059	1.4427	4	A_{-1}	0.09,0.30,0.45, 0.20 ,0.09,0.09
9	y_1	0.9218	0.4391	0.2057	3	A_1	0.08,0.25, 0.62 ,0.16,0.08,0.08
10	y_3	0.1052	1.1098	1.1012	4	A_0	0.07,0.21,0.58, 0.25 ,0.07,0.07
11	y_4	0.4603	0.9723	1.7197	4	A_{-1}	0.07,0.18,0.48, 0.30 ,0.07,0.07
12	y_2	0.7299	1.3156	0.3022	3	A_0	0.06,0.12, 0.55 ,0.22,0.06,0.06
13	y_3	0.8643	1.4278	0.6479	3	A_0	0.06,0.11, 0.61 ,0.18,0.06,0.06
14	y_2	0.7299	1.5137	0.5087	3	A_0	0.05,0.10, 0.70 ,0.15,0.05,0.05
15	y_4	0.7018	1.1051	0.9487	3	A_0	0.04,0.10, 0.78 ,0.13,0.04,0.04
16	y_2	0.6812	1.3481	0.8023	3	A_0	0.04,0.09, 0.82 ,0.12,0.04,0.04
17	y_2	0.6989	1.4218	0.7984	3	A_0	0.03,0.08, 0.85 ,0.11,0.03,0.03
18	y_3	0.7351	1.5054	0.8123	3	A_0	0.03,0.08, 0.88 ,0.11,0.03,0.03
19	y_2	0.7825	1.5928	0.8231	3	A_0	0.03,0.07, 0.90 ,0.10,0.03,0.03
20	y_2	0.8132	1.6798	0.8315	3	terminate	0.02,0.07, 0.93 ,0.09,0.02,0.02

4.6 Comparative analysis: accessing the performance over many trials

In most papers involving comparisons between Phase I designs, these are made between either the new design and the “3+3” design [2,3,6] or between the original CRM and modified versions of it [5,7,8,29,32,40,41]. Most of the methods of comparison involve the use of pseudo-randomised data and go through several thousand simulation runs to obtain the final expected results. However, most comparisons involving simulations have their own criteria of assessment (as summarised by Edler [4]). There is therefore no standard way of comparing the

various methods proposed in the literature. In this section, the focus is on the functional capability based on the basis of their performance in four different scenarios.

4.6.1 Single end point study (Toxicity)

The simulation study done in the majority of the Phase I trial simulations reported in the literature [4,7,37,39,46] will be largely adapted in this section. To make the explanation of the simulation study much clearer, this method is given a name called Bayesian Utility Design which is denoted as BUD. This simulation aims to estimate, among six dose levels, the dose level associated with a probability of toxicity response closest to the target probability value. Assume prior estimate of the toxic probabilities are given by $p_1 = 0.05$, $p_2 = 0.1$, $p_3 = 0.2$, $p_4 = 0.3$, $p_5 = 0.5$ and $p_6 = 0.7$ which correspond to setting: $\alpha_1 = 0.95$, 0.9 , 0.8 , 0.7 , 0.5 and 0.3 , with $\alpha_2 = 1 - \alpha_1$ for dose levels 1 to 6 respectively. Here, for the single outcome case, the Dirichlet reduces to a Beta distribution with just two parameters.

The simulation of BUD is compared with SUDD (Design D in Storer [1]), CRM and EWOC. For CRM and EWOC, the six dose levels are generated where: $d_1 = -1.47$, $d_2 = -1.1$, $d_3 = -0.69$, $d_4 = -0.42$, $d_5 = 0$, $d_6 = 0.42$. To generalise the comparison, the target probability is fixed at $\theta_{\text{tox}} = 0.33$ and the cohort size is 3 patients. The dose-toxicity function used by CRM and EWOC is a hyperbolic tangent model:

$$f(d, q) = \left\{ (\tanh d + 1) / 2 \right\}^q \quad (4.43)$$

with an exponential prior for parameter q . For EWOC, the tolerance level is set to be 0.25, as used by Babb *et al* [31]. For SUDD, at the end of a trial, a dose-toxicity model can be fitted to the data and the MTD estimate found by maximum likelihood. In this simulation, the hyperbolic tangent model is adopted. The final dose

recommended by SUDD is the one, among the six doses, that is closest to the maximum likelihood estimate.

To look at how the trial would terminate, SUDD, CRM and EWOC, use a fixed sample size of 24. This sample size is chosen based on practical consideration and is also closest to those used by Storer [1], O’Quigley *et al* [5], and Babb *et al* [31]. For BUD, two different stopping criteria are considered. The first one uses the proposed stopping criterion as was discussed in Section 4.3 with a pre-fixed TTV value of 0.9; we denote this as BUD1. The second one uses a fixed sample of 24; this is referred to as BUD2.

The utility weight values for BUD are shown in Table 4.14a. The comparison is based on four different scenarios generated from a hyperbolic tangent dose-toxicity model under different parameters used. In Scenario I, the data generated is such that it is similar to the prior estimate. For Scenario II, the “actual” toxic probabilities are set higher while Scenarios III and IV are set lower than in the first case (Table 4.14b).

Table 4.14. Information depicting the (a) Decision table and (b) ‘actual’ toxic probabilities for single endpoint comparison

	$y_1(T_0)$	$y_2(T_1)$
Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$
Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 3.75$
De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$

(a)

Scenarios	d_1	d_2	d_3	d_4	d_5	d_6
I	0.05	0.10	0.20	0.30	0.50	0.70
II	0.30	0.40	0.52	0.61	0.76	0.87
III	0.09	0.16	0.27	0.38	0.57	0.75
IV	0.00	0.00	0.04	0.09	0.25	0.49

(b)

In this study and the dual endpoint study (Section 4.6.2), 1000 replicate trials are conducted for each scenario so as to obtain summary “performance indicators” of how each design works in a particular setting. The comparisons of the designs are based on the percentage of correct recommendations for each dose level and the mean total number of patients used (Table 4.15).

In Scenario I (Table 4.15), the correct dose level is DL 4, as this has “actual” probability of toxicity closest to target probability of 0.33. CRM correctly recommends dose level 4 with a modal percentage of 53.4%, while for SUDD this was 56.5%. As for BUD1, this was 41.9% and BUD2 was 45.6%. EWOC appears to be more conservative where the recommended dose is at level 3 with 42.6% which is below the MTD. It is noticed that the performance of BUD is affected by the different stopping criteria. The fixed sample used by BUD2 gives rise to a slightly higher percentage of correct MTD recommendations than the other stopping rule. This is due to the larger average number of patients in the trial.

For Scenario II, the correct dose level is level 1. BUD2 strongly recommends this with a 56.5% while BUD1 was 51.5%. For SUDD, it estimates 56.4% and EWOC estimates at 89.4%. For CRM, it marginally selects DL 2 (45.8%) over DL 1(41.1%). It is noticed that all the designs have a rather high percentage of patients above the MTD. The probable reasons could be that, in this case, the first dose is already too toxic. Furthermore, most of the patients treated above MTD are treated at the next higher dose.

In Scenario III, the correct dose level is level 3. However, CRM recommends dose level 4 with 58.5%. BUD1 marginally recommend dose level 4 (40.1%) over dose level 3 (39.8%) while BUD2 recommends dose level 4 (47.2%) over dose level 3 (33%). For SUDD, it prefers dose level 4 of 46.7% while EWOC conservatively

prefer dose level 2 of 42%. In this scenario, it is noticed that BUD, CRM and SUDD treat a rather high percentage above the MTD. On closer examination, it is still tolerable as the “actual” probability of toxicity at d_4 is 0.38 (Table 4.14b), which is not far from the target probability value of 0.33.

In Scenario IV, the correct dose is level 5 and all three designs made the correct recommendation with CRM and BUD2 outperforming SUDD while BUD1 did not fare too badly, still recommend at 54.9%.

Overall, all designs responded well to the four scenarios. BUD performs relatively better than SUDD in term of recommending a higher percentage at the desired dose and stays conservative at doses higher than the MTD. This is particularly true on all the four scenes of Table 4.15 where one noticed that BUD has a lower percentage in recommending dose which is higher than MTD as compared to SUDD. In the case of Scenario 1 where the MTD is dose level 4, BUD1 and BUD2 recommend a lower percentage value on dose level 5 where the value are 22% and 19.8% respectively as compared to SUDD which has a slightly higher percentage of recommending dose level 5 at 24.7%. Similar results are also observed for the next three scenarios. The stopping criterion of BUD1 shows that the design could end early as compared with the fixed sample size of BUD2. However, there is a trade-off between accuracy and stopping early as the higher percentage of recommending the MTD as displayed by BUD1 is lower than BUD2.

Table 4.15. Comparison of SUDD, CRM, EWOC and BUD design with target probability of 0.33 and a fixed sample of 24 patients.(recommended dose in bold)

Scenarios	Designs	Recommendation (%)						Mean number of patients
		1	2	3	4	5	6	
I	SUDD	0.0	0.8	16.2	56.5	26.2	0.3	24.0
	EWOC	0.7	18.6	42.6	37.1	1.0	0.0	24.0
	CRM	0.0	0.9	14.9	53.4	30.6	0.2	24.0
	BUD1	0.0	0.9	33.1	41.9	22.0	2.1	20.1
	BUD2	0.0	0.7	29.7	45.6	21.9	2.1	24.0
II	SUDD	56.4	33.4	9.6	0.5	0.1	0.0	24.0
	EWOC	89.4	10.2	0.3	0.1	0.0	0.0	24.0
	CRM	41.1	45.8	11.9	1.0	0.2	0.0	24.0
	BUD1	51.5	38.5	9.7	0.3	0.0	0.0	18.1
	BUD2	56.5	34.0	9.3	0.2	0.0	0.0	24.0
III	SUDD	0.4	7.5	35.7	46.7	9.6	0.1	24.0
	EWOC	6.3	42.0	36.1	15.5	0.1	0.0	24.0
	CRM	0.2	5.5	34.6	49.7	10.0	0.0	24.0
	BUD1	0.4	10.0	39.8	40.1	9.5	0.2	21.6
	BUD2	0.2	9.7	33.0	47.2	9.9	0.0	24.0
IV	SUDD	0.0	0.0	0.0	1.3	57.8	40.9	24.0
	EWOC	0.0	0.0	0.0	46.4	53.6	0.0	24.0
	CRM	0.0	0.0	0.0	1.7	62.0	36.3	24.0
	BUD1	0.0	0.0	0.0	5.2	54.9	39.9	17.2
	BUD2	0.0	0.0	0.0	1.4	60.5	38.1	24.0

4.6.2 Dual end point study (Toxicity and Efficacy)

In the literature, there are few studies that explicitly discuss the efficacy aspect in the context of Phase I dose finding trials. Some exceptions are O’Quigley [13], Thall and Russell [12] and Braun [14]. In this second set of comparison studies, BUD is tailored to fit into the HIV studies discussed by O’Quigley *et al* [13], where information on efficacy is obtained during the trial and is felt to be just as important as the toxicity consideration. In O’Quigley’s [13] latest work (which is denoted as CRMII) he uses a frequentist method to develop dose escalation designs for the study of antiretroviral treatment for children infected with HIV. His method generalises the likelihood (CRM) [37] to the bivariate case.

In this simulation, 4 dose levels are used and the target probability of toxicity and efficacy is similar to that used in O’Quigley’s bivariate CRM simulation study with a fixed maximum number of 40 patients. There are 4 different scenarios shown in Table 4.16.

Table 4.16. Simulated data for dual endpoint comparison study.

Scenarios		d_1	d_2	d_3	d_4
I	PT_l	0.06	0.17	0.25	0.30
	PE_l	0.21	0.84	0.80	0.71
	$p(T_0,E_1)$	0.20	0.70	0.60	0.50
II	PT_l	0.13	0.30	0.40	0.50
	PE_l	0.80	0.71	0.83	0.80
	$p(T_0,E_1)$	0.70	0.50	0.50	0.40
III	PT_l	0.00	0.05	0.15	0.30
	PE_l	0.10	0.32	0.82	0.71
	$p(T_0,E_1)$	0.10	0.30	0.70	0.50
IV	PT_l	0.00	0.00	0.10	0.14
	PE_l	0.20	0.30	0.56	0.81
	$p(T_0,E_1)$	0.20	0.30	0.50	0.70

These are chosen to be the same as those used by O’Quigley [13]. In each one of the scenarios, the recommended dose is chosen based on the outcome where the probability of non-toxicity and efficacy has the highest value. O’Quigley calls this the probability of success and he uses a value of 0.7. The prior estimates of BUD for toxicity and efficacy are chosen to be the same as data of scenario I (Table 4.16) i.e.

$$PT_1 = 0.06, PT_2 = 0.17, PT_3 = 0.25, PT_4 = 0.30;$$
$$PE_1 = 0.21, PE_2 = 0.84, PE_3 = 0.80, PE_4 = 0.71.$$

This will then result in 4 combination outcomes of Dirichlet parameter, ρ_{il} ($i=1,...,4$) for each dose level as shown in Table 4.17. Similar to the single end-point study, two stopping criteria similar to BUD1 and BUD2 are adopted.

For a direct comparison with O’Quigley’s example [13], the result will look at the percentage recommendation for each dose level, the mean number of patients receiving the dose and the mean total number of patients used.

The results of Table 4.18 look promising and comparable to CRMII. Most of the modal percentages for the first three Scenarios are over 90%. Scenario IV appears to be the hardest case in reaching a higher percentage at the recommended dose where the recommended dose at dose level 4 is 79% for BUD1 and 85% for BUD2 as compared to CRMII of 88%. This is because, while the best dose is the highest, all the lower levels have non-negligible chances of some success. The success rate at dose level 3 is indeed close to that was considered acceptable, and this dose is recommended some 19% of the time for BUD1, 14% for BUD2 and 12% for CRMII.

Table 4.17 The *a priori* Dirichlet parameters ρ for dual outcomes comparison studies.

<i>a priori</i> Dirichlet Parameter For BUD design		Dose level			
		1	2	3	4
	ρ_1	0.740	0.133	0.150	0.203
	ρ_2	0.200	0.697	0.600	0.497
	ρ_3	0.050	0.027	0.050	0.087
	ρ_4	0.010	0.143	0.200	0.213

Table 4.18 Optimal dose recommendation and patients allocation for the four scenarios between two competing designs of BUD and CRMII (recommended dose in bold).

Scenarios	Designs	Recommendation (%)				Mean number of patients receiving dose				Mean total number of patient
		1	2	3	4	1	2	3	4	
I	BUD1	2.0	94.0	4.0	0.00	6.06	14.08	1.32	0.00	22
	BUD2	3.5	95.5	1.0	0.00	8.6	30.6	0.8	0.00	40
	CRMII	1.0	97.0	2.0	0.00	5.52	18.0	0.48	0.00	24
II	BUD1	98.0	2.0	0.00	0.00	19.5	5.5	0.00	0.00	25
	BUD2	98.0	2.0	0.00	0.00	31.2	8.8	0.00	0.00	40
	CRMII	95.0	5.0	0.00	0.00	14.4	4.56	0.00	0.00	19
III	BUD1	0.00	3.0	93.0	4.0	7.2	7.8	12.3	2.7	30
	BUD2	0.00	2.0	94.0	4.0	9.6	10.4	16.4	3.6	40
	CRMII	0.00	0.00	95.0	5.0	1.75	15.4	15.4	2.45	35
IV	BUD1	0.00	2.0	19.0	79.0	3.0	6.9	9.3	10.8	30
	BUD2	0.00	1.0	14.0	85.0	3.9	9.3	12.4	14.4	40
	CRMII	0.00	0.00	12.0	88.0	0.00	17.02	15.2	14.26	46

4.7 Sensitivity analysis

There are several aspects to consider in assessing the robustness of the BUD. These include the role of the prior and the utility setting used. Implicitly, the value of TTV has some unseen effect on the trial terminating early which may affect the accuracy of the results. To investigate all of these, the next few simulations are carried out based on Scenario I of single endpoint study (Table 4.14b).

4.7.1 Modifying the prior

The sensitivity analysis is first carried out on the prior by reducing the prior variance (Equation 4.4) through a factor $f(<1)$ from the original setting while keeping the prior mean constant. The purpose is to create a varying shift in the parameter of the beta distribution such that it allows study on the robustness of the design via shifting the prior value. This creates a shift in the parameter ρ_2 .

The aspect of sensitivity is further investigated by using a hyperbolic tangent function (see Equation 4.43) to represent the prior probability of toxicity for each dose level. This is similar to the dose-toxicity model used by O’Quigley *et al* [5] in the CRM design. The prior probability of toxicity can be varied by shifting the hyperbolic tangent curve via changes in the parameter q . Increases in q corresponds to decreases in ρ_2 (Table 4.20). The value q will be varied from 0.5, 0.75, 1.0, 1.25, 1.5, 1.75 and 2 respectively.

The result of both the sensitivity study via manipulation of the prior variance and parameter q is shown in Table 4.19 and Table 4.20 respectively. The table is organised into 5 different segments. Segment 1 relates the varying shift in the variance multiplication factor (as shown in Table 4.19) or the shift in the parameter q (as shown in Table 4.19). Segment 2 displays the resulting changes in the ρ parameter

corresponding to the parameter of the beta distribution. The percentage of correct recommendations for each dose level, the average total number of patient used and the average total number of observed toxicity is represented by segment 3, 4 and 5 respectively. The bold values as shown in the table are the original results of scenario 1 as previously shown in Table 4.15.

In Table 4.19, the result does not vary too much. However, it was noted that a better performance in the design is possible if the multiplication factor is further reduced to 0.5 whereby 50.6% recommended dose level 4 as the MTD as compared to 41.9% used by the original setting. Besides, it utilises fewer average numbers of patients and lower value for the average total number of toxicity.

In Table 4.20, there is little variation in the percentage of recommending the correct dose level for $0.5 \leq q \leq 1.5$. However, for $q > 1.75$, the modal percentage value of dose level 4 drops substantially. This is partly due to a prior setting which is shifting from a gently gradient curve of the probability of toxicity for each specific dose level to a steep gradient where higher probability is skewed towards the higher dose level as shown when the parameter q is between 1.7 and 2. Under normal circumstances, the distribution of the prior value tend not to be overly skewed towards a dose level as seen by the case when $q = 1.7$ and 2. Therefore, in practice, such allocation of the prior value will be equally assigned between the dose levels.

4.7.2 Modifying the utility

Sensitivity analysis is also performed on the utility setting by modifying ε as seen in Equation 4.8. From the explicit mathematical relationship between the target probability and utility (see Equation 4.8), changes in ε will result in modifying the utility setting. The purpose is to investigate the design robustness from a utility point

of interest as well as to study the effect of the ε variation on the final outcome of the design.

Table 4.21 and 4.22 show the results based on two kinds of utility setting. The benchmark of the result uses a similar scenario of a single end point study of Table 4.14b.

In Table 4.21, utility value for u_{11} , u_{21} , u_{31} , u_{32} and u_{12} are fixed while u_{22} is variable obtained from the formulation of Equation 4.8. The variation of the latter utility coefficients is dependent on the ε where it varies at 0.05, 0.1, 0.3 and 0.5. Marginal variation in the results is observed when ε is between 0.05 and 0.1. However, for $\varepsilon > 0.1$ the mode, while still at dose level 3, decreases quite rapidly.

Simulations involving the variation of the other u_{ij} also give similar conclusions (Table 4.22). In general, the design appears robust provided $\varepsilon < 0.1$. This suggests that the choice of utility value should be subjected by a constraint of $\varepsilon < 0.1$.

4.7.3 Modifying the stopping criterion TTV

The validity of finding an appropriate range of value for TTV is studied carefully such that the accuracy of BUD would not be compromised. Table 4.23 show the results and it is noted that there is a significant reduction in accuracy when $TTV < 0.6$. The high percentage of recommending the correct DL began to deviate from its intended path. In order to achieve an accurate recommended dose and yet being able to stop early, the recommended range for TTV should be restricted to between 0.7 and 0.9.

Table 4.19 Sensitivity analysis for the prior via variation in the variance value.

ϑ × factor	ρ parameter for each dose level						Recommendation at dose level (%)						Ave. total number of patients	Ave. total number of toxicities
	1	2	3	4	5	6	1	2	3	4	5	6		
1	$\rho_1=0.95$	$\rho_1=0.90$	$\rho_1=0.75$	$\rho_1=0.65$	$\rho_1=0.50$	$\rho_1=0.30$	0.0	0.09	33.1	41.9	22.0	2.1	20.1	2.29
	$\rho_2=0.05$	$\rho_2=0.10$	$\rho_2=0.25$	$\rho_2=0.35$	$\rho_2=0.50$	$\rho_2=0.70$								
0.95	$\rho_1=0.95$	$\rho_1=0.91$	$\rho_1=0.77$	$\rho_1=0.68$	$\rho_1=0.39$	$\rho_1=0.25$	0.0	0.8	34.0	43.9	19.1	2.2	19.3	2.79
	$\rho_2=0.05$	$\rho_2=0.09$	$\rho_2=0.23$	$\rho_2=0.32$	$\rho_2=0.61$	$\rho_2=0.75$								
0.9	$\rho_1=0.96$	$\rho_1=0.91$	$\rho_1=0.79$	$\rho_1=0.71$	$\rho_1=0.34$	$\rho_1=0.25$	0.0	0.89	37.6	46.2	14.0	1.3	19.7	2.99
	$\rho_2=0.04$	$\rho_2=0.09$	$\rho_2=0.21$	$\rho_2=0.29$	$\rho_2=0.66$	$\rho_2=0.75$								
0.8	$\rho_1=0.96$	$\rho_1=0.92$	$\rho_1=0.82$	$\rho_1=0.76$	$\rho_1=0.28$	$\rho_1=0.21$	0.0	0.7	34.9	50.6	13.8	0.0	20.0	2.43
	$\rho_2=0.04$	$\rho_2=0.08$	$\rho_2=0.18$	$\rho_2=0.24$	$\rho_2=0.72$	$\rho_2=0.79$								
0.5	$\rho_1=0.98$	$\rho_1=0.95$	$\rho_1=0.90$	$\rho_1=0.87$	$\rho_1=0.15$	$\rho_1=0.12$	0.0	0.7	34.9	50.6	13.8	0.0	19.9	2.43
	$\rho_2=0.02$	$\rho_2=0.05$	$\rho_2=0.10$	$\rho_2=0.13$	$\rho_2=0.85$	$\rho_2=0.88$								

Table 4.20 Sensitivity analysis for the prior via variation in the parameter q .

q	Alpha parameter for each dose level						Recommendation at dose level (%)						Ave. total number of patients	Ave. total number of toxicities
	1	2	3	4	5	6	1	2	3	4	5	6		
0.5	$\rho_1=0.78$	$\rho_1=0.68$	$\rho_1=0.5$	$\rho_1=0.41$	$\rho_1=0.29$	$\rho_1=0.16$	0.00	4.5	35.8	45.6	14.1	0.0	19.5	2.51
	$\rho_2=0.22$	$\rho_2=0.32$	$\rho_2=0.5$	$\rho_2=0.59$	$\rho_2=0.71$	$\rho_2=0.84$								
0.75	$\rho_1=0.89$	$\rho_1=0.82$	$\rho_1=0.65$	$\rho_1=0.54$	$\rho_1=0.41$	$\rho_1=0.24$	0.00	0.9	33.4	44.5	18.9	2.3	20.0	2.82
	$\rho_2=0.11$	$\rho_2=0.18$	$\rho_2=0.35$	$\rho_2=0.46$	$\rho_2=0.59$	$\rho_2=0.76$								
1	$\rho_1=0.95$	$\rho_1=0.90$	$\rho_1=0.75$	$\rho_1=0.65$	$\rho_1=0.50$	$\rho_1=0.30$	0.0	0.09	33.1	41.9	22.0	2.1	20.1	2.29
	$\rho_2=0.05$	$\rho_2=0.10$	$\rho_2=0.25$	$\rho_2=0.35$	$\rho_2=0.50$	$\rho_2=0.70$								
1.25	$\rho_1=0.98$	$\rho_1=0.93$	$\rho_1=0.82$	$\rho_1=0.73$	$\rho_1=0.58$	$\rho_1=0.36$	0.00	0.9	33.1	42.7	19.3	3.9	19.7	2.93
	$\rho_2=0.02$	$\rho_2=0.07$	$\rho_2=0.18$	$\rho_2=0.27$	$\rho_2=0.42$	$\rho_2=0.64$								
1.5	$\rho_1=0.99$	$\rho_1=0.97$	$\rho_1=0.87$	$\rho_1=0.79$	$\rho_1=0.65$	$\rho_1=0.43$	0.00	0.8	32.4	38.5	17.1	11.2	20.1	2.62
	$\rho_2=0.01$	$\rho_2=0.03$	$\rho_2=0.13$	$\rho_2=0.21$	$\rho_2=0.35$	$\rho_2=0.57$								
1.75	$\rho_1=0.99$	$\rho_1=0.98$	$\rho_1=0.91$	$\rho_1=0.84$	$\rho_1=0.70$	$\rho_1=0.46$	0.00	0.7	34.7	26.6	23.1	14.9	19.9	2.83
	$\rho_2=0.01$	$\rho_2=0.02$	$\rho_2=0.09$	$\rho_2=0.16$	$\rho_2=0.30$	$\rho_2=0.54$								
2.0	$\rho_1=1.00$	$\rho_1=0.99$	$\rho_1=0.94$	$\rho_1=0.88$	$\rho_1=0.75$	$\rho_1=0.51$	0.00	0.6	33.3	24.0	26.8	15.3	20.0	2.73
	$\rho_2=0.00$	$\rho_2=0.01$	$\rho_2=0.06$	$\rho_2=0.12$	$\rho_2=0.25$	$\rho_2=0.49$								

Table 4.21 Sensitivity analysis for the utility by setting $u_{11}=3.3$, $u_{21}=1.6$, $u_{32}=6.7$, u_{31} and $u_{12}=0.0$ as constant value and treat u_{22} as variable of interest.

ε	Recommendation at dose level (%)						Ave. total number of patients	Ave. total number of toxicities			
	1	2	3	4	5	6					
0.05	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 3.6030$	0.0	0.9	33.1	41.9	22.0	2.1	20.1	2.29
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.1	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 3.7545$	0.0	1.0	34.2	43.9	17.0	3.9	20.0	2.94
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.3	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 4.3606$	0.0	1.2	37.5	31.5	24.6	5.2	21.0	2.32
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.5	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.6$	$u_{22} = 4.9667$	0.0	1.5	37.8	32.2	20.9	7.6	20.7	2.51
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								

Table 4.22 Sensitivity analysis for the utility by setting $u_{11}=3.3$, $u_{22}=3.75$, $u_{32}=6.7$, u_{31} and $u_{12}=0.0$ as constant value and treat u_{21} as variable of interest.

ε	Recommendation at dose level (%)						Ave. total number of patients	Ave. total number of toxicities			
	1	2	3	4	5	6					
0.05	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.5276$	$u_{22} = 3.75$	0.0	0.9	33.1	41.9	22.0	2.1	20.1	2.29
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.1	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.6022$	$u_{22} = 3.75$	0.0	1.0	33.8	43.7	17.6	3.9	20.2	2.31
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.3	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 1.9007$	$u_{22} = 3.75$	0.0	1.0	38.2	31.0	24.5	5.3	21.1	2.45
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								
0.5	$y_1(T_0)$		$y_2(T_1)$								
	Escalate, A_1	$u_{11} = 3.3$	$u_{12} = 0.0$								
	Maintain, A_0	$u_{21} = 2.1992$	$u_{22} = 3.75$	0.1	1.8	38.9	35.8	19.2	4.2	20.9	2.55
	De-escalate, A_{-1}	$u_{31} = 0.0$	$u_{32} = 6.7$								

Table 4.23. Sensitivity analysis for various stopping criterion of TTV with a maximum sample size of 40.

TTV	Recommendation (%)						Mean number of patients
	1	2	3	4	5	6	
0.4	68.9	28.3	2.8	0.0	0.0	0.0	7.6
0.5	32.1	29.5	26.1	11.8	0.5	0.0	8.2
0.6	15.1	17.9	39.2	27.6	0.2	0.0	12.4
0.7	1.3	16.1	30.1	37.9	14.6	0.0	17.6
0.8	0.6	2.7	37.7	40.5	17.1	1.4	19.5
0.9	0.0	0.9	33.1	41.9	22.0	2.1	20.1

4.8 Validity of a Dirichlet prior

Gasparini and Eisele [61] and O’Quigley [62] question the deficiencies in the operating characteristic of a curve-free and model based CRM when a Dirichlet prior is used. The main difficulty is its inability to escalate to the highest dose level even after having observed a long run of non-toxicities. The main reason is primarily due to minimal correlation between the probabilities of toxicities of the adjacent dose level. An experiment was done using the Dirichlet prior (Table 4.24) where a similar series of non-toxicities are run over an extension of 10 dose levels. The simulation is significantly bias whereby the hypothetical scenario is set below the target probability value as shown in Table 4.25. The target probability of the four combination outcomes is similar to Example 2 of Section 4.5.2. The starting dose has to be at the lowest level. The result (Table 4.26) highlights that the deficiencies of Dirichlet prior can be ignored based on the evidence that final dose is attainable. The fact that both the prior and posterior are the conjugate distribution which estimate the patient outcomes on each respective dose level which therefore prevent serial correlation

between the probability of toxicity. The original problem of restrictive dose escalation due to series of non-toxicities will not surface in this case.

Table 4.24 Bias scenario for analysing the effect of Dirichlet prior

Dose level	1	2	3	4	5	6	7	8	9	10
$p(\text{toxicity})$	0.00	0.01	0.02	0.04	0.06	0.08	0.10	0.12	0.15	0.17
$p(\text{efficacy})$	0.21	0.30	0.40	0.50	0.55	0.60	0.65	0.70	0.80	0.84

Table 4.25 *a priori* Dirichlet parameter for analysing Dirichlet prior effect

Dose level	1	2	3	4	5	6	7	8	9	10
$Prior\sim p(\text{tox})$	0.01	0.05	0.09	0.10	0.12	0.14	0.16	0.18	0.20	0.25
$Prior\sim p(\text{eff})$	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.81	0.82	0.84
ρ_1	0.89	0.76	0.64	0.54	0.44	0.34	0.25	0.16	0.14	0.12
ρ_2	0.10	0.19	0.27	0.36	0.44	0.52	0.60	0.66	0.67	0.63
ρ_3	0.01	0.04	0.06	0.06	0.06	0.06	0.05	0.04	0.04	0.04
ρ_4	0.00	0.01	0.03	0.04	0.06	0.08	0.10	0.14	0.15	0.21

Table 4.26 Result summary for analysing the Dirichlet prior effect

Patient No.	Patient Outcome	$U(A_1)$	$U(A_0)$	$U(A_{-1})$	Dose Level	Resulting action	$\hat{\gamma}_1$
1	y_1	1.2789	1.1332	0.3018	1	A_1	0.50,0.25,0.25,0.25,0.25,0.25,0.25,0.25,0.25,0.25,0.25
2	y_1	1.3729	1.2342	0.4018	2	A_1	0.40,0.40,0.19,0.19,0.19,0.19,0.19,0.19,0.19,0.19,0.19
3	y_1	1.1769	0.9332	0.4058	3	A_1	0.33,0.33,0.33,0.16,0.16,0.16,0.16,0.16,0.16,0.16,0.16
4	y_1	1.2789	1.1322	0.6518	4	A_1	0.28,0.28,0.28,0.28,0.16,0.16,0.16,0.16,0.16,0.16,0.16
5	y_1	1.3289	0.8332	0.3018	5	A_1	0.25,0.25,0.25,0.25,0.25,0.12,0.12,0.12,0.12,0.12,0.12
6	y_1	1.5789	1.1732	0.2783	6	A_1	0.22,0.22,0.22,0.22,0.22,0.22,0.11,0.11,0.11,0.11,0.11
7	y_1	1.4259	1.2567	0.5785	7	A_1	0.20,0.20,0.20,0.20,0.20,0.20,0.20,0.10,0.10,0.10,0.10
8	y_1	0.9875	0.7956	0.2156	8	A_1	0.18,0.18,0.18,0.18,0.18,0.18,0.18,0.18,0.09,0.09,0.09
9	y_1	1.3254	1.1247	0.8756	9	A_1	0.17,0.17,0.17,0.17,0.17,0.17,0.17,0.17,0.17,0.17,0.08
10	y_2	0.1052	1.1032	1.7197	10	A_0	0.15,0.15,0.15,0.15,0.15,0.15,0.15,0.15,0.15,0.15,0.15
11	y_2	0.4603	1.2196	0.6039	10	A_0	0.11,0.11,0.11,0.11,0.11,0.11,0.11,0.11,0.11,0.11,0.38
12	y_3	0.7299	1.6123	0.3022	10	A_0	0.09,0.09,0.09,0.09,0.09,0.09,0.09,0.09,0.09,0.51,0.51
13	y_2	0.8643	1.8056	0.1519	10	A_0	0.08,0.08,0.08,0.08,0.08,0.08,0.08,0.08,0.08,0.67,0.67
14	y_2	0.7102	1.8693	0.2875	10	A_0	0.07,0.07,0.07,0.07,0.07,0.07,0.07,0.07,0.07,0.76,0.76
15	y_2	0.6985	1.8954	0.2134	10	A_0	0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.84,0.84
16	y_2	0.6584	1.9012	0.2047	10	terminate	0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.06,0.90,0.90

CHAPTER 5

Interactive utility weight in a single and Combination dose therapy

The proposed Bayesian Utility Design (BUD) demonstrated the possibility of estimating an acceptable recommended dose under different clinical scenarios. However, one potential difficulty with the BUD is the need for eliciting a suitable utility weight value. Although this has an implicit relationship with the target probability (i.e. the choice of the target probability implies a certain form of utility weight), the investigator may find it difficult to specify an appropriate utility weight. The problem of finding a suitable utility weight is that it gets more complex if the number of outcomes and decision level increases. This would generate a large matrix dimension which makes the design ‘bulky’ and less efficient.

This chapter introduces an interactive characteristic to the utility weight system that adapts to the accumulating data. This simplifies the process of eliciting a proper weight value that could sometimes be arbitrary and intuitive. One of the key interests for the enhanced BUD method is to deal with situation of combination dose therapy. In Oncology, such combination therapy studies is commonly found, for example, in combination chemotherapies, in selective immunotoxins combined with T-cell infusion, in graft-versus-host disease prophylaxis following ablative chemotherapy in bone marrow transplantation. The reasons commonly suggested for dose combination [15] are:

1. Biochemical synergism,
2. Differential susceptibility of tumour cells to different agents,

3. Higher achievable dose intensity by exploiting nonoverlapping toxicities to the host.

In all cases, it is necessary for evaluating antitumour efficacy to find doses of the drugs that are tolerable when administered together. Due to the nature of combining dose treatment, the situation is more complicated as the biochemical and biological phenomena occurring with the combination are generally quite complex and may cause therapeutic effects that are difficult to predict. The problem of constructing an algorithm for choosing doses sequentially is obviously more difficult than the analogous single-agent problem. The method of BUD will further investigate the application of a combination therapy which involves an interactive element. The fundamental principle of BUD remains unchanged for this modified design. The main focus will be on how the interactive aspect of the utility weight can be applied on a single and combination dose therapy.

5.1 Model and design criteria

This modified version of BUD is renamed Bayesian Interactive Utility Design (BIUD). The characteristic of a fix utility weight system is replaced by a parametric approach such that it can influence a utility weight which has an association with the probability of toxicity. This parametric utility weight function consists of a weight model which reflects a preference of action for both toxicity and non-toxicity outcomes. In a combination dose study, typically of 2 agents, the respective course of action is to escalate, de-escalate or maintain at the same dose level for dose agent 1 and 2 depending on the DLT of each respective dose agent, DLT_1 or DLT_2 . The utility weight model has an interactive mechanism which includes the patient outcomes and

the resulting probability of toxicity that updates the weight function which set preference over the consequences of possible actions to be taken.

Generally, BIUD shares the same operational procedures with BUD, except for the need to elicit parameters for the utility weight model. The design begins with a parametric family associated with the probability of toxicity for each dose agent and the corresponding *a priori* information for the parameters. The synergy of two dose agents can be obtained by combining the toxicity information to yield four combinations of outcomes. Based on the decision theoretic framework, the parametric utility weight model is defined for each dose agent. The specification of the utility weight model quantified with the relative consequences associated with each of the three decisions which may be taken when the results of each patient is known. Progressively, as one collects data, one updates the prior distribution of the toxicity which also leads to updating the utility weight model. Similar to BUD, the optimal decision for finding the next recommended dose is by maximising the expected utility value of each dose agent and the recommendation is made simultaneously for both dose agents. The sequence of actions for dose selections is defined as follows:

- (1) The target probability of each dose agent is first defined. The clinician will then elicit the prior information of the parameter associated with the probability of toxicity. These prior probabilities can be used to incorporate any pre-trial information that may be available for dose agent 1 and 2. In the absence of such information, they would reflect the pre-trial opinions of the investigators. The priors could be made to be vague, in which case the data from the trial will dominate the procedure, and the decisions made during the trial will be very much influenced by the prior probabilities used.

- (2) The design then specifies the dual utility weight system which quantifies the relative consequences associated with each of the three different decisions which may be taken when the results of each patient is known. The level of decisions for the combined dose consists of 2 separate sets of standardised actions on whether to escalate to a higher dose; assign the same dose; or de-escalate to a lower dose. The choice of these actions is dependent on patient's DLT effect, due to each specific dose agent.
- (3) In the implementation stage, treatment begin at dose level l for each respective dose agent m , d_{ml} ($m = 1,2; l = 1,...,k$) on the j^{th} entered patient ($j = 1,...,N$) where N is the maximum sample size of patient. The toxicity $Y_{mj} \in (0,1)$ is a binary random variable for each specific dose agent with "1" denoting severe toxic response. The latter will update the posterior probability of toxicities of each dose agent and its corresponding utility weight model. The decision as to which dose level to be used is then decided, taking into account all the information obtained so far pertaining to the dose levels in question. Formally, the way in which the decision-making process is carried out via the maximisation of the expected utility, where the utility function is expressed from a model which is interactive with the patient outcomes. The optimal decision for the $j^{th} + 1$ patient is given by:

	(i)	$A_{1,-1}$ (De-escalate)	if $E_l[A_{1,-1}] > E_l[A_{1,0}], E_l[A_{1,1}]$,
Dose agent 1	(ii)	$A_{1,0}$ (Maintain)	if $E_l[A_{1,0}] > E_l[A_{1,-1}], E_l[A_{1,1}]$,
	(iii)	$A_{1,1}$ (Escalate)	if $E_l[A_{1,1}] > E_l[A_{1,0}], E_l[A_{1,-1}]$.

- (i) $A_{2,-1}$ (De-escalate) if $E_l[A_{2,-1}] > E_l[A_{2,0}]$, $E_l[A_{2,1}]$,
- Dose agent 2 (ii) $A_{2,0}$ (Maintain) if $E_l[A_{2,0}] > E_l[A_{2,-1}]$, $E_l[A_{2,1}]$,
- (iii) $A_{2,1}$ (Escalate) if $E_l[A_{2,1}] > E_l[A_{2,0}]$, $E_l[A_{2,-1}]$.

where $A_{m,v}$ denotes action of de-escalation ($v = -1$), maintain ($v = 0$), and escalation ($v = 1$) for each respective dose agent ($m = 1, 2$). $E_l[A_{m,v}]$ is the expected utility of three possible actions defined by

$$E_l[A_{m,v}] = \{(\tilde{\omega}_v)_{m0} \times (1 - PT_{ml})\} + \{(\tilde{\omega}_v)_{m1} \times (PT_{ml})\}$$

where PT_{ml} is the non-decreasing probability of toxicity for both dose agents ($0 \leq PT_{1l} \leq \dots \leq PT_{1k} \leq 1$; $0 \leq PT_{2l} \leq \dots \leq PT_{2k} \leq 1$) and can be expressed by $PT_{1l} = p(Y_{1j}=1 | d_{1l})$ and $PT_{2l} = p(Y_{2j}=1 | d_{2l})$. The parametric utility weight function for the outcome of non-toxicity ($r = 0$) and toxicity ($r = 1$) is represented by $(\tilde{\omega}_v)_{mr}$.

5.1.1 Probability of toxicity for combination dose agent

The synergy of 2 dose agents results in four possible outcomes of interest for each patient in the study. This is similar to the four combination outcomes of toxicity and efficacy as explained in the preceding chapter. These four outcomes consist of a combined DLT effect from both of the agents, $(\bar{T}_1, \bar{T}_2)$, $(\bar{T}_1, T_2)$, $(T_1, \bar{T}_2)$ and (T_1, T_2) , where $\bar{T}_1$ and T_1 are respectively denote as DLT outcomes of non-toxicity and toxicity for dose agent 1. Similarly, $\bar{T}_2$ and T_2 are respectively DLT outcomes of non-toxicity and toxicity for dose agent 2. These four combination outcomes reflect the patient's possible response at a particular dose level. By assuming independence in the probability of DLT for dose agent 1 and 2, similar expression of Equation 4.1

can be applied where the four possible probabilities of combination outcomes can be expressed by

$$\begin{aligned}
 \theta_{1j} &= p(\bar{T}_1, \bar{T}_2) = (1 - PT_{1l})(1 - PT_{2l}), \\
 \theta_{2j} &= p(\bar{T}_1, T_2) = (1 - PT_{1l})(PT_{2l}), \\
 \theta_{3j} &= p(T_1, \bar{T}_2) = (PT_{1l})(1 - PT_{2l}), \\
 \theta_{4j} &= p(T_1, T_2) = (PT_{1l})(PT_{2l}).
 \end{aligned} \tag{5.1}$$

The data from each patient can be expressed as one of the four outcome combinations which can be represented by $\mathbf{y} = (y_{1j}, y_{2j}, y_{3j}, y_{4j})$ where y_{1j} denote data for $(\bar{T}_1, \bar{T}_2)$, y_{2j} denotes data for $(\bar{T}_1, T_2)$, y_{3j} denote data for $(T_1, \bar{T}_2)$ and y_{4j} denotes data for (T_1, T_2) . The input information of these data consists of a binary value where $y_{1j}, y_{2j}, y_{3j}, y_{4j} \in (0, 1)$ with “1” representing an occurrence of the outcome combination and a “0” otherwise. The outcome occurrence for each patient can be generalised by

$$\sum_{i=1}^4 y_{ij} = 1.$$

The modelling of patient response for the four combination outcomes uses similar Bayesian approach from the preceding chapter. A Dirichlet prior and a Maximum likelihood are used. These yield a natural conjugate of Dirichlet distribution of combination DLT outcome, θ where $0 \leq \theta_{ij} \leq 1$ and, of the form

$$p_l(\theta | \rho + \mathbf{y}) = \frac{\Gamma\left(\sum_{i=1}^4 \rho_{ij} + y_{ij}\right)}{\prod_{i=1}^4 \Gamma(\rho_{ij} + y_{ij})} \theta_{1j}^{\rho_{1j} + y_{1j} - 1} \dots \theta_{4j}^{\rho_{4j} + y_{4j} - 1}. \tag{5.2}$$

Where the Dirichlet parameter, $\rho_{1j}, \rho_{2j}, \rho_{3j}, \rho_{4j}$ ($\rho_{ij} > 0$), corresponds to *a priori* information associated with the probability of combination outcomes. The choice of ρ_{ij} values should reflect clinical opinion. This can be obtained indirectly by specifying the mean and variances of each θ_{ij} . The corresponding equations are:

$$E[\theta_{ij}] = \frac{\rho_{ij}}{\sum_{i=1}^4 \rho_{ij}} \quad (5.3)$$

$$\text{and} \quad \text{Var}[\theta_{ij}] = \frac{E[\theta_{ij}](1 - E[\theta_{ij}])}{1 + \sum_i \rho_{ij}}. \quad (5.4)$$

where $\sum_{i=1}^4 \rho_{ij} = 1$, this is to minimise the high variance due to lack of information in the prior distribution.

Biologically, toxicity and efficacy are unified entities from human response after taking a dosage of drug. However, in the analysis of these combinations of outcome, statistical independence of these two events can still be assumed as independent as indicated by Bryant – Day’s [73, 74] in their Phase I and II trial where their statistical validation is based on odds-ratio $\Phi = 1$. They have proven that the error risk in the outcome of finding a dose that satisfies the independence of dual outcomes is minimal and has little impact on the overall results. From the outcome occurrence point of view, the relative effect of efficacy and toxicity will not be influenced as the responses from the two outcomes do not behave in similar fashion as shown in the schematic illustration of Figure 5.1.

Figure 5.1 Schematic representation of the difference in pattern between an Efficacy – dose curve and Toxicity – dose curve

5.1.2 Probability of toxicity for single dose agent

The information on the probability of DLT for each dose agent is essential in updating the dynamic characteristic of the utility weight model. The modelling of the probability distribution is similar to the combination DLT where in this case a Beta prior and Binomial likelihood is assumed to yield a natural conjugate of Beta distribution of toxicity outcome PT_{ml} where $0 \leq PT_{ml} \leq 1$.

$$p_{ml}(PT|\mu + y, \beta - y + 1) = \frac{\Gamma(\mu_{ml} + \beta_{ml} + 1)}{\Gamma(\mu_{ml} + y_{mj})\Gamma(\beta_{ml} + 1 - y_{mj})} PT_{ml}^{\mu_{ml} + y_{mj} - 1} (1 - PT_{ml})^{\beta_{ml} + y_{mj} - 1} \quad (5.5)$$

The Beta parameter of μ_{ml} and β_{ml} ($\mu_{ml} > 0$, $\beta_{ml} > 0$) corresponds to *a priori* information associated with the probability of toxicity and non-toxicity respectively. Similarly, the choice of μ_{ml} and β_{ml} can be obtained indirectly by specifying the mean and variance of PT_{ml} .

$$E[PT_{ml}] = \frac{\mu_{ml}}{\mu_{ml} + \beta_{ml}} \quad (5.6)$$

$$\text{and } Var[PT_{ml}] = \frac{\mu_{ml}\beta_{ml}}{(\mu_{ml} + \beta_{ml})^2(\mu_{ml} + \beta_{ml} + 1)}, \quad (5.7)$$

where $\mu_{ml} + \beta_{ml} = 1$ and μ_{ml} is associated to prior probabilities of toxicity.

In line with the monotonicity criteria, the probability of toxicity has to be an increasing function of dose level. However, the estimate of the posterior distribution of toxicity is independent of adjacent dose levels. Therefore, PT_{ml} which may not be non-decreasing in d_{ml} , may greatly affect the parametric adjustment of the utility weight model. Adjustment of PT_{ml} may have to be required by using the method of isotonic regression [63]. Let $(PT_{ml})_j$ represent the probability of toxicity at the j^{th} patient. Assuming a strict monotonic constraint where $0 \leq (PT_{m1})_j \leq (PT_{m2})_j \leq \dots \leq (PT_{mk})_j < 1$. If an adjacent pair of toxicity estimates violates the basic assumption of monotonicity at the t^{th} patient where $(PT_{ml})_t > (PT_{ml+1})_t$ ($j = 1, 2, \dots, t, \dots, N$), this pair is then replaced by their average defined as

$$(PT_{ml})_t = (PT_{ml+1})_t = \frac{\sum_{j=1}^t (PT_{ml})_j + \sum_{j=1}^t (PT_{ml+1})_j}{2t}. \quad (5.8)$$

The procedure is repeated until the resulting averages satisfy the required order restriction,

$$(PT_{ml})_t = \dots = (PT_{ml+z})_t = \frac{\sum_{j=1}^t (PT_{ml})_j + \dots + \sum_{j=1}^t (PT_{ml+z})_j}{(1+z)t}. \quad (5.9)$$

where z is the last ordered dose level which does not satisfy the monotonic constraint.

5.2 Interactive utility model for dual dose agents

A dynamic system is implemented in the utility weight for 2 separate dose agents. The general idea is to update the utility weight, as and when information on probability of toxicity from the trial becomes available. This causes the expected utility for each decision to have an implicit relationship with the current knowledge of the probability of toxicity allowing for the combined target dose to be reached. The utility weight system for both the agents are independent of each other and the probability of toxicity for each dose agent only affects its respective utility weight model.

5.2.1 The Method

The functional characteristic of the utility weight system is the same for both dose agents. The basic purpose of the utility weight is to assign value to quantify the level of weight associated with the consequences of each action depending on the patient's toxicity outcomes. These utility weights can be expressed as a function to reflect a preference of consequence to each respective action under each patient's dichotomous outcome. The function is updated whenever data from the patient accrued into the trial is obtained. This in turn changes the utility weight which may potentially result in different actions to be optimal. This process continues until the stopping criterion is satisfied.

Consider a simple utility weight model denoted as $(\tilde{\omega}_v)_{mr} = \phi(\sigma_v, q_{mr})$ where its corresponding function is some consequence of preference for each respective

action associated to both the outcomes of non-toxicity ($r = 0$) and toxicity ($r = 1$) from the respective parameter of q_{m0} and q_{m1} . The decision σ_v has three ordinal levels where σ_1 represents “Escalating the dose”; σ_0 represents “Maintaining the dose level”; and σ_{-1} represents “De-escalating the dose level”. The functional aspect of $(\tilde{\omega}_v)_{mr}$ is very much determined by the parameter q_m , which has an interactive relationship with the current probability of toxicity. In the outcomes where the patient experiences non-toxicity, a function $\phi(\sigma_v, q_{m0})$ has to satisfy a condition where $\phi(\sigma_1, q_{m0}) > \phi(\sigma_0, q_{m0}) > \phi(\sigma_{-1}, q_{m0})$. This is essentially what it is expected, as higher utility weight is assigned to the action of escalating the dose followed by maintaining the dose and a lower weight for de-escalating the dose level. Gradually, as more patients enter the trial, the probability of toxicity will consequently reach the target probability value. The weight function at this point should intuitively shift to a strategic position via changes in q_{m0} value where the utility weight of maintaining the dose takes precedence $\{\phi(\sigma_0, q_{m0}) > \phi(\sigma_1, q_{m0}) > \phi(\sigma_{-1}, q_{m0})$ or $\phi(\sigma_0, q_{m0}) > \phi(\sigma_{-1}, q_{m0}) > \phi(\sigma_1, q_{m0})\}$. The rationale is to ensure higher weight is given to the action of maintaining the dose over other actions.

In the outcome of toxicity, the requirement is vice versa where $\phi(\sigma_{-1}, q_{m1}) > \phi(\sigma_0, q_{m1}) > \phi(\sigma_1, q_{m1})$. Similarly, at the target probability of interest, the utility weight for the action of maintaining the dose will gain bias over the other two actions.

Many choices of the utility weight model are possible as long as the utility function has an interactive parameter that directly relates to the probability of toxicity and thereby have an effect on the utility of choice which would affect the optimal choice for the next recommended dose level. A modified version of a lognormal model is first proposed as a utility weight function for both dose agents:

$$(\tilde{\omega}_v)_{mr} = \phi(\sigma_v, q_{mr}) = \frac{1}{\sqrt{2\pi q_{mr}^2 \sigma_v^2}} \exp \left[\frac{-(\log \sigma_v - \zeta_0)^2}{2q_{mr}^2} \right], \quad (5.10)$$

where ζ_0 is a fix value at 0.075 that will ensure $(\tilde{\omega}_v)_{mr}$ is constrained within the space of $(\tilde{\omega}_v)_{mr} \in (0,1)$ and $\sigma_v \in (0,1)$. Three values are then obtained from the model that represents the utility weight $(\tilde{\omega}_v)_{mr}$ based on the corresponding actions of $\sigma_{.1}$, σ_0 and σ_1 where they are equally spaced within an interval of 0 and 1, such that $\sigma_{.1} = 0.33$, $\sigma_0 = 0.67$ and $\sigma_1 = 1.0$. The latter is of fixed value and will be used for the subsequent calculation of the utility weight value.

The parametric value of q_{m0} and q_{m1} have an association with the target probability of toxicity $PT_{m,tgt}$ in which it has a lower and upper bound denoted by $PT_{m,tgt}^L$ and $PT_{m,tgt}^U$ respectively. The main purpose is to provide an interval estimate for the probability of toxicity when defining q_{mr} . These bounds can be expressed such that it is $100(1-\alpha)\%$ confident that PT_{ml} lies between $PT_{m,tgt}^L$ and $PT_{m,tgt}^U$.

From the fact that the probability of toxicity has a posterior beta distribution (Equation 5.5), hence the $100(1-\alpha)\%$ confidence interval for $PT_{m,tgt}$ can be approximated by

$$PT_{m,tgt}^L = PT_{m,tgt} - Z_{\alpha/2} \left(\sqrt{\text{var}[PT_{ml}] / N} \right), \quad PT_{m,tgt}^U = PT_{m,tgt} + Z_{\alpha/2} \left(\sqrt{\text{var}[PT_{ml}] / N} \right) \quad (5.11)$$

where
$$\text{Var}[PT_{ml}] = \frac{\mu_{ml} \beta_{ml}}{(\mu_{ml} + \beta_{ml} + 1)(\mu_{ml} + \beta_{ml})^2}$$

and
$$\mu_{ml} = N(PT_{m,tgt}), \quad \beta_{ml} = N(1 - PT_{m,tgt})$$

$Z_{\alpha/2}$ is the α^{th} percentile of the standard normal distribution. The parametric value of μ_{ml} and β_{ml} are estimated by assuming the number of patients with and without toxicity effect at the target probability of toxicity from a maximum sample size of N .

Figure 5.2 illustrates the utility weight model based on the lognormal curve which is skewed towards the left. The parametric value of q_{mr} is at a preset value of 1.4 to depict the initial utility curve pattern in the outcome of toxicity.

Figure 5.2 Utility weight curve (Lognormal model) in the outcome of toxicity

With a given value of q_{mr} while σ_1 , σ_0 and σ_1 are fixed at 0.33, 0.67 and 1 respectively. It yields a utility weight for the next recommended dose level at $(\tilde{w}_{-1})_{mr} > (\tilde{w}_0)_{mr} > (\tilde{w}_1)_{mr}$. The interaction of the weight model with the probability of toxicity is very much dependent on q_{mr} where it has a function with respect to the probability of toxicity. In the case of non-toxicity outcome, parameter q_{mr} is then again strategically shifted, such that the utility curve now skewed towards the right as shown in Figure 5.3.

Figure 5.3 Utility weight curve (Lognormal model) in the outcome of non-toxicity

Figure 5.4 illustrates another probable scenario where the probability of toxicity reaches the interval bound of the target probability $PT_{m,tgt}^L$ and $PT_{m,tgt}^U$. The utility weight, $(\tilde{w}_v)_{mr}$, is shifted based on the latest q_{mr} value where the utility of choice is biased towards the decision of maintaining the dose level over other where $(\tilde{w}_0)_{m0} > (\tilde{w}_{-1})_{m0} > (\tilde{w}_1)_{m0}$. The whole rationale behind the elicitation of q_{mr} is that it determines how the movement of the utility curve is dependent on the current status of the probability of toxicity. This will be discussed in the next section.

Figure 5.4 Utility weight curve in the outcome where the probability of toxicity reaches the target value.

5.2.2 Elicitation of parametric q_{mr}

The general rationale of having a q_{mr} is to ensure that the utility weight model behaves accordingly to each changing probability of toxicity as and when more patient is accrued into the trial. The value of q_{mr} is intuitively set between 0 and 1.5 for all analysis.

Figure 5.5 displays a lognormal curve of utility weight, $(\tilde{\omega}_v)_{mr}$, and its corresponding parameter, q_{mr} , where it highlighted three regions of interest for each respective decision outcomes. The three curves are represented by σ_{-1} , σ_0 and σ_1 where $\sigma_{-1}=0.33$, $\sigma_0=0.67$ and $\sigma_1=1$. The main intention is to identify the initial and stationary value of q_{m0} and q_{m1} .

In the outcome of toxicity, we would expect $(\tilde{\omega}_{-1})_{mr} > (\tilde{\omega}_0)_{mr} > (\tilde{\omega}_1)_{mr}$ where the utility of de-escalating takes precedence over maintaining and escalating the dose level. This characteristic is predominantly defined in the shaded region C (regC) of Fig 5.5. The q_{mr} of interest on regC is defined by the intersecting curves of σ_0 and σ_{-1} where:

$$q_{m1}^{stn} = \sqrt{\frac{(\ln \sigma_0 - \xi_o)^2 - (\ln \sigma_{-1} - \xi_o)^2}{2 \ln(\sigma_{-1}/\sigma_0)}} \quad (5.12)$$

This is also the same intersecting point shared by the upper limit of regB. The upper limit of regC, q_{m1}^* , is set at 1.5 as $(\tilde{\omega}_{-1})_{mr}$ has the highest score as compared to $(\tilde{\omega}_0)_{mr}$ and $(\tilde{\omega}_1)_{mr}$. q_{m1}^* at 1.5 is defined as the starting value for q_{m1} in the out come of toxicity.

Figure 5.5 Lognormal graphical plot of $(\tilde{w}_v)_{mr}$ vs q_{mr} for the three action of interest: σ_{-1} , σ_0 and σ_1

In another possible situation where the first few patients experience non-toxicity outcomes, one would expect the curve line of σ_1 to be higher than σ_0 and σ_{-1} where it satisfies $(\tilde{w}_1)_{mr} > (\tilde{w}_0)_{mr} > (\tilde{w}_{-1})_{mr}$. The initial parameter of q_{m0} (denoted as q_{m0}^*) can be identified in Region A (regA). The unique value of q_{m0}^* can be obtained at the intercepting point between the curve line of σ_1 and $(\tilde{w}_v)_{mr} = 1$ where Equation 5.10 is re-expressed with respect to q_{mr} ,

$$q_{m0}^* = \frac{1}{2} \left\{ \frac{-\zeta_o^2 + 4\zeta_o \log \sigma_1 - 2 \log \sigma_1^2}{W \left[\frac{1}{2} \left(-\zeta_o^2 \sqrt{2\pi} \sigma_1^4 + 4\zeta_o \sqrt{2\pi} \sigma_1^4 \log \sigma_1 - 2\sqrt{2\pi} \sigma_1^4 \log \sigma_1^2 \right) \right]} \right\} \quad (5.13)$$

where $W[\cdot]$ is the Lambert function.

During the course of the trial, as more information relating to patient's toxicity response is made available, the model parameters is updated accordingly, subsequently giving rise to a new system of preference which depends on the current state of the probability of toxicity. If the probability of toxicity is within the interval of the target level, the updated weight model will recommend the same dose level for the next patient. At the interval target probability of interest, q_{mr} has a stationary point that lies in between the lower and upper bound of region B(regB) (see Figure 5.5). These bounds are identified based on the condition that the action of σ_0 has a bias over σ_1 and σ_{-1} which can be defined by q_{m0}^{stin} and q_{m1}^{stin} as shown in Figure 5.5. The equation of q_{m0}^{stin} can be derived from the intersecting curves of σ_0 and σ_{-1} which yield:

$$q_{m0}^{stin} = \sqrt{\frac{(\ln \sigma_0 - \xi_o)^2 - (\ln \sigma_{-1} - \xi_o)^2}{2 \ln(\sigma_0/\sigma_{-1})}} \quad (5.14)$$

The parameter of q_{m1}^{stin} shares the same lower bound with regC as defined in the earlier equation of 5.12. During the interval bound of target probability of interest, q_{mr} is a constant value (denoted by q_{m*}^{stin}) and can be uniquely identified from the point where the curve line of σ_1 intercepts with σ_{-1} such that $(\tilde{\omega}_1)_{mr} = (\tilde{\omega}_{-1})_{mr} < (\tilde{\omega}_0)_{mr}$.

$$q_{m*}^{stin} = \sqrt{\frac{(\ln \sigma_1 - \xi_o)^2 - (\ln \sigma_{-1} - \xi_o)^2}{2 \ln(\sigma_1/\sigma_{-1})}} \quad (5.15)$$

To make sense of how the critical q_{mr} value can be used, Figure 5.6 shows the interactive function of q_{mr} versus the probability of toxicity.

Figure 5.6. Parametric plot depicting the profile of q_{m0} and q_{m1} where the modified Lognormal is the model of interest.

The functional equations of q_{m0} and q_{m1} are shown in Equations 5.16 and 5.17 respectively. In the case where probability of toxicity, PT_{ml} is between 0 and $PT_{m,tgt}^L$ ($0 \leq PT_{ml} \leq PT_{m,tgt}^L$), q_{m0} and q_{m1} start from an initial values defined by q_{m0}^* and q_{m1}^* respectively. As PT_{ml} approaches the lower bound of the target probability ($PT_{m,tgt}^L$), q_{m0} and q_{m1} are directed toward a boundary region of q_{m0}^{sn} and q_{m1}^{sn} . In the region where the probability of toxicity lies between the upper and lower bound of $PT_{m,tgt}$ ($PT_{m,tgt}^L < PT_{ml} < PT_{m,tgt}^U$) with q_{m0} and q_{m1} remaining at q_{m*}^{sn} . The rationale is to ensure a strategic shift in the weight model such that the utility weight for maintaining the dose level is always bias towards a highest value. This makes sense, as one would expect a higher utility weight to maintain the same dose level for the next patient when the probability of toxicity is near the target level. In the case where PT_{ml} is between $PT_{m,tgt}^U$ and 1 ($PT_{m,tgt}^U \leq PT_{ml} \leq 1$), the equations direct q_{m0} and q_{m1} back to its initial point of equation as shown in Equation 5.16 and 5.17.

$$q_{m0} = \begin{cases} \frac{q_{m0}^{stn} - q_{m0}^*}{PT_{m,tgt}^L} PT_{m0} + q_{m0}^* & \text{if } 0 \leq PT_{m0} \leq PT_{m,tgt}^L \\ q_{m0}^{stn} & \text{if } PT_{m,tgt}^L < PT_{m0} < PT_{m,tgt}^U \\ \frac{(q_{m0}^{stn} - q_{m0}^*) PT_{m0} - (q_{m0}^*) PT_{m,tgt}^U + q_{m0}^{stn}}{1 - PT_{m,tgt}^U} & \text{if } PT_{m,tgt}^U \leq PT_{m0} \leq 1 \end{cases} \quad (5.16)$$

$$q_{m1} = \begin{cases} \frac{q_{m1}^{stn} - q_{m1}^*}{PT_{m,tgt}^L} PT_{m1} + q_{m1}^* & \text{if } 0 \leq PT_{m1} \leq PT_{m,tgt}^L \\ q_{m1}^{stn} & \text{if } PT_{m,tgt}^L < PT_{m1} < PT_{m,tgt}^U \\ \frac{q_{m1}^{stn} - (q_{m1}^*) PT_{m,tgt}^U - (q_{m1}^{stn} - q_{m1}^*) PT_{m1}}{1 - PT_{m,tgt}^U} & \text{if } PT_{m,tgt}^U \leq PT_{m1} \leq 1 \end{cases} \quad (5.17)$$

Table 5.1 illustrates a decision table depicting an overview of the relationship between $(\tilde{\omega}_v)_{mr}$ and the three decisions together with its respective outcomes while Table 5.2 displays all possible values for parameter q_{mr} under various values of PT_{m0} . The target probability of toxicity is first defined as 0.33 (as this value is commonly used in Phase I clinical trial [4,5,10,13]) and using a maximum sample size of $N = 30$, the 95% confidence interval for $PT_{m,tgt}$ is obtained where $PT_{m,tgt}^L = 0.3$ and $PT_{m,tgt}^U = 0.36$. By systematically varying the value of PT_{m0} from 0 to 1, various results of q_{mr} based on Equations 5.16 and 5.17 can be observed (Table 5.2). In summary, the utility setting of BIUD is a modal based approach; where the eliciting of the weight value is controlled by the parametric variable of q_{mr} which is mainly dependent on the current state of the probability of toxicity. The boundary condition, in this case can be represented by Table 5.2 where it lists out all the possible utility value under the required value of q_{m0} and q_{m1} . Figure 5.7 shows what this model looks like for various value of q_{mr} . At the point of the target probability, q_{m0} and q_{m1} converge to q_{m0}^{stn} ; it

therefore satisfies the condition where $(\tilde{\omega}_0)_{m0} > (\tilde{\omega}_{-1})_{m0} > (\tilde{\omega}_1)_{m0}$ and $(\tilde{\omega}_0)_{m1} > (\tilde{\omega}_{-1})_{m1} > (\tilde{\omega}_1)_{m1}$. Similar model characteristic also applies to the second dose agent.

Table 5.1. Decision table for: (a) dose agent 1 and (b) dose agent 2.

Dose agent 1			Dose agent 2		
	Non toxic	Toxic		Non toxic	Toxic
Escalate	$(\tilde{\omega}_1)_{10}$	$(\tilde{\omega}_1)_{11}$	Escalate	$(\tilde{\omega}_1)_{20}$	$(\tilde{\omega}_1)_{21}$
Maintain	$(\tilde{\omega}_0)_{10}$	$(\tilde{\omega}_0)_{11}$	Maintain	$(\tilde{\omega}_0)_{20}$	$(\tilde{\omega}_0)_{21}$
De-escalate	$(\tilde{\omega}_{-1})_{10}$	$(\tilde{\omega}_{-1})_{11}$	De-escalate	$(\tilde{\omega}_{-1})_{20}$	$(\tilde{\omega}_{-1})_{21}$

(a) (b)

Table 5.2 Utility weight values and its corresponding q_{m0} and q_{m1} parameter utilising modified Lognormal model

	PT_{m1}	q_{m0}	q_{m1}	$(\tilde{\omega}_{-1})_{m0}$	$(\tilde{\omega}_0)_{m0}$	$(\tilde{\omega}_1)_{m0}$	$(\tilde{\omega}_{-1})_{m1}$	$(\tilde{\omega}_0)_{m1}$	$(\tilde{\omega}_1)_{m1}$
1	0.05	0.42	1.40	0.0574	0.7406	0.9348	0.6016	0.4030	0.2845
2	0.10	0.44	1.30	0.0776	0.7492	0.8936	0.6125	0.4299	0.3063
3	0.15	0.46	1.21	0.1004	0.7539	0.8558	0.6179	0.4571	0.3291
4	0.20	0.48	1.11	0.1255	0.7554	0.8210	0.6165	0.4909	0.3586
5	0.25	0.51	1.01	0.1661	0.7528	0.7738	0.6033	0.5291	0.3939
6	0.30	0.53	0.91	0.1945	0.7486	0.7452	0.5725	0.5720	0.4369
7	0.35	0.79	0.79	0.5025	0.6295	0.5027	0.5025	0.6295	0.5027
8	0.40	0.52	0.95	0.1803	0.7509	0.7592	0.5874	0.5543	0.416
9	0.45	0.51	0.99	0.1661	0.7528	0.7738	0.5987	0.5375	0.4018
10	0.50	0.50	1.04	0.1523	0.7543	0.7889	0.6088	0.5172	0.3826
11	0.55	0.49	1.09	0.1387	0.7551	0.8047	0.6150	0.4982	0.3651
12	0.60	0.48	1.13	0.1255	0.7554	0.8210	0.6176	0.4838	0.3523
13	0.65	0.47	1.18	0.1127	0.7551	0.8381	0.6185	0.4668	0.3374
14	0.70	0.46	1.22	0.1004	0.7539	0.8558	0.6176	0.4539	0.3264
15	0.75	0.45	1.27	0.0887	0.7520	0.8743	0.6148	0.4386	0.3136
16	0.80	0.44	1.32	0.0776	0.7492	0.8936	0.6106	0.4243	0.3017
17	0.85	0.42	1.36	0.0574	0.7406	0.9348	0.6064	0.4134	0.2928
18	0.90	0.41	1.41	0.0485	0.7345	0.9568	0.6003	0.4005	0.2825
19	0.95	0.40	1.45	0.0404	0.7272	0.9799	0.5948	0.3906	0.2747
20	1.00	0.39	1.50	0.0331	0.7184	1.0040	0.5875	0.3789	0.2656

Figure 5.6. Utility weight curves for various values of q_{mr} utilising modified Lognormal model.

5.2.3 Other utility weight model

Other than the modified lognormal model, one plausible model that can fit into the utility weight function requirement is a simple Sine function,

$$(\tilde{w}_v)_{mr} = \phi(\sigma_v, q_{mr}) = \text{Sin}(\sigma_v + q_{mr}). \tag{5.18}$$

The parameters of interest, q_{m0} and q_{m1} are non-unique thus it does not share similar value with what was elicited for the Lognormal counterpart. Figure 5.8 illustrates a similar plot as in Figure 5.5 where the relation of the utility weights versus its corresponding parameter q_{mr} . The three curves of interest (σ_1 , σ_0 and σ_1) are used to identify the initial and the stationary value of q_{m0} and q_{m1} .

Figure 5.8 Sine model graphical plot of $(\tilde{w}_v)_{mr}$ vs q_{mr} for the three action of interest: σ_{-1} , σ_0 and σ_1

At the event of non-toxicity, the starting value, q_{m0}^* , is selected at regA where it is non-unique and by distance measure, the ideal choice of q_{m0}^* is set to '0' as the utility weight satisfy $(\tilde{w}_1)_{m0} > (\tilde{w}_0)_{m0} > (\tilde{w}_{-1})_{m0}$. This achieves the aim of giving an initial bias in escalating the dose rather than the action of maintaining or de-escalating the dose level.

In the outcome of toxicity, q_{m1}^* is elicited from regC. Similarly, by distance measure, the ideal choice of q_{m1}^* is 1.5 where the utility weight satisfies $(\tilde{w}_{-1})_{m1} > (\tilde{w}_0)_{m1} > (\tilde{w}_1)_{m1}$.

At the interval bound of the target probability, q_{m*}^{stn} revolves around regB where the utility weight satisfies $(\tilde{w}_0)_{mr} > (\tilde{w}_1)_{mr} \geq (\tilde{w}_{-1})_{mr}$ or $(\tilde{w}_0)_{mr} > (\tilde{w}_{-1})_{mr} \geq (\tilde{w}_1)_{mr}$. Similar to the Lognormal model, regB strictly lies in

between the lower and upper bound of $q_{m^*}^{stin}$ (denoted by q_{m0}^{stin} and q_{m1}^{stin} respectively).

These bounds are identified based on the condition that the utility of maintaining the dose level, $(\tilde{\omega}_0)_{mr}$ has a bias over $(\tilde{\omega}_1)_{mr}$ and $(\tilde{\omega}_{-1})_{mr}$.

q_{m0}^{stin} is derived from the intersecting curves of σ_0 and σ_1 ,

$$q_{m0}^{stin} = \text{ArcSin} \left(\sqrt{\frac{\text{Sin}^2 \sigma_0 - 2 \text{Sin} \sigma_0 \text{Sin} \sigma_1 + \text{Sin}^2 \sigma_1}{\text{Cos}^2 \sigma_0 - 2 \text{Cos} \sigma_0 \text{Cos} \sigma_1 + \text{Cos}^2 \sigma_1 + \text{Sin}^2 \sigma_0 - 2 \text{Sin} \sigma_0 \text{Sin} \sigma_1 + \text{Sin}^2 \sigma_1}} \right) \quad (5.19)$$

q_{m1}^{stin} , on the other hand, is derived from the intersecting curves of σ_{-1} and σ_0 ,

$$q_{m1}^{stin} = \text{ArcSin} \left(\sqrt{\frac{\text{Sin}^2 \sigma_{-1} - 2 \text{Sin} \sigma_{-1} \text{Sin} \sigma_0 + \text{Sin}^2 \sigma_0}{\text{Cos}^2 \sigma_{-1} - 2 \text{Cos} \sigma_{-1} \text{Cos} \sigma_0 + \text{Cos}^2 \sigma_0 + \text{Sin}^2 \sigma_{-1} - 2 \text{Sin} \sigma_{-1} \text{Sin} \sigma_0 + \text{Sin}^2 \sigma_0}} \right) \quad (5.20)$$

The stationary value of $q_{m^*}^{stin}$ can be defined via an intercepting point of σ_1 and σ_{-1} where the utility weight of $\left[(\tilde{\omega}_1)_{mr} = (\tilde{\omega}_{-1})_{mr} \right] \leq (\tilde{\omega}_0)_{mr}$ which is shown by,

$$q_{m^*}^{stin} = \text{ArcSin} \left(\sqrt{\frac{\text{Sin}^2 \sigma_{-1} - 2 \text{Sin} \sigma_{-1} \text{Sin} \sigma_1 + \text{Sin}^2 \sigma_1}{\text{Cos}^2 \sigma_{-1} - 2 \text{Cos} \sigma_{-1} \text{Cos} \sigma_1 + \text{Cos}^2 \sigma_1 + \text{Sin}^2 \sigma_{-1} - 2 \text{Sin} \sigma_{-1} \text{Sin} \sigma_1 + \text{Sin}^2 \sigma_1}} \right) \quad (5.21)$$

Since σ_{-1} , σ_0 and σ_1 are predefined fixed value of 0.33, 0.67 and 1.0 respectively, the initial and stationary parametric value can be defined as follows: $q_{m0}^* = 0$, $q_{m1}^* = 1.5$, $q_{m0}^{stin} = 0.74$, $q_{m1}^{stin} = 1.07$ and $q_{m^*}^{stin} = 0.9$. The utility weight curves at the initial stage of the study are shown in Figure 5.9. These two curves, as expected, demonstrates an initial bias that was required by the utility weight where

Non-toxicity $\implies \{(\tilde{\omega}_{-1})_{m0}=0.33\} < \{(\tilde{\omega}_0)_{m0}=0.62\} < \{(\tilde{\omega}_1)_{m0}=0.84\}.$

Toxicity $\implies \{(\tilde{\omega}_{-1})_{m1}=0.97\} > \{(\tilde{\omega}_0)_{m1}=0.83\} > \{(\tilde{\omega}_1)_{m1}=0.60\}.$

Figure 5.9 Utility weight curves associated to outcomes of (a) non-toxicity and (b) toxicity utilising the Sine model.

Table 5.3 and Figure 5.10 further illustrate how the Sine model will look like for various values of q_{mr} under similar condition where the target probability is set to 0.33.

Table 5.3 Utility weight values and its corresponding q_1 and q_2 parameter utilising Sine model

	PT_{ml}	q_{m0}	q_{m1}	$(\tilde{\omega}_{-1})_{m0}$	$(\tilde{\omega}_0)_{m0}$	$(\tilde{\omega}_1)_{m0}$	$(\tilde{\omega}_{-1})_{m1}$	$(\tilde{\omega}_0)_{m1}$	$(\tilde{\omega}_1)_{m1}$
1	0.05	0.12	1.43	0.4380	0.7080	0.9001	0.9815	0.8650	0.6530
2	0.10	0.25	1.36	0.5508	0.7936	0.9490	0.9925	0.8979	0.7044
3	0.15	0.37	1.28	0.6468	0.8607	0.9799	0.9991	0.9302	0.7589
4	0.20	0.49	1.21	0.7334	0.9155	0.9967	0.9996	0.9536	0.8026
5	0.25	0.61	1.14	0.8095	0.9571	0.9992	0.9953	0.9723	0.8423
6	0.30	0.74	1.07	0.8774	0.9861	0.9862	0.9860	0.9863	0.8780
7	0.35	0.90	0.90	0.9450	1.0000	0.9450	0.9450	1.0000	0.9450
8	0.40	0.69	1.10	0.8538	0.9772	0.9930	0.9906	0.9809	0.8632
9	0.45	0.63	1.13	0.8211	0.9627	0.9982	0.9942	0.9746	0.8477
10	0.50	0.58	1.16	0.7915	0.9479	0.9999	0.9970	0.9674	0.8314
11	0.55	0.52	1.20	0.7535	0.9271	0.9987	0.9993	0.9565	0.8085
12	0.60	0.46	1.23	0.7127	0.9030	0.9939	0.9999	0.9474	0.7905
13	0.65	0.40	1.27	0.6693	0.8756	0.9855	0.9995	0.9340	0.7653
14	0.70	0.35	1.30	0.6314	0.8503	0.9757	0.9980	0.9230	0.7457
15	0.75	0.29	1.33	0.5837	0.8173	0.9608	0.9957	0.9107	0.7254
16	0.80	0.23	1.37	0.5340	0.7813	0.9425	0.9912	0.8934	0.6973
17	0.85	0.17	1.40	0.4823	0.7424	0.9207	0.9870	0.8795	0.6755
18	0.90	0.12	1.43	0.4380	0.7080	0.9001	0.9815	0.8650	0.6530
19	0.95	0.06	1.47	0.3833	0.6644	0.8724	0.9731	0.8441	0.6222
20	1.00	0.00	1.50	0.3272	0.6184	0.8415	0.9657	0.8276	0.5985

Figure 5.10. Utility weight curves for various values of q_{mr} utilising Sine model.

5.3 Dose allocation

Each dose agent has an independent utility weight model. The expected utility of the decisions for each dose agent is based on its respective utility weight and the combined information on the probability of combination outcome of both agents. The overall recommendation for the combined dose agent can be expressed by the governing equation of the optimal action,

$$\text{Dose Agent 1} \left\{ \begin{array}{l} \text{Escalate1} = (\tilde{\omega}_1)_{10} \times \theta_{1j} + (\tilde{\omega}_1)_{10} \times \theta_{2j} + (\tilde{\omega}_1)_{11} \times \theta_{3j} + (\tilde{\omega}_1)_{11} \times \theta_{4j} \\ \text{Maintain1} = (\tilde{\omega}_0)_{10} \times \theta_{1j} + (\tilde{\omega}_0)_{10} \times \theta_{2j} + (\tilde{\omega}_0)_{11} \times \theta_{3j} + (\tilde{\omega}_0)_{11} \times \theta_{4j} \\ \text{De-escalate1} = (\tilde{\omega}_{-1})_{10} \times \theta_{1j} + (\tilde{\omega}_{-1})_{10} \times \theta_{2j} + (\tilde{\omega}_{-1})_{11} \times \theta_{3j} + (\tilde{\omega}_{-1})_{11} \times \theta_{4j} \end{array} \right. \quad (5.22)$$

$$\text{Dose Agent 2} \left\{ \begin{array}{l} \text{Escalate2} = (\tilde{\omega}_1)_{20} \times \theta_{1j} + (\tilde{\omega}_1)_{21} \times \theta_{2j} + (\tilde{\omega}_1)_{20} \times \theta_{3j} + (\tilde{\omega}_1)_{21} \times \theta_{4j} \\ \text{Maintain2} = (\tilde{\omega}_0)_{20} \times \theta_{1j} + (\tilde{\omega}_1)_{21} \times \theta_{2j} + (\tilde{\omega}_0)_{20} \times \theta_{3j} + (\tilde{\omega}_0)_{21} \times \theta_{4j} \\ \text{De-escalate2} = (\tilde{\omega}_{-1})_{20} \times \theta_{1j} + (\tilde{\omega}_{-1})_{21} \times \theta_{2j} + (\tilde{\omega}_{-1})_{20} \times \theta_{3j} + (\tilde{\omega}_{-1})_{21} \times \theta_{4j} \end{array} \right. \quad (5.23)$$

where the probability of combination outcomes is applied equally for both agents to allow synergism in the two agents.

The next combined dose is then allocated to the $(j+1)^{th}$ patient according to the action which maximises the expected utility of dose agents 1 and 2. The trial will only terminate when it satisfies the stopping criterion of each respective dose agent which is similar to a single dose agent.

5.4 Simulations

It is instructive to look at how this method can be first applied to a single dose agent, to get a feel for how things might work on a somewhat complex combination dose therapy. Two sub-sections will illustrate the simulation study for a single and a combination dose study.

5.4.1 Single dose agent study

5.4.1.1 Operating characteristics and comparison with BUD

In this section, the operating characteristics of BIUD are first illustrated using different explicit pseudo scenarios. Comparison study with BUD is also analysed under similar objective. It is not possible to cover all cases; however, the main goal is to present a reasonably wide spectrum of situations in order to get a feel for how things might work in practice.

Let's assume there are six dose levels and the target probability of toxicity is $PT_{tgt} = 0.33$.

For both the BUD and BIUD, the same prior is defined for each of the six dose levels. This can be represented by the pair of beta distribution parameters with values: $\beta = 0.95, 0.9, 0.8, 0.7, 0.5, 0.3$ for dose levels 1 to 6 respectively, and $\mu_l = 1 - \beta_l$ throughout. The utility weight model of Lognormal function (Equations 5.10) and Sine function (Equation 5.18) are used and the results will be displayed separately on two different tables based on each similar set of scenarios. The corresponding lower and upper bounds of the target probability of toxicity at 95% confidence interval is 0.3 and 0.36.

The simulations are based on 1000 repeated trials for six different scenarios. Each scenario is represented by the “pseudo” (hypothetical) probability of toxicity for each dose level, as shown in Table 5.4. In each of the first three scenarios, there exists a specific dose level which has very close proximity to the target level, whereas in the last three scenarios one can only find a level that is the closest to the target level. If an existing level were close to the target, one would expect the method to converge to that level. However, if the target lies midway between two available levels, then there is an equal chance of being allocated to those two levels. The method will thus

demonstrate an appropriate decision, as one would intuitively expect in this regard. The basis of the comparison between BUD and BIUD is based on the percentage of correct recommendation for each dose level and the mean total number of patient tested.

Table 5.4 Simulated data for comparison study

	d_1	d_2	d_3	d_4	d_5	d_6
Scenario I	0.05	0.10	0.20	0.30	0.50	0.70
Scenario II	0.10	0.15	0.30	0.40	0.55	0.75
Scenario III	0.30	0.40	0.50	0.60	0.75	0.90
Scenario IV	0.00	0.00	0.03	0.05	0.25	0.50
Scenario V	0.01	0.03	0.10	0.15	0.35	0.60
Scenario VI	0.20	0.90	0.90	0.90	0.90	0.90

All methods in the simulation start at the lowest dose. The maximum sample size of this simulation is restricted to 30.

The results from Table 5.5 show that BIUD generally out performs BUD in terms of a higher rate of recommending the MTD close to the target level and with fewer sample sizes. However, there is little difference between the two methods in terms of the final recommendation of the selected dose level. Being able to result in early termination of the trial, and hence a smaller sample size, is an expected advantage of BIUD over BUD. This is due to the interactive nature of the utility weight system. As far as the final recommendation is concerned, the ability of both the BUD and BIUD to react accordingly to toxicity outcomes shows that both methods provide similar recommendation with BIUD showing precedence in higher percentage rate. BIUD is conservative in term of having lower percentage of recommending higher dose as compared to BUD.

Table 5.5 Comparison between BUD and BIUD where modified Lognormal utility weight model is used.

Scenarios	Designs	Recommendation (%)						Mean total number of patient
		d_1	d_2	d_3	d_4	d_5	d_6	
I	BUD	0.0	0.9	33.1	41.9	22.0	2.1	17.2
	BIUD	0.1	0.8	37.9	50.7	10.5	0.0	15.9
II	BUD	0.9	20.9	39.2	37.9	1.1	0.0	18.7
	BIUD	1.3	18.0	47.9	32.0	0.8	0.0	16.7
III	BUD	66.9	31.7	0.9	0.5	0.0	0.0	16.6
	BIUD	72.1	26.4	1.2	0.3	0.0	0.0	16.2
IV	BUD	0.0	0.0	0.0	2.7	82.4	14.9	19.7
	BIUD	0.0	0.0	0.0	3.3	86.2	10.5	18.3
V	BUD	0.0	0.2	1.4	39.6	58.1	0.7	20.1
	BIUD	0.0	0.0	0.8	40.2	58.7	0.3	19.2
VI	BUD	97.0	3.0	0.0	0.0	0.0	0.0	15.3
	BIUD	98.8	1.2	0.0	0.0	0.0	0.0	14.6

For the utility weights model which uses Sine function, the results of Table 5.6 show that there is little deviation from the Lognormal model. This demonstrates robustness in the sensitivity of two different weight models which does not have much influence on the overall performance of the design. However, one would expect the result to be otherwise if a different model had been adopted, if it does not satisfy the requirement as stated in Section 5.2.1.

Table 5.6 Comparison between BUD and BIUD where Sine function of the utility weight model is used

Scenarios	Designs	Recommendation (%)						Mean total number of patient
		d_1	d_2	d_3	d_4	d_5	d_6	
I	BUD	0.0	0.9	33.1	41.9	22.0	2.1	17.2
	BIUD	0.0	1.1	39.7	48.1	11.1	0.0	16.5
II	BUD	0.9	20.9	39.2	37.9	1.1	0.0	18.7
	BIUD	0.9	17.7	48.2	32.2	1.0	0.0	17.1
III	BUD	66.9	31.7	0.9	0.5	0.0	0.0	16.6
	BIUD	70.0	27.1	1.8	1.1	0.0	0.0	16.0
IV	BUD	0.0	0.0	0.0	2.7	82.4	14.9	19.7
	BIUD	0.0	0.0	0.0	3.6	85.1	11.3	18.9
V	BUD	0.0	0.2	1.4	39.6	58.1	0.7	20.1
	BIUD	0.0	0.0	0.8	41.2	58.6	0.2	19.5
VI	BUD	97.0	3.0	0.0	0.0	0.0	0.0	15.3
	BIUD	98.1	1.9	0.0	0.0	0.0	0.0	14.1

5.4.1.2 Phase I clinical trial of Carboplatin and Docetaxel for advance non-small cell lung cancer: A practical example

This section further explores the methodology of BIUD on how it can be applied in a practical setting of a Phase I dose escalation trial of Carboplatin and Docetaxel for advanced non-small cell lung cancer [64]. The main purpose of this study is to determine the MTD of Carboplatin combined with a fixed dose of Docetaxel (60 mg/m²). The fixed dose of Docetaxel was the recommended dose for Phase II study based on Phase I studies done in Japan [65,66]. The dose finding studies done by Kazuo *et al* team [64] uses the Continual Reassessment Method [5]. A total of seven dose levels are considered in this study, and each escalating level is dependent on increasing the Carboplatin target area under the plasma concentration curve (*tAUC*) against a fixed dose of Docetaxel at 60 mg/m² (as shown in Table 5.7). No information on prior probabilities of toxicity was shown in Kazuo *et al*'s paper. Thus, let's assume these to be $\mu_1 = 0.05$, $\mu_2 = 0.1$, $\mu_3 = 0.2$, $\mu_4 = 0.3$, $\mu_5 = 0.4$, $\mu_6 = 0.5$, $\mu_7 = 0.7$. Kazuo *et al* made use of a logistic model as a dose-response relationship for the CRM design. BIUD, however, does not require a dose response curve and the probability distribution of toxicity outcome is based on posterior beta distribution as explained in Section 5.1.2. The utility weight model in this particular case is a Lognormal function. The target probability of toxicity is set at $PT_{tgt} = 0.5$ and the total sample size is prespecified at $N = 30$. The corresponding lower and upper bound of the target probability of toxicity at 95% confidence interval is 0.468 and 0.532.

Kazuo *et al* did not specify the size of cohort in their paper. Let assume this to be 1. For ethical reason, the starting dose is at the lowest level. The data for the BIUD simulation uses the information from the trial outcome [64] as shown in Table 5.7. The “true” MTD (according to Table 5.7) is dose level 6 with a probability of toxicity at 0.5.

Table 5.7 Dose level and true data of dose limiting toxicity [64]

Dose Level	tAUC of Carboplatin (mg/ml/min)	Docetaxel (mg/m ²)	No. of patients	DLT	Probability of toxicity
1	3	60	2	0	0.0
2	3.5	60	2	0	0.0
3	4	60	1	0	0.0
4	4.5	60	2	0	0.0
5	5	60	2	0	0.0
6	5.5	60	4	2	0.5
7	6	60	3	3	1.0

Table 5.8 shows the results where BIUD is being experimented for this trial. The simulation of the outcome y_j is based on the true probability of toxicity of Table 5.7. The experiment commences at d_1 , no toxic response is observed for the first patient. From the resulting expected utility calculated, BIUD assigns the 2nd patient to d_2 . Once again no response is observed. The design then continues to escalate from d_3 to d_6 where the first toxicity is experienced on the 6th patient. The dose level thus de-escalates to level 5. On the 8th patient, no DLT is experienced on dose level 6, however the probability of toxicity value is now 0.54. Thus the design recommends retaining the same dose for the next patient. However, patient 9 experiences non DLT effect, thus resulting in an escalation to dose level 7 before immediately de-escalating back to level 6 when DLT was registered at patient 10. For the remainder of the experiment, only level 6 is used; result of the 9th and final observation at level 6, was enough to bring the trial to a halt as shown by $\hat{\gamma}_6=0.92$ which exceeded the TTV value of 0.9. Dose level 6 is finally decided as the recommended dose for Phase II trial. This agrees with the conclusion of the CRM design of the original study [64] with the probability of toxicity analysed by BIUD for level 6 being 0.46 and that in level 7 being 0.77. These values are somewhat similar to those from the CRM used in the actual study except for level 7 where level 6 is 0.436 and that in level 7 is 0.53.

Table 5.8 Simulated trial under utility weight design

Patient j	Current dose d_i	PT_i	y_j	$U(A_1)$	$U(A_0)$	$U(A_{-1})$	Resulting action	$\hat{\gamma}_i$
1	d_1	0.04	0	0.6957	0.4323	0.2291	A_1	0.50 ,0.25,0.25,0.25,0.25,0.25,0.25
2	d_2	0.07	0	0.6764	0.4743	0.2734	A_1	0.40, 0.40 ,0.19,0.19,0.19,0.19,0.19
3	d_3	0.15	0	0.6414	0.5642	0.3665	A_1	0.33,0.33, 0.33 ,0.16,0.16,0.16,0.16
4	d_4	0.22	0	0.6130	0.6550	0.4640	A_1	0.28,0.28,0.28, 0.28 ,0.14,0.14,0.14
5	d_5	0.35	0	0.6210	0.5721	0.4217	A_1	0.25,0.25,0.25,0.25, 0.25 ,0.12,0.12
6	d_6	0.71	1	0.1897	0.5706	0.8797	A_{-1}	0.22,0.22,0.22,0.22,0.22, 0.22 ,0.11
7	d_5	0.29	0	0.6330	0.6070	0.4086	A_1	0.20,0.20,0.20,0.20, 0.28 ,0.20,0.10
8	d_6	0.54	0	0.5981	0.6127	0.4721	A_0	0.17,0.17,0.17,0.17,0.24, 0.24 ,0.09
9	d_6	0.40	0	0.6612	0.6503	0.4632	A_1	0.15,0.15,0.15,0.15,0.20, 0.30 ,0.08
10	d_7	0.77	1	0.4821	0.5432	0.8921	A_{-1}	0.13,0.13,0.13,0.13,0.18,0.27, 0.12
11	d_6	0.51	1	0.5218	0.6632	0.4237	A_0	0.12,0.12,0.12,0.12,0.16, 0.33 ,0.10
12	d_6	0.48	0	0.5408	0.6502	0.4532	A_0	0.11,0.11,0.11,0.11,0.14, 0.39 ,0.09
13	d_6	0.45	0	0.5521	0.6372	0.4617	A_0	0.10,0.10,0.10,0.10,0.13, 0.45 ,0.08
14	d_6	0.54	1	0.5028	0.6418	0.4921	A_0	0.09,0.09,0.09,0.09,0.12, 0.51 ,0.07
15	d_6	0.50	0	0.5667	0.6654	0.4419	A_0	0.08,0.08,0.08,0.08,0.11, 0.59 ,0.06
16	d_6	0.47	0	0.5556	0.6549	0.4721	A_0	0.07,0.07,0.07,0.07,0.10, 0.66 ,0.05
17	d_6	0.43	0	0.5781	0.6256	0.4818	A_0	0.07,0.07,0.07,0.07,0.09, 0.74 ,0.05
18	d_6	0.51	1	0.5626	0.6779	0.4754	A_0	0.06,0.06,0.06,0.06,0.08, 0.83 ,0.04
19	d_6	0.46	0	0.5729	0.6497	0.4656	terminate	0.05,0.05,0.05,0.05,0.07, 0.92 ,0.03

The next experiment uses 1000 simulation runs for the same case study to verify the accuracy of BIUD in recommending the correct dose level. Simultaneously, the study also conducts a sensitivity analysis by using various prior probability of toxicity setting.

Based on the same true data used in the earlier example, the simulation studies are carried out using three different settings for the prior probability. As depicted in Table 5.9, the first prior setting represents a more uniform monotonic ordering in the probability of toxicity from dose level 1 to 7 which is similar to the single trial study that was previously illustrated. The second setting follows the same value of the true probability of toxicity as shown in Table 5.7. The third setting, on the other hand, illustrates the situation in which the clinician may “under” predict the data of the trial where the prior probability of toxicity is less than what its true value actually is. The results from Table 5.9 show no major deviations in the recommended dose level regardless of any changes in the prior probability value. This suggests that BIUD is robust to variation in the elicited of prior probability of toxicity.

Table 5.9 Sensitivity analysis for the prior via variation in the variance value

		Dose level							Mean total number of patient
		d_1	d_2	d_3	d_4	d_5	d_6	d_7	
1	Prior prob. of toxicity	0.05	0.1	0.2	0.3	0.4	0.5	0.7	21.6
	Recommended dose(%)	0.0	0.0	0.0	0.2	15.1	81.1	3.6	
2	Prior prob. of toxicity	0.00	0.00	0.00	0.00	0.00	0.50	0.99	20.2
	Recommended dose(%)	0.0	0.0	0.0	0.1	12.5	84.1	3.2	
3	Prior prob. of toxicity	0.00	0.01	0.05	0.15	0.25	0.35	0.50	21.4
	Recommended dose(%)	0.0	0.0	0.0	0.3	12.9	83.9	2.9	

5.4.2 Combination dose study

Two simulated studies are used to illustrate the method. The study of interest concerns a combination of two drugs, 1 and 2 to be administered to patient with advanced tumour. Since most common dose limiting toxicities encountered are usually classified into Haematologic (H) and Non-Haematologic (NH) toxicities. There are therefore two types of DLT, DLT_H and DLT_{NH} corresponding to DLTs due to drug 1 and drug 2 respectively.

Six dose levels are assumed for both agents and the target probability of toxicity for 1 and 2 are respectively given as $PT_{1tgt} = 0.3$ and $PT_{2tgt} = 0.5$. The cohort size is 1 patient. The prior probabilities of toxicity for dose agent 1 and 2 are assumed respectively as,

$$\mu_{11}=0.05 \ \mu_{12}=0.10 \ \mu_{13}=0.20 \ \mu_{14}=0.30 \ \mu_{15}=0.50 \ \mu_{16}=0.70$$

$$\mu_{21}=0.05 \ \mu_{22}=0.10 \ \mu_{23}=0.20 \ \mu_{24}=0.30 \ \mu_{25}=0.50 \ \mu_{26}=0.70$$

The pseudo data of patient outcome uses the same set of values as the prior, thus the acceptable combination dose should revolved around dose 4 of agent 1 and dose 5 of agent 2.

Table 5.10 shows the results of the simulation in which for ethical reason the experimentation begin at dose 1 for both agents.

No toxic response of H and NH is observed for the first entered patient. According to the calculated decision choice of BIUD, it indicates that the second patient should be given dose level 2 for both agents and once again no response is observed. The optimal decision is to escalate to level 3 for both agents and thereafter it continues to escalate to level 4 after observing a non-toxic response. At level 4, the 4th patient experiences non-toxic response. Due to limited data point, the probability of toxicity is still very much influenced by its prior information therefore $PT_{14} = 0.22$ which is nearer to the interval bound of the target probability. The utility weight of dose agent 1 reacted by having a marginally equal value between the decision of escalating or maintaining the dose level. The design, being conservative, decides to maintain the dose level 4 of agent 1 while dose agent 2 will escalate to the next higher level. As for the 5th patient, Non-Haematologic toxicity is active; the optimal decision indicates that dose agent 1 will escalate one notch up to level 4 while level 5 of agent 2 de-escalates to a lower level. For the remainder of the experiment only level 4 and 5 of both agents are tried. Out of the 15 remaining patients, 5 Haematologic and Non-Haematologic toxicities responses are observed. The stopping criterion indicates that $\bar{\gamma}_{14} = 0.97$ and $\bar{\gamma}_{25} = 0.93$ which terminate the trial at dose level 4 for agent 1 and dose 5 for agent 2.

A number of other points are highlighted by the study of Table 5.10. At the initial stage of the experiment, the prior information at the probability of toxicity has a major effect on the decision making process of the method. Take for instance the 4th patient, despite non-toxic response the optimal decision was to maintain dose agent 1 and escalate dose agent 2. The probability of toxicity at that instance reflect the prior information where dose level 4 of agent 1 is close to the target probability of toxicity which consequently result in a decision to retain the same dose level for the next

patient. Subsequently, it then de-escalated back to dose level 4 when toxicity is present at agent 1 which highlight the sensitivity of the design to de-escalate due to toxicity.

Table 5.11 presents another simulation result where the target probability of toxicity for agent 1 and 2 are both fixed at 0.3. The acceptable choice of combined dose is level 4 for agent 1 and 2. Same as the earlier example, the first patient is treated at dose 1 for both agents. Thereafter, the method is trying to decide between a combination dose of 3 and 4 for agent 1 and 2. It finally settles for dose level 4 for both agents as the desired combined dose after 20 patients have been included.

These 2 examples are not too extreme and give some feeling as to what the design will anticipate in practice. More examples where both the desired agents can be located at two extreme levels are among those considered in the next section.

Table 5.10 Simulated trial under utility weight design where $PT_{1igt} = 0.3$ and $PT_{2igt} = 0.5$

Patient j	Current dose d_{1t}, d_{2t}	PT_{1t}, PT_{2t}	y_{1t}, y_{2t}	$E_k(A_{1,1})$	$E_k(A_{1,0})$	$E_k(A_{1,-1})$	$E_k(A_{2,1})$	$E_k(A_{2,0})$	$E_k(A_{2,-1})$	Resulting action		$\hat{\gamma}_{1t}$	$\hat{\gamma}_{2t}$
										Agent 1	Agent 2		
1	1, 1	0.04, 0.04	0, 0	0.599	0.441	0.324	0.588	0.411	0.301	↑	↑	0.50, 0.25, 0.25, 0.25, 0.25, 0.25	0.50, 0.25, 0.25, 0.25, 0.25, 0.25
2	2, 2	0.07, 0.08	0, 0	0.592	0.481	0.363	0.570	0.420	0.323	↑	↑	0.40, 0.40, 0.19, 0.19, 0.19, 0.19	0.40, 0.40, 0.19, 0.19, 0.19, 0.19
3	3, 3	0.15, 0.16	0, 0	0.568	0.501	0.372	0.557	0.438	0.361	↑	↑	0.33, 0.33, 0.33, 0.16, 0.16, 0.16	0.33, 0.33, 0.33, 0.16, 0.16, 0.16
4	4, 4	0.22, 0.23	0, 0	0.536	0.538	0.391	0.548	0.459	0.375	=	↑	0.28, 0.28, 0.28, 0.28, 0.14, 0.14	0.28, 0.28, 0.28, 0.28, 0.14, 0.14
5	4, 5	0.19, 0.64	0, 1	0.558	0.504	0.393	0.171	0.651	0.705	↑	↓	0.25, 0.25, 0.25, 0.30, 0.12, 0.12	0.25, 0.25, 0.25, 0.25, 0.25, 0.12
6	5, 4	0.66, 0.18	1, 0	0.217	0.608	0.788	0.561	0.439	0.367	↓	↑	0.23, 0.23, 0.23, 0.28, 0.14, 0.11	0.23, 0.23, 0.23, 0.23, 0.26, 0.23, 0.11
7	4, 5	0.36, 0.55	1, 0	0.457	0.768	0.513	0.457	0.607	0.514	=	=	0.21, 0.21, 0.21, 0.31, 0.13, 0.10	0.21, 0.21, 0.21, 0.24, 0.26, 0.10
8	4, 5	0.30, 0.46	0, 0	0.489	0.802	0.532	0.501	0.798	0.587	=	=	0.19, 0.19, 0.19, 0.34, 0.11, 0.09	0.19, 0.19, 0.19, 0.22, 0.32, 0.09
9	4, 5	0.25, 0.56	0, 1	0.501	0.687	0.478	0.512	0.650	0.463	=	=	0.17, 0.17, 0.17, 0.39, 0.10, 0.08	0.17, 0.17, 0.17, 0.20, 0.38, 0.08
10	4, 5	0.38, 0.45	1, 0	0.482	0.543	0.892	0.482	0.543	0.892	=	=	0.16, 0.16, 0.16, 0.45, 0.10, 0.07	0.16, 0.16, 0.16, 0.19, 0.44, 0.07
11	4, 5	0.30, 0.59	0, 1	0.467	0.713	0.623	0.473	0.728	0.611	=	=	0.15, 0.15, 0.15, 0.50, 0.09, 0.07	0.15, 0.15, 0.15, 0.17, 0.49, 0.07
12	4, 5	0.24, 0.50	0, 0	0.473	0.656	0.581	0.489	0.741	0.643	=	=	0.14, 0.14, 0.14, 0.56, 0.08, 0.06	0.14, 0.14, 0.14, 0.16, 0.55, 0.06
13	4, 5	0.36, 0.44	1, 0	0.489	0.704	0.612	0.438	0.672	0.631	=	=	0.13, 0.13, 0.13, 0.62, 0.07, 0.06	0.13, 0.13, 0.13, 0.15, 0.61, 0.06
14	4, 5	0.31, 0.39	0, 0	0.483	0.721	0.594	0.428	0.573	0.689	=	↓	0.12, 0.12, 0.12, 0.69, 0.07, 0.05	0.12, 0.12, 0.12, 0.14, 0.67, 0.05
15	4, 4	0.24, 0.14	0, 0	0.495	0.667	0.579	0.687	0.543	0.453	=	↑	0.11, 0.11, 0.11, 0.75, 0.06, 0.04	0.11, 0.11, 0.11, 0.15, 0.60, 0.04
16	4, 5	0.36, 0.52	1, 1	0.509	0.721	0.625	0.491	0.738	0.626	=	=	0.10, 0.10, 0.10, 0.80, 0.06, 0.04	0.10, 0.10, 0.10, 0.14, 0.66, 0.03
17	4, 5	0.30, 0.47	0, 0	0.498	0.715	0.631	0.503	0.712	0.603	=	=	0.09, 0.09, 0.09, 0.86, 0.05, 0.03	0.09, 0.09, 0.09, 0.13, 0.71, 0.03
18	4, 5	0.25, 0.58	0, 1	0.428	0.659	0.589	0.499	0.739	0.623	=	=	0.08, 0.08, 0.08, 0.90, 0.05, 0.03	0.08, 0.08, 0.08, 0.12, 0.77, 0.02
19	4, 5	0.34, 0.51	1, 0	0.465	0.649	0.572	0.479	0.642	0.576	=	=	0.07, 0.07, 0.07, 0.94, 0.04, 0.02	0.07, 0.07, 0.07, 0.11, 0.84, 0.02
20	4, 5	0.29, 0.47	0, 0	0.478	0.661	0.587	0.502	0.632	0.512	=	=	0.06, 0.06, 0.06, 0.96, 0.04, 0.02	0.06, 0.06, 0.06, 0.10, 0.89, 0.02
21	4, 5	0.25, 0.55	0, 1	0.506	0.641	0.578	0.491	0.623	0.539	terminate		0.05, 0.05, 0.05, 0.97, 0.03, 0.01	0.05, 0.05, 0.05, 0.09, 0.93, 0.01

Table 5.11 Simulated trial under utility weight design where $PT_{1tgt} = 0.3$ and $PT_{2tgt} = 0.3$

Patient j	Current dose d_{1t}, d_{2t}	PT_{1t}, PT_{2t}	y_{1t}, y_{2t}	$E(A_{1,1})$	$E(A_{1,0})$	$E(A_{1,-1})$	$E(A_{2,1})$	$E(A_{2,0})$	$E(A_{2,-1})$	Resulting action		$\hat{\gamma}_{1t}$	$\hat{\gamma}_{2t}$
										Agent 1	Agent 2		
1	1, 1	0.04, 0.04	0, 0	0.599	0.441	0.324	0.588	0.411	0.301	↑	↑	0.50, 0.25, 0.25, 0.25, 0.25, 0.25	0.50, 0.25, 0.25, 0.25, 0.25, 0.25
2	2, 2	0.08, 0.08	0, 0	0.592	0.481	0.363	0.573	0.420	0.320	↑	↑	0.40, 0.40, 0.19, 0.19, 0.19, 0.19	0.40, 0.40, 0.19, 0.19, 0.19, 0.19
3	3, 3	0.15, 0.15	0, 0	0.547	0.572	0.452	0.545	0.4350	0.361	=	↑	0.33, 0.33, 0.33, 0.16, 0.16, 0.16	0.33, 0.33, 0.33, 0.16, 0.16, 0.16
4	3, 4	0.11, 0.47	0, 1	0.576	0.525	0.406	0.236	0.614	0.737	↑	↓	0.28, 0.28, 0.30, 0.14, 0.14, 0.14	0.28, 0.28, 0.28, 0.28, 0.14, 0.14
5	4, 3	0.22, 0.11	0, 0	0.425	0.668	0.562	0.559	0.427	0.337	=	↑	0.25, 0.25, 0.27, 0.20, 0.12, 0.12	0.25, 0.25, 0.27, 0.25, 0.12, 0.12
6	4, 4	0.37, 0.39	1, 0	0.264	0.728	0.623	0.449	0.646	0.543	=	=	0.23, 0.23, 0.25, 0.24, 0.11, 0.11	0.23, 0.23, 0.25, 0.28, 0.11, 0.11
7	4, 4	0.31, 0.33	0, 0	0.374	0.589	0.492	0.324	0.714	0.637	=	=	0.21, 0.21, 0.23, 0.29, 0.10, 0.10	0.21, 0.21, 0.23, 0.34, 0.10, 0.10
8	4, 4	0.25, 0.27	0, 0	0.549	0.725	0.605	0.501	0.589	0.489	=	=	0.19, 0.19, 0.21, 0.35, 0.09, 0.09	0.19, 0.19, 0.21, 0.40, 0.09, 0.09
9	4, 4	0.36, 0.38	1, 1	0.451	0.701	0.623	0.478	0.725	0.591	=	=	0.17, 0.17, 0.19, 0.40, 0.08, 0.08	0.17, 0.17, 0.19, 0.46, 0.08, 0.08
10	4, 4	0.29, 0.31	0, 0	0.503	0.731	0.611	0.489	0.731	0.603	=	=	0.16, 0.16, 0.18, 0.46, 0.07, 0.07	0.16, 0.16, 0.17, 0.51, 0.07, 0.07
11	4, 4	0.25, 0.27	0, 0	0.511	0.712	0.604	0.501	0.711	0.582	=	=	0.15, 0.15, 0.17, 0.51, 0.07, 0.07	0.15, 0.15, 0.16, 0.59, 0.07, 0.07
12	4, 4	0.20, 0.23	0, 0	0.667	0.541	0.451	0.513	0.592	0.473	↑	=	0.14, 0.14, 0.16, 0.58, 0.06, 0.06	0.14, 0.14, 0.15, 0.65, 0.06, 0.06
13	5, 4	0.44, 0.38	1, 1	0.437	0.521	0.891	0.510	0.718	0.605	↓	=	0.13, 0.13, 0.15, 0.52, 0.09, 0.06	0.13, 0.13, 0.14, 0.70, 0.06, 0.06
14	4, 4	0.36, 0.33	1, 0	0.438	0.727	0.592	0.552	0.726	0.624	=	=	0.12, 0.12, 0.14, 0.59, 0.08, 0.05	0.12, 0.12, 0.13, 0.74, 0.05, 0.05
15	4, 4	0.30, 0.26	0, 0	0.443	0.717	0.561	0.485	0.673	0.584	=	=	0.11, 0.11, 0.13, 0.64, 0.07, 0.04	0.11, 0.11, 0.12, 0.79, 0.04, 0.04
16	4, 4	0.25, 0.38	0, 1	0.469	0.692	0.523	0.489	0.726	0.592	=	=	0.10, 0.10, 0.12, 0.69, 0.06, 0.04	0.10, 0.10, 0.11, 0.84, 0.04, 0.04
17	4, 4	0.36, 0.31	1, 0	0.489	0.722	0.572	0.506	0.719	0.600	=	=	0.09, 0.09, 0.11, 0.74, 0.05, 0.03	0.09, 0.09, 0.10, 0.89, 0.03, 0.03
18	4, 4	0.29, 0.26	0, 0	0.501	0.718	0.589	0.513	0.677	0.593	=	=	0.08, 0.08, 0.10, 0.79, 0.04, 0.03	0.08, 0.08, 0.09, 0.92, 0.03, 0.03
19	4, 4	0.23, 0.37	0, 1	0.589	0.675	0.507	0.467	0.734	0.648	=	=	0.07, 0.07, 0.09, 0.86, 0.04, 0.02	0.07, 0.07, 0.08, 0.95, 0.02, 0.02
20	4, 4	0.33, 0.31	1, 0	0.554	0.731	0.623	0.579	0.708	0.664	terminate		0.06, 0.06, 0.08, 0.90, 0.03, 0.02	0.06, 0.06, 0.07, 0.96, 0.02, 0.02

5.4.2.1 Comparison analysis: accessing the performance over many trials

In this section, different scenarios are considered to study the operating characteristics of the method in finding a suitable combination dose under different plausible extreme cases. These scenarios broadly describe all possibilities that encompassed what might be the true state of the nature in Phase I combination dose therapy trial. Similar to the earlier example, 6 ordered dose level are assumed for both agents. In all cases, the prior probabilities of toxicity follow exactly the same value from the example used in previous section.

Each of the following tables of results is based on estimates from 1000 simulation run. Using similar analysis from a single dose study, the simulation, in general, is trying to illustrate the final acceptable combination dose via the percentage of correct recommendation of each dose level for agent 1 and 2. The higher the percentage value would generally tell the final recommended combined dose. The simulation result also displays the mean number of toxicity of each respective dose agent and the final posterior probability of toxicity for each dose agent.

The results from Table 5.12 are based on 4 scenarios where by each situation reveals a specific combination dose which is exactly the target level. In the first scenario, the dose response data is the same as the prior probability of toxicity and this results in recommending an acceptable combination dose of 54.3% for dose agent 1 and 50.6% for dose agent 2. The maximum value of mean observed toxicities of each respective dose level is within an acceptable limit of less than 4 occurrence of toxicity. The posterior probability of toxicity for each dose agent shows little deviation from the dose response data. The remainder of this table gives results of the simulation based on other variations of the scenarios. In general, the results look very encouraging under a data, which has a normal dose-response relationship.

The next analysis in Table 5.13 considers how the method would be feasible under extreme scenarios. In scenario 1, the data of toxic probabilities of dose agent 1 vastly differentiates from the very lowest one which is at the appropriate level. The data of toxicity probabilities of dose agent 2 is kept similar to that of its *a priori* estimates. Not surprisingly, the recommended combined dose for agent 1 reaches a high point of 84.6% and 41.4% for agent 2. In scenario 2, the situation is reversed whereby dose agent 2 has high toxic probabilities apart from the lowest level. In scenario 3, both agents are kept at a high toxic probability between the higher dose and the lower dose level. The remainder of the table gives results of the simulation based on other extreme scenarios. In general, the results look encouraging with the method always recommending a high percentage value for the correct combined dose level.

Table 5.12 Simulated results of four hypothetical scenarios under normal conditions

	Dose agent 1						Dose agent 2					
	1	2	3	4	5	6	1	2	3	4	5	6
1	'true' probability of toxicity											
	Recommended dose (%)											
	1.70	5.50	16.20	54.30	22.00	0.30	5.36	1.82	8.49	23.70	50.61	10.02
	Mean number of toxicity of each level											
2	Posterior probability of toxicity											
	0.07	0.22	1.54	3.58	2.08	0.06	0.06	0.15	0.56	2.62	5.66	1.84
	0.04	0.07	0.12	0.31	0.58	0.71	0.03	0.09	0.17	0.27	0.55	0.81
	Mean number of toxicity of each level											
3	Posterior probability of toxicity											
	0.1	0.2	0.3	0.4	0.5	0.7	0.1	0.3	0.5	0.6	0.7	0.8
	5.2	13.8	42.7	32.6	5.5	0.2	4.70	19.7	50.88	20.10	4.61	0.01
	Mean number of toxicity of each level											
4	Posterior probability of toxicity											
	0.16	0.92	3.07	2.74	0.62	0.013	0.21	1.91	4.53	3.42	1.17	0.12
	0.05	0.10	0.25	0.46	0.58	0.70	0.05	0.22	0.44	0.61	0.70	0.77
	Mean number of toxicity of each level											
5	Posterior probability of toxicity											
	0.1	0.3	0.4	0.5	0.6	0.7	0.05	0.1	0.2	0.3	0.5	0.7
	7.2	51.7	31.4	8.40	1.1	0.0	5.31	3.12	6.34	25.0	49.0	11.1
	Mean number of toxicity of each level											
6	Posterior probability of toxicity											
	0.27	2.9	3.91	1.45	0.17	0.003	0.06	0.15	0.57	2.28	5.12	1.62
	0.06	0.26	0.42	0.55	0.59	0.70	0.02	0.1	0.16	0.27	0.53	0.76
	Mean number of toxicity of each level											
7	Posterior probability of toxicity											
	0.0	0.05	0.1	0.2	0.3	0.5	0.1	0.5	0.6	0.7	0.8	0.9
	0.0	3.02	10.28	24.7	51.3	10.7	8.9	65.8	19.2	5.4	0.7	0.0
	Mean number of toxicity of each level											
8	Posterior probability of toxicity											
	0.002	0.07	0.33	1.55	2.56	0.61	0.41	4.87	3.7	2.1	0.44	0.01
	0.03	0.07	0.10	0.17	0.39	0.67	0.10	0.45	0.56	0.64	0.68	0.77
	Mean number of toxicity of each level											

Table 5.13 Simulated results of four hypothetical scenarios under extreme conditions

	Dose agent 1						Dose agent 2					
	1	2	3	4	5	6	1	2	3	4	5	6
1												
'true' probability of toxicity	0.25	0.9	0.9	0.9	0.9	0.9	0.05	0.1	0.2	0.3	0.5	0.7
Recommended dose (%)	84.6	15.4	0.0	0.0	0.0	0.0	6.17	9.81	12.33	23.4	41.42	6.87
Mean number of toxicity of each level	2.45	5.04	0.15	0.02	0.0	0.0	0.06	0.16	0.34	1.31	2.94	0.88
Posterior probability of toxicity	0.27	0.51	0.52	0.53	0.6	0.72	0.03	0.10	0.19	0.29	0.55	0.77
2												
'true' probability of toxicity	0.05	0.1	0.2	0.3	0.5	0.7	0.1	0.5	0.9	0.9	0.9	0.9
Recommended dose (%)	1.80	11.4	17.1	49.8	19.3	0.00	38.7	55.9	5.4	0.00	0.00	0.00
Mean number of toxicity of each level	0.08	0.20	1.25	2.73	1.62	5.80	0.47	6.62	3.68	0.29	0.02	0.00
Posterior probability of toxicity	0.04	0.07	0.13	0.32	0.56	0.71	0.12	0.46	0.63	0.64	0.68	0.77
3												
'true' probability of toxicity	0.2	0.9	0.9	0.9	0.9	0.9	0.2	0.9	0.9	0.9	0.9	0.9
Recommended dose (%)	63.4	35.89	0.7	0.0	0.0	0.0	80.6	18.5	0.8	0.1	0.00	0.0
Mean number of toxicity of each level	0.87	3.25	0.12	0.0	0.0	0.0	0.88	3.41	0.21	0.05	0.0	0.0
Posterior probability of toxicity	0.16	0.41	0.43	0.45	0.54	0.70	0.21	0.43	0.43	0.46	0.55	0.71
4												
'true' probability of toxicity	0.0	0.0	0.0	0.05	0.3	0.9	0.0	0.0	0.0	0.05	0.3	0.9
Recommended dose (%)	0.0	0.0	0.0	8.1	78.3	13.6	0.0	0.0	1.0	12.8	52.1	34.1
Mean number of toxicity of each level	0.0	0.0	0.0	0.31	5.26	1.78	0.0	0.0	0.0	0.23	4.62	6.34
Posterior probability of toxicity	0.03	0.07	0.08	0.09	0.31	0.77	0.04	0.07	0.11	0.13	0.30	0.87

CHAPTER 6

Conclusions

6.1 Concluding remarks

Phase I trials are by their primary goal dose-finding studies. It is the very first study in which a new drug is administered to human subjects. The main objective is to determine a safe and maximum tolerated dose (MTD) of a new drug or combination of drugs. Phase I trial designs have arisen rather empirically without any strong statistical foundation. The three main characteristics of a Phase I trials consist of choosing a smaller sample size of patients, taking a longer time to observe the endpoint, and are strictly constrained by the ethical requirement in choosing doses conservatively. Therefore, the standard or classical methods that have been steadily adopted by most clinicians are designed to screen drugs quickly and identify a dose level that does not exhibit too much toxicity on a very small group of patients. These classical methods are not designed with the intention of producing accurate estimates of a target quartile. However, this is not to say that these designs do not have their place in accomplishing certain goals.

Other investigators [1,2,3] have applied an alternative route towards modifying and extending the classical designs such that the accuracy of determining the MTD can be improved. Methods such as the Storer's 2-stage design [2] and the Random walk rules have generalised several "up and down" designs [41,67] and provided a unifying theory for targeting any quartile of interest. These approaches are therefore easy to implement, intuitive to investigators and do not require complex computational algorithm.

For other designs, which have a stronger analytic foundation such as the continual reassessment method (CRM) and Bayesian decision theoretic approach are complicated to explain to non-statisticians and computationally challenging. CRM is beginning to gain popularity and trust amongst clinicians and therefore subsequently applied on an actual Phase I trial. The mathematical complexities in the design are still deemed as too “heavy” for most clinical investigators. Thus, the key to their usefulness lies in the packaging of the methods in user-friendly software that run quickly and are well documented. In the original design of CRM, the main attractive feature is the ability to have a better estimate of the MTD. In principle, the methodology allows one to combine any prior information available regarding the value of the MTD with subsequent data collected in the Phase I trial to obtain an updated estimate of the probability of toxicity. This will eventually cause CRM to select the dose level that has a probability of toxicity closest to its target quartile, although its practical performance should be evaluated in the small sample setting typical of Phase I trial. Despite these advantages, there is a trade-off which is common in most designs. The method has been criticised by several investigators in which the scepticism about the Bayesian approach is such that the choice of a prior distribution can be vague and does not reflect the initial condition of the dose-toxicity relationship. It is clear in the Phase I setting that the choice of a prior distribution can have a measurable effect on the estimate of MTD. However, O’Quigley [13] argued that the basic framework of CRM can easily be adapted to a non-Bayesian setting and can conform in practice more closely to traditional methods [6].

6.2 Contribution and limitation of the design

In this thesis, the motivation is to develop a phase I design that will also include an element of efficacy in determining an optimal dose based on the two outcomes.

The proposed idea is to develop a Bayesian decision methodology for dose escalation studies that are based on both observations of toxicity events and evidence of efficacy benefit. Unlike most other proposed Phase I design, where focus is on toxicity alone, the goal is to find the optimal dose accurately, while using a minimal number of subjects. Thall and Russell [12] proposed a two-endpoint design where it typically requires a relatively large number of patients to be used. It makes sense, as a higher sample size is required in determining the accuracy of the recommended dose when it involves two endpoints of interest. This however limits the design's practical value, especially in the area of oncology.

The fundamental principle of the proposed design is to find the optimal decision to be made at each sequential stage of the trial by maximising the expected value of the utility. Each patient's outcome updates the prior distribution for that dose level to give a posterior distribution that is combined with the utilities weight to give the optimal action. This iteration ensures that any decision made will be based on all available patient information. Due to the dual endpoint of the design, certain studies may focus on having one event which has precedence over the other for example an investigator may feel that toxicity is more important than efficacy as is usual in most Phase I trials in practice. This is because, in the area of oncology, a chosen optimal dose with little toxicity is not likely to have a major tumourogenic effect. Such a belief could be reflected in the utility defined where a different weight is given to a specific event of interest.

In the simulated example of Chapter 4, six dose levels are used as illustration. In practice however, any number of dose levels could be used. For example, 4 dose levels are used in the combination outcome example. Similarly, while a single patient enters the trial at each time, the design will work equally well given other cohort sizes.

In practice, the Dirichlet prior parameter, ρ , would have to be elicited from the investigator(s). These are obtained indirectly from the opinion on the probable expected values of each θ_i and the variances, $\text{var}[\theta_i]$, of the vague priors. The choice of ρ plays an important role in the way the design works. One believes that choosing a vague prior distribution is appropriate as it reflects the relative lack of information as would be expected when planning a Phase I trial and the values of ρ_i is constrained between 0 and 1. Should the investigator set these too high, say $\rho_i > 1$, then this will reduce the variance. In this case the Dirichlet prior may then dominate the data to such an extent, that the final optimal dose is dependent only on the prior and not the actual patient data. This is clearly undesirable.

With regard to defining the starting dose for the design the investigator may choose to use either of the two approaches of Section 4.4.2. An investigator who may be concerned with the prospect of potentially starting the first patient on too high a dose level (as may be the case if this dose level corresponds to the target probability) can use the preliminary trial approach. On the other hand, if the starting dose level corresponds to the level with prior probability closest to the target probability of toxicity, the first patient who enters the trial may be subjected to the high risk of experiencing severe toxicity. This is not desirable and its use has been criticised by Korn *et al* [7] and Goodman, Zahuruk and Piantadosi [8] in the original CRM [5] approach. However, this problem is not an issue with the maximum likelihood

version of the CRM [37]. In practice, the safety of the patient will be looked upon as the highest priority.

In the example for dual outcome (Section 4.5.2) where it is based on reference from O’Quigley’s [13] simulated example in HIV study, the starting dose associated with *a priori* parameters corresponding to the target probability vector of outcomes is selected. In this example it is clear that the target probability suggests dose level 3 to be the starting dose as it is nearest to the target value of success. However, this may not always be the case as the target probability of the outcome combinations may, for example, suggest different dose levels. In such a case one might propose the use of a distance measure between ρ parameter and the target probability vector.

In the simulation study, the performance of BUD was comparable to that of CRM and EWOC while SUDD was lagging behind in some of the scenarios. BUD uses two kinds of stopping criteria where BUD1 focuses on the proposed stopping rule while BUD2 uses an empirical stopping criterion of fixed sample size. For simplicity, CRM, EWOC, SUDD and BUD2 use the same empirical stopping rule with fixed sample size. An alternative stopping rule based on convergence of the recommended dose suggested by O’Quigley and Reiner [42] and O’Quigley [62] would seem like a better option to apply for CRM. However, this will not be easy to implement in SUDD. Nevertheless, the stopping rule of a fixed sample will still achieve a generalised comparison of the performance among the three designs. From the proposed stopping criterion, there is a trade-off between accuracy and stopping early as highlighted by the comparison study. BUD1 demonstrates that the stopping criterion could terminate the trial early but will then suffer a reduction in the current high percentage of recommendations at the MTD as compared with BUD2 which has a fixed sample size.

In the comparison study for dual end-point trial, BUD demonstrates competitiveness with the CRM II design. In addition, the methodology of BUD is direct and simple when switching from a single to a dual outcome design. The probability of outcomes in the proposed method is independent of the adjacent dose level. This reinforces the robustness of this method in dealing with any violation of monotonic constraint especially those that are found in the efficacy element as demonstrated in scenarios I – III of the dual end point study (Chapter 4, Table 4.18). It is noticed that the probability of efficacy does not increase monotonically with dose level. However, the results show that BUD is able to correctly recommend the dose level which has the highest probability of an efficacious and non-toxic outcome. Thus, in situations such as this, conventional methods such as the “3+3” method and SUDD may not be applicable. In a different situation, whereby toxicity might be regarded more important than efficacy, this can be reflected easily in the design via appropriate changes in the utility weight values used.

For a Phase I trial that involves a combination dose therapy, a modified BUD design (denoted as Bayesian Interactive Utility Design also known as BIUD) incorporates a parametric utility weight model that replaces the usual predefined utility weight value. This parametric weight model has an implicit relationship with the target probability of toxicity which affect the final choices of the overall optimal decision. To allow synergy, the toxicity outcome of each dose agent is combined to form a combination of outcomes. The choice of the utility weight model does not limit to the modified Lognormal function and the Sine function. Other model options can also be considered as long as it satisfies the condition as stated in Chapter 5. The functional aspect of q_{mr} aims at bridging a link between the toxicity outcome and the utility weight model. Therefore, it plays a significant connection for ensuring that the

utility weight is adjusted according to the probability of toxicity. In the simulation study, the comparison is made between BUD and BIUD. As expected, BIUD outperformed BUD in terms of a higher probability of obtaining the MTD closest to the target level and with fewer sample sizes. The reason for such good performance is due to the interactive nature of the utility weight system which allows the trial to converge easily to the target probability value and thus be able to terminate the trial early. In the simulation study for the combination dose study, the results conclude that BIUD produced a somewhat accurate estimate in finding an acceptable combination dose in which it is non-overlapping.

Similar to any established methodological phase I design; there are challenges in which the designs have not been able to overcome. These challenges which can complicate a phase I trial further are (1) ethical requirement to approach the MTD conservatively; (2) relative subjective opinion of the response (toxic / non toxic) or the different categorical level of toxicity that may affect a better decision of escalating or deescalating the dose level; (3) the heterogeneity of the subject population, and (4) the possible difficulty in classifying response due to early drop-out for reasons unrelated to toxicity; and lastly (5) challenge or difficulty in incorporating prior information when adopting a design with Bayesian context.

One of the challenges that BUD and BIUD are unable to resolve is: inclusion of the heterogeneity element in the overall decision making process. The proposed BUD and BIUD are designed based on the assumption that all patients are a homogeneous group. However, for patients in Phase I cancer clinical trials are a heterogeneous lot, differing in age, sex, race, etc. Depending on the nature of the drug, a single MTD might not be appropriate for all these patients. For example, the recommended dosage at a given iteration of the BUD method might not seem

appropriate for the next patient, an older female; given that all the previous patients (on whose responses dosage is based) are young males. Due to the constraint of limited sample size in Phase I cancer trial, it is not possible to categorically separate patients in terms of age, sex, race etc and this explains why all the clinical trial studies are solely based on homogeneous groups as the main aim is to obtain a safe and optimal dose at the shortest time possible with a minimal number of patients. The heterogeneity inclusion of the clinical trial study could be analysed in detail in the subsequent Phase II and III trials where a bigger sample size is possible.

Finally, this research emphasizes a broader approach in analysing phase I clinical trial study. The research aims to obtain a safe and optimal dose based on: (1) toxicity and efficacy outcome; (2) the opinion from the investigator by setting suitable (sometime intuitive) utility weight values. This new approach that uses the Bayesian decision theory will be useful for the clinician as a systematic tool to better analyse phase I clinical trial study and to provide a more accurate estimate of the optimal dose that looks at both toxicity and efficacy outcomes. Unlike other Phase I or I/II methods where the focus can only be either toxicity alone or an equal consideration of both toxicity and efficacy; the unique attribute of BUD and BIUD has an element of utility weight that allows the investigator to set preference between toxicity and efficacy. For example, in some trial study where efficacy is deemed to be more important than toxicity, the investigator can quantify it by setting a higher weight value on efficacy and a lower value on toxicity. BUD and BIUD have the option of also setting equal weigh on both toxicity and efficacy where they can be of equal footing. The implicit relationship of the utility with the target probability of outcomes enables the BUD to quickly converge to the optimal dose with a minimum number of patients. An improved version of BUD which is known as BIUD has incorporated an interactive

utility where it can be self adjusted according to the current probability of outcomes to recommend a more appropriate utility weight that will end the trial early as demonstrated by the simulated numerical results. The challenges faced by the design consists of two fundamental limitations which offers future research plans to work on.. One of the limitations is the assumption of homogeneity for all groups regardless of race, age and gender in the practice of a phase I clinical trial. The fact that cancer trial involves heterogeneity and one may argue that the MTD defined for one group may not be suitable for another group which is senior in age. On the other hand, if one looks at the current practice of a Phase I trial where the focus has never been about assigning different MTD or optimal dose for different groups of people and is mainly due to the constraint of not having enough sample size to do that. Another limitation is the theoretical build-up of BUD and BIUD when looking at dual outcomes is based on an assumption of independent between toxicity and efficacy. Biologically, toxicity and efficacy are non separable entities and have a unified human response after taking the dosage. The challenge of biologically integrating these two elements of toxicity and efficacy are actually beyond the scope of this research and will have to involve external parameter such as pharmacokinetic (PK) information in the Bayesian inference which can inherently complicate the overall computation of the current work. On the other hand, this is not to say that addition of the PK element is going to disrupt BUD and BIUD but rather it can definitely improve the current design further as ultimately it will provide a much more accurate estimate of the optimal dose as each patient's PK data is also subsequently updated in the Bayesian inference. In this aspect, this part of the research will be worthwhile to include as the future research plan to improve the design further. Thus, the current assumption of independence can

still stand for BUD and BIUD as indicated by Bryant-Day [73, 74] in their Phase I/II published work.

6.3 Prospective outlook

The work and results from this thesis focuses on the sequential and parametric aspects of the model to optimise a decision of recommending a correct dose level at a current stage until the optimal dose level is obtained..

In the context of MTD, it has been a general feeling that the target dose is the same for every member of the patient population, as no allowances are made for individual patient differences in susceptibility to treatment. The challenge now is to find a way such that it can estimate the probability distribution of MTD for a population of patient in a Phase I clinical trial. One of the probable ways to get over this problem is to use a parametric dose response function that models the probability of toxicity in each subject with two main effects: the toxicity effect of drug administered and the Pharmacokinetics (PK) measurement. The Bayesian approach provides the main scientific foundation for combining the information of each subject's toxicity data and PK measurement to estimate the posterior distribution of the MTD. The inter-patient variability of the toxic effect faced by the phase I trial is often a growing problem for Phase II study as the current estimate of MTD is always imprecise which will lead to more imprecise estimates in the Phase II trial study. The information provided by the proposed probability distribution of MTD helps to solve the discrepancies of inter-patient variability and provide more information of the dose due to the individualised PK measurement which will affect the decision of dose escalation.

In the aspect of introducing multiple endpoints to the CRM design, it is with interest to propose that this modified CRM can be used to analyse multiple endpoints as in the new decision theoretic design. The proposed idea is such that there are now 4 dimensional target probability of outcome vector (θ_1 , θ_2 , θ_3 and θ_4) associated with the optimal dose level. The prior will have a vector which is associated with each of the k dose levels. The posterior distribution of the outcome is obtained once the prior is updated. The process will continue till a stopping criterion is satisfied. The challenge at this point is the complexity of the method as four outcomes will generate multidimensional calculations which will make computation much more vigorous and in turn lower the efficiency of the original CRM concept. However, further work needs to be done to better understand and resolve these issues. To add on, informative prior distributions will be introduced rather than just work with vague priors.

In another research direction, it will look at how CRM can accommodate multiple levels of toxicity. In other words, instead of binary toxicity of 0 and 1, what happens if the outcome toxicity is graded from 0 to 10 where 0 is “no toxic response” and 10 representing “life threatening toxicity”. The idea is to associate each dose level with a mean toxicity score. This is unlike the original CRM design where each dose level is associated with a probability of toxicity value. The main goal is to find a dose level that has a toxicity level closest to the acceptable mean of the toxicity score (closest but not above). CRM methodology will be used to update the prior scores with the data which will be in the form of an observed toxicity score rather than just make an assumption as to whether there is toxicity or not. The next recommended dose should then be the one with a toxicity score closest to the desired score target.

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Appendix I

Fortran 90 source code for Dirichlet distribution:

```

integer, parameter :: sample_num = 11000
integer, parameter :: sample_max = sample_num
Integer n,iseed,number,sno,elem_i
Integer sample_i

Real a(4),x(4),x_sample(sample_max,4)
Real mean(4),variance(4)
Real total,Ave(4),approxerr(4)

!      WRITE (*,*) 'ENTER THE VALUE FOR THE FOUR PARAMETERS..'
!      READ 3, a(1),a(2),a(3),a(4)
! 3      FORMAT (4F4.2)

a(1) = 1.5
a(2) = 22.4
a(3) = 5.1
a(4) = 1.7

n = 4

WRITE (*, *) ' '
WRITE (*, *) 'Distribution parameters : '
WRITE (*, *) ' '
do elem_i=1,4
write(*,')(16,g14.6)'elem i,a(elem_i)
end do

call get_seed (iseed)

write(*,*)'random number seed ISEED=',iseed
write(*,*)'Number of samples is',sample_num

do sample_i = 1,sample_num

CALL dirichlet_sample (n,a,iseed,x)

  do elem_i=1,4
    x_sample(sample_i,elem_i)=x(elem_i)
  end do

end do

write (*,*) ' '
write (*,*) 'First few samples:'
write(*,*) ' '

  do sample_i=1,11000,1100
    write (*,')(16,4g14.6)'sample_i,x_sample(sample_i,1:4)
  end do

call rcol_mean(sample_max,sample_num,4,x_sample,mean)
call rcol_variance(sample_max,sample_num,4,x_sample,variance)

write(*,*)' '
write(*,*)'observed means,variances are:'

```

```

write(*,*) ' '

do elem_i=1,4
write(*,'(i6,g14.6)') elem_i,mean(elem_i),variance(elem_i)
end do

total=a(1)+a(2)+a(3)+a(4)
Ave(1)=a(1)/total
Ave(2)=a(2)/total
Ave(3)=a(3)/total
Ave(4)=a(4)/total

write(*,*) ' '
write(*,*) 'Expected Dirichlet value :'

do elem_i=1,4
write(*,'(i6,g14.6)') elem_i,Ave(elem_i)
end do

write(*,*) ' '
write(*,*) 'Approximated error of a sample size :'

do elem_i=1,4
approxerr(elem_i)={(mean(elem_i)-Ave(elem_i))/Ave(elem_i))*100
write(*,'(i6,g14.6)') elem_i,approxerr(elem_i)
end do

end

```

```

SUBROUTINE dirichlet_sample ( n, a, iseed, x )

```

```

!
!
integer n
real a(n)
integer i
integer iseed
real x(n)
real x_sum
!
CALL dirichlet_check ( n, a )

do i = 1, n
CALL gamma_sample ( a(i), 1.0, iseed, x(i) )
end do

!
!   Normalize the result.
!
CALL rvec_sum ( n, x, x_sum )

do i = 1, n
x(i) = x(i) / x_sum
end do

return
end

```

```

SUBROUTINE exponential_1_sample ( iseed, x )
!
!
  real a
  real b
  real cdf
  integer iseed
  real uniform_01_sample
  real x
  !
  cdf = uniform_01_sample ( iseed )

  a = 0.0
  b = 1.0
  CALL exponential_cdf_inv ( cdf, a, b, x )

  return

end

SUBROUTINE exponential_cdf_inv ( cdf, a, b, x )
!
  real a
  real b
  real cdf
  real x

  ! Check.
  !

  if ( b <= 0.0 ) then
    write ( *, * ) ' '
    write ( *, * ) 'EXPONENTIAL_CDF_INV - Fatal error!'
    write ( *, * ) ' B <= 0.0'
    stop
  end if

  if ( cdf < 0.0 .or. cdf > 1.0 ) then
    write ( *, * ) ' '
    write ( *, * ) 'EXPONENTIAL_CDF_INV - Fatal error!'
    write ( *, * ) ' CDF < 0 or 1 < CDF.'
    stop
  end if

  x = a - b * log ( 1.0 - cdf )
  return
end

SUBROUTINE normal_01_sample ( iseed, x )
!
!*****
!

```

```

      real, parameter :: PI =
3.14159265358979323846264338327950288419716939937510
      !
      integer iseed
      integer iset
      real uniform_01_sample
      real v1
      real v2
      real x
      real xsave
      !
      save iset
      save xsave

      data iset / 0 /
      data xsave / 0.0 /
      !
      if ( iset == 0 ) then

v1 = uniform_01_sample ( iseed )

      if ( v1 <= 0.0 ) then
write ( *, * ) ' '
write ( *, * ) 'NORMAL_01_SAMPLE - Fatal error!'
write ( *, * ) ' V1 <= 0.'
write ( *, * ) ' V1 = ', v1
write ( *, * ) ' ISEED = ', iseed
stop
end if

v2 = uniform_01_sample ( iseed )
if ( v2 <= 0.0 ) then
write ( *, * ) ' '
write ( *, * ) 'NORMAL_01_SAMPLE - Fatal error!'
write ( *, * ) ' V2 <= 0.'
write ( *, * ) ' V2 = ', v2
write ( *, * ) ' ISEED = ', iseed
stop
end if

x = sqrt ( - 2.0 * log ( v1 ) ) * cos ( 2.0 * PI * v2 )
xsave = sqrt ( - 2.0 * log ( v1 ) ) * sin ( 2.0 * PI * v2 )
iset = 1
else
x = xsave
iset = 0
end if
return
end

      SUBROUTINE dirichlet_check ( n, a )
      !
!*****
      !
      integer n
      !
      real a(n)
      integer i

```

```

logical positive
!
positive = .false.

do i = 1, n

  if ( a(i) < 0.0 ) then
    write ( *, * ) ' '
    write ( *, * ) 'DIRICHLET_CHECK - Fatal error!'
    write ( *, * ) ' A(I) < 0.'
    write ( *, * ) ' For I = ', i
    write ( *, * ) ' A(I) = ', a(i)
    stop
  else if ( a(i) > 0.0 ) then
    positive = .true.
  end if
end do
if ( .not. positive ) then
  write ( *, * ) ' '
  write ( *, * ) 'DIRICHLET_CHECK - Fatal error!'
  write ( *, * ) ' All parameters are zero!'
  stop
end if
return
end

```

```

SUBROUTINE gamma_sample ( a, b, iseed, x )
!
!

```

```

REAL, parameter :: a1 = 0.3333333
REAL, parameter :: a2 = -0.2500030
REAL, parameter :: a3 = 0.2000062
real, parameter :: a4 = -0.1662921
real, parameter :: a5 = 0.1423657
real, parameter :: a6 = -0.1367177
real, parameter :: a7 = 0.1233795
real, parameter :: e1 = 1.0
real, parameter :: e2 = 0.4999897
real, parameter :: e3 = 0.1668290
real, parameter :: e4 = 0.0407753
real, parameter :: e5 = 0.0102930
REAL, parameter :: q1 = 0.04166669
REAL, parameter :: q2 = 0.02083148
REAL, parameter :: q3 = 0.00801191
REAL, parameter :: q4 = 0.00144121
REAL, parameter :: q5 = -0.00007398
REAL, parameter :: q6 = 0.00024511
REAL, parameter :: q7 = 0.00024240
!

```

```

real a
real b
real bcoef
real c
real d
real e
integer iseed
real p
real q
real q0
real r

```



```

real s
real si
real s2
real t
real u
real uniform_01_sample
real v
real w
real x

!
! A < 1.
!

10 if ( a < 1.0 ) then
    continue
    p = ( 1.0 + 0.3678794 * a ) * uniform_01_sample ( iseed )

    CALL exponential_1_sample ( iseed, e )
    if ( p >= 1.0 ) then
        x = - log ( ( 1.0 + 0.3678794 * a - p ) / a )
        if ( e >= ( 1.0 - a ) * log ( x ) ) then
            x = x / b
            return
        end if
    else
        x = exp ( log ( p ) / a )
        if ( e >= x ) then
            x = x / b
            return
        end if
    end if
    go to 10

!
! 1 <= A.
!

else
    s2 = a - 0.5
    s = sqrt ( a - 0.5 )
    d = sqrt ( 32.0 ) - 12.0 * sqrt ( a - 0.5 )
    CALL normal_01_sample ( iseed, t )
    x = ( sqrt ( a - 0.5 ) + 0.5 * t ) ** 2
    if ( t >= 0.0 ) then
        x = x / b
        return
    end if
    u = uniform_01_sample ( iseed )
    if ( d * u <= t ** 3 ) then
        x = x / b
        return
    end if
    r = 1.0 / a
    q0 = ( ( ( ( ( q7 * r + q6 ) * r + q5 ) * r + q4 )
+      * r + q3 ) * r + q2 ) * r + q1 ) * r
    if ( a <= 3.686 ) then
        bcoef = 0.463 + s - 0.178 * s2
        si = 1.235
        c = 0.195 / s - 0.079 + 0.016 * s
    else if ( a <= 13.022 ) then
        bcoef = 1.654 + 0.0076 * s2
        si = 1.68 / s + 0.275
        c = 0.062 / s + 0.024
    else

```

```

      bcoef = 1.77
      si = 0.75
      c = 0.1515 / s
    end if

    if ( sqrt ( a - 0.5 ) + 0.5 * t > 0.0 ) then

      v = 0.5 * t / s
      if ( abs ( v ) > 0.25 ) then
        q = q0 - s * t + 0.25 * t**2 + 2.0 * s2 * log ( 1.0 + v )
      else
        q = q0 + 0.5 * t**2 * ( ( ( ( ( a7 * v + a6 ) * v + a5 )
+      * v + a4 ) * v + a3 ) * v + a2 ) * v + a1 ) * v
      end if

      if ( log ( 1.0 - u ) <= q ) then
        x = x / b
        return
      end if

    end if

20      continue

      CALL exponential_1_sample ( iseed, e )

      u = 2.0 * uniform_01_sample ( iseed ) - 1.0
      t = bcoef + sign ( si * e, u )

      if ( t >= - 0.7187449 ) then

        v = 0.5 * t / s

        if ( abs ( v ) > 0.25 ) then
          q = q0 - s * t + 0.25 * t**2 + 2.0 * s2 * log ( 1.0 + v )
        else
          q = q0 + 0.5 * t**2 * ( ( ( ( ( a7 * v + a6 ) * v + a5
+        * v + a4 ) * v + a3 ) * v + a2 ) * v + a1 ) * v

        end if
        if ( q > 0.0 ) then

          if ( q > 0.5 ) then
            w = exp ( q ) - 1.0
          else
            w = ( ( ( e5 * q + e4 ) * q + e3 ) * q + e2 ) *
+          q + e1 ) * q
          end if

          if ( c * abs ( u ) <= w * exp ( e - 0.5 * t**2 ) ) then
            x = ( s + 0.5 * t )**2 / b
            return
          end if

        end if

      end if

      go to 20

    end if

```

```

        end

        SUBROUTINE rvec_sum ( n, a, sum )
!
!*****
!
        integer n
!
        real a(n)
        integer i
        real sum
!
        sum = 0.0
        do i = 1, n
            sum = sum + a(i)
        end do

        return
        end

        FUNCTION uniform_01_sample ( iseed )
!
!
        integer, parameter :: ia = 16807
        integer, parameter :: ib15 = 32768
        integer, parameter :: ib16 = 65536
        integer, parameter :: ip = 2147483647
!
        integer iprbi
        integer iseed
        integer ixhi
        integer k
        integer leftlo
        integer loxa
        real uniform_01_sample
!
!       ! Don't let ISEED be 0.
!
        if ( iseed == 0 ) then
            iseed = ip
        end if

!
!       ! Get the 15 high order bits of ISEED.
!
        ixhi = iseed / ib16
!
!       ! Get the 16 low bits of ISEED and form the low
product.
!
        loxa = ( iseed - ixhi * ib16 ) * ia
!
!       ! Get the 15 high order bits of the low
product.
!
        leftlo = loxa / ib16
!
!       ! Form the 31 highest bits of the full
product.
!

```

```

        iprhi = ixhi * ia + leftlo
                                !
                                ! Get overflow past the 31st bit of full
product.                        !
                                !
        k = iprhi / ib15
                                !
                                ! Assemble all the parts and
presubtract IP. The parentheses are
                                ! essential.
                                !
        iseed = ( ( ( loxa - leftlo * ib16 )
+      - ip ) + ( iprhi - k * ib15 ) * ib16 ) + k
                                !
                                ! Add IP back in if necessary.
                                !
        if ( iseed < 0 ) then
        iseed = iseed + ip
        end if

                                !
                                ! Multiply by 1 / (2**31-
1).
                                !
        uniform_01_sample = real ( iseed ) * 4.656612875e-10
        return
        end

        subroutine get_seed ( iseed )
!
!
        integer, parameter :: I_MAX = 2147483647
!
        integer iseed
        double precision temp
        integer values(8)
        !
        character ( len = 10 ) time90
        character ( len = 8 ) today90
        character ( len = 5 ) zone
        !
        !
        call date_and_time ( today90, time90, zone, values )
        !
        !
        temp = 0.0

        temp = temp + dble ( values(2) - 1 ) / 11.0
        temp = temp + dble ( values(3) - 1 ) / 30.0
        temp = temp + dble ( values(5) ) / 23.0
        temp = temp + dble ( values(6) ) / 59.0
        temp = temp + dble ( values(7) ) / 59.0
        temp = temp + dble ( values(8) ) / 999.0
        temp = temp / 6.0

        if ( temp <= 0.0 ) then
        temp = 1.0 / 3.0
        else if ( temp >= 1.0 ) then
        temp = 2.0 / 3.0
        end if

```

```

iseed = int ( dble ( I_MAX ) * temp )
!
!
if ( iseed == 0 ) then
iseed = 1
end if

if ( iseed == I_MAX ) then
iseed = I_MAX - 1
end if

return
end

!
subroutine rcol_variance ( lda, m, n, a, variance )
integer lda
integer m
integer n

real a(lda,n)
integer i
integer j
real mean
real variance(n)
!
do j = 1, n

mean = 0.0
do i = 1, m
mean = mean + a(i,j)
end do
mean = mean / real ( m )

variance(j) = 0.0
do i = 1, m
variance(j) = variance(j) + ( a(i,j) - mean )**2
end do

if ( m > 1 ) then
variance(j) = variance(j) / real ( m - 1 )
else
variance(j) = 0.0
end if

end do

return
end
!
subroutine rcol_mean ( lda, m, n, a, mean )
integer lda
integer m
integer n

real a(lda,n)
integer i
integer j

```

```
real mean(n)
do j = 1, n
  mean(j) = 0.0
  do i = 1, m
    mean(j) = mean(j) + a(i,j)
  end do
  mean(j) = mean(j) / real ( m )
end do
return
end
```