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Escalation with Overdose Control using a Toxicity Score for Personalized Maximum Tolerated Dose in Phase I Clinical Trials

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Boston University
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Abstract

Escalation with Overdose Control using a Toxicity Score for Personalized Maximum Tolerated Dose in Phase I Clinical Trials

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The goal of many cancer Phase I clinical trials is to establish the level of dose toxicity tolerance in order to estimate the maximum tolerated dose (MTD) used for future trials. Common methods are divided into rule-based and model-based methods for dose escalation. The most popular method currently used is the 3+3 rule-based design. This method is simple and convenient, but has been shown to predict the true MTD in about 35% of trials. Model-based designs establish a dose response relationship that is equal to a pre-specified probability of dose limiting toxicity (DLT). Escalation with overdose control (EWOC) is a Bayesian adaptive design for selecting dose levels in cancer Phase I clinical trials while controlling the posterior probability of exceeding the MTD. We extend EWOC to incorporate a novel toxicity score with the addition of covariates for personalized medicine (EWOC-NETS with covariates). Under our extensions, we found significant differences in the estimated MTD between EWOC, EWOC-NETS, and EWOC-NETS with covariates for 4 simulated scenarios. Our developed method is also safer with respect to toxicity and overdosing.

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1 Introduction

Randomized clinical trials are often considered the gold standard in experimental testing of a newly developed drug or agent. The main goals of clinical trials are to determine safety and efficacy of the drug or agent in question. Clinical trials are divided into four phases, where each subsequent phase is only conducted after a "successful" trial in the previous phase. Success is often defined differently in each of the four phases. Phase I of a clinical trial is most often the first time that the agent or drug is tested in humans, and is only conducted with a prior belief of safety and efficacy from previous research in animal studies.

Treatments of cancer often involve highly toxic compounds that are aimed to kill or suppress the functions of cancerous cells and tumors. However, these treatment methods also impact normal functioning cells and organs, which determines the toxicity level of the treatment. In cancer clinical trials, many of the new agents or drugs are expected to be cytotoxic, defined as being toxic to both normal and abnormal functioning cells. The primary objective of a Phase I trial in cancer research is to determine the maximum tolerated dose (MTD) in a human cancer patient [1]. The MTD is clinically defined as the dose for which the probability of a dose-limiting toxicity (DLT) is equal to a pre-specified proportion. The DLT is defined as a medically unacceptable toxicity experienced at the MTD. In selecting the value of the pre-specified probability, this parameter is set relatively high (30-50%) when the DLT is considered to be correctable and non-fatal and extremely low when it is life threatening (5-10%). Although the main objective of a Phase I trial is to determine the MTD, secondary goals include early assessment of the agent's efficacy as well as the pharmacokinetics of the agent or drug [2].

Since a Phase I trial is the first usage of a proposed agent or drug in human

patients, Phase I trials act as a barrier and are extremely important to the drug or agent development. In contrast to other clinical trials, cancer clinical trials usually involve patients at advanced disease stages who have exhausted all other treatments, and therefore participating in the Phase I trials as a last resort. However, these trials are not conducted without ethical considerations, as novel cytotoxic agents can be extremely harmful even with no benefit to the patient. In addition, it is imperative that the Phase I trial is designed such that the number of patients treated at low, non-therapeutic doses and the number treated at severely toxic overdoses is minimized.

1.1 Rule-Based Methods in Phase I Trials

Phase I trials are deemed to be the most effective when one is able to accurately determine the MTD in the fewest patients. This effectively assigns the maximum number of patients in the Phase I cohort to doses at or around the MTD. Cancer Phase I clinical trials are typically dose-escalation designs, where a cohort of patients (typically 1-3 patients per cohort) is given a dose level and observed for the presence of a DLT. The next cohort of patients is then given a dose level that is dependent on the results of the previous cohort. Currently the simplest and still most commonly used method for estimating the MTD is the 3+3 design, which guides up and down dosing decisions using a modified Fibonacci series to determine the dose level for each cohort. The Fibonacci series ensures that dose increases are larger at earlier doses, and smaller at later doses. The 3+3 design is an example of a rule-based method, which utilizes pre-specified rules based on observations of the DLT from the clinical data to determine the MTD. Although simple and easy to implement, the 3+3 design often treats a large proportion of patients at an inefficacious dose. As a result, the use of the 3+3 design may incorrectly fail to reject the null hypothesis, resulting in a Type II Error. The new agent or drug is then deemed ineffective when a benefit is

actually present [3].

There have been several extensions to the original 3+3 design, including the best of five design and accelerated titration design. Both of these designs attempt to increase the rate of dose escalation in order to be more aggressive in the assignment of dose levels. However, these methods are also not advantageous in that their accuracy is not guaranteed and can result in misleading conclusions. Specifically, rule based designs are inefficient in establishing the dose that meets the specified target toxicity level (TTL), which is the probability that patients that will experience a DLT in the trial. In addition, rule based designs only utilize information from the previous cohort, and ignore all data previously accumulated. Lastly, the final MTD and recommended dose for Phase II trials is selected from a range of pre-specified dose levels, rather than a continuous set of dose levels bounded by a minimum and maximum dose [4]. Regardless, rule based designs are the most commonly used due to their simplicity. They do not require special software and are often conservative with dose escalation. However, more advanced and accurate methods are needed to more accurately determine the MTD, which can be accomplished with model-based designs.

1.2 Model-Based Methods in Phase I Trials

Model-based designs use statistical models that actively seek a dose level to produce the pre-specified probability of a DLT or TTL. These models utilize toxicity data from all enrolled patients in order to construct a more precise dose-toxicity curve. The general concept of all model-based designs is based off the TTL, where the dose-toxicity curve is constantly updated using Bayesian methods. The posterior distribution of the MTD is evaluated to identify the dose that is closest to the TTL,

resulting in the estimated MTD.

The first model-based design was developed by O'Quigley et al. in 1996 and was named the continual reassessment method (CRM). The basic methodology of the CRM consists of constantly updating of the dose-toxicity level after each patient using the posterior distribution of the MTD. The next patient is then given the dose that is currently the best estimated MTD [5]. Therefore, the main difference of model-based methods from rule-based methods is the utilization of all patient data in updating the MTD. The CRM was first developed under a two parameter logistic model, although other models including the hyperbolic tangent and power model have also been considered. In addition to the model, a TTL is chosen to indicate the overall probability for a DLT in each patient. Using the TTL and a specified model, the MTD can be solved for analytically using patient data. The CRM utilizes a Bayesian approach with priors set for the MTD and probability of a DLT at the lowest dose. The CRM has been shown to select the correct dose approximately 45% of the time in several simulated scenarios, where the 3+3 design only selected the correct dose approximately 35% of the time. The CRM is also flexible in that its operating characteristics can be easily optimized, such as continuous dose levels, varying cohort sizes, and complex stopping rules [6].

1.3 Escalation with Overdose Control (EWOC)

Escalation with Overdose Control (EWOC) is a Bayesian adaptive design for selecting doses in cancer Phase I trials. The main difference between the CRM and EWOC is the implementation of a safety measure, defined as controlling the posterior probability of exceeding the maximum tolerated dose. Essentially, EWOC is constructed such that the probability of overdosing a patient based on current data

is equal to or less than a pre-specified value known as the feasibility bound. This feasibility bound is usually selected based on prior beliefs of toxicity [7]. Trials commence at the lowest dose level and escalate based on the responses of the patients, eventually converging to the maximum tolerated dose as rapidly as possible through the logistic model. It is expected that EWOC will only under-dose patients at the beginning of the trial, and that most patients past a certain time will be treated at doses sufficiently close to the MTD. Similar to other model-based designs, the underlying assumption is a monotonically increasing function of dose and toxicity, indicating that agents are more toxic as the dose levels increase. Previous studies have shown that EWOC was able to treat 55% of patients at optimal dose levels, compared to only 35% for rule-based designs [4]. While these numbers are similar when comparing EWOC and the CRM, EWOC is considered to be much safer as a result of the added feasibility bound [8].

While EWOC is advantageous to previously developed methods in both rule and model based designs, there are limitations that hinder the full effectiveness of the method. In all previous methods and EWOC, the outcome of a patient is measured as a binary response. Therefore, toxicity is either present (dose-limiting toxicity) or absent [9]. However, toxicities vary in their severity, ranging from nausea and vomiting to lymphedema and severe damage of one's organs. The National Cancer Institute (NCI) labels toxicities at six levels, with levels 1-4 indicating non-DLT toxicities and levels 5-6 indicating a DLT toxicity. In the binary case, levels 1-4 are treated equally as non-DLT and levels 5-6 treated equally as DLT. In reality, the toxicity levels of non-DLT/DLT are not the same and should be considered different when using modeling techniques.

The binary toxicity outcome is also limited in that we only observe a single maximum toxicity. In reality, a subject in Phase I could experience multiple toxicities,

including multiple non-DLT toxicites and multiple DLT toxicities. Since all toxicity data are regularly collected in a Phase I trial, the extra data does not complicate or burden the actual trial. By changing the binary measure for the DLT and incorporating the number of toxicities, all data gathered in a trial can now be used to better estimate the next dose level and the overall MTD.

1.4 Extensions and Goals

In addressing the limitations of a binary response, Chen et al. proposed a novel toxicity scoring system to characterize toxicity as a continuous response [10]. The proposed score is a function of the highest level of toxicity and all other toxicities, with a weight parameter to vary the importance of the non-maximum toxicities. This function therefore takes into account all available toxicity data, including the levels of toxicity and number of toxicities [11]. The extended score is comprised of a Normalized Equivalent Toxicity Score (NETS) for each patient and a Target Normalized Equivalent Toxicity Score (TNETS) which is analogous to the TTL. Therefore, EWOC must be reparameterized with the incorporation of NETS in the logistic model instead of a binary indicator for DLT, forming EWOC-NETS [10].

In cancer research and the development of cancer drugs, personalized medicine has recently become an extremely hot topic. Specifically, it is of great interest whether certain cancer drugs are more or less effective/toxic in a subgroup of patients. We can first begin modeling personalized medicine in the form of covariates that are added into the logistic model. In the simplest, we consider a single discrete covariate, where one subgroup of subjects exhibits a particular gene and the other group does not. This covariate can then be added into the model in order to assess whether the dose levels significantly change between these two groups. Therefore, the estimated MTD

is adjusted for the covariate rather than the overall MTD. Continuous covariates can also be considered, such as the patient's weight, percent of tumor growth, or time from cancer diagnosis. These covariates could potentially be important factors in assessing the adjusted MTD, which could differ vastly to the overall MTD.

These two extensions can be added onto the originally developed EWOC model in order to increase the accuracy of the model for the MTD. We believe that this is the first method to incorporate covariates into EWOC, ultimately forming the method EWOC-NETS with Covariates. To assess the performance of this model, simulation studies will be conducted between EWOC-NETS and EWOC-NETS with Covariates provided under multiple scenarios.

The thesis is organized as follows: 1) the proposed methods and simulation scenarios are described in Section 2; 2) the results of the simulations and performance of the models are shown in Section 3; and 3) a thorough discussion of the practicality and limitations of the developed methods are discussed in Section 4.

2 Methods

This section is comprised of multiple parts. First, we introduce EWOC and its formulation originally developed by Babb in 1998 [7]. We then describe the continuous scoring system for toxicity (NETS) developed by Chen in 2013 [10]. Following NETS, we combine EWOC and NETS to form EWOC-NETS and show how to reparameterize the model. We then introduce both discrete and continuous covariates in order to form the final model EWOC-NETS with covariates. Finally, we discuss our simulations.

2.1 EWOC

Under EWOC, the dose level and toxicity relationship is modeled as follows:

$$P(DLT|Dose = x) = F(\beta_0 + \beta_1 x) \tag{1}$$

where x is the specified dose level, F is a specified distribution function (tolerance distribution), and β_0 and β_1 are unknown parameters. β_1 is assumed to be greater than 0 such that the probability of the DLT is a monotonic increasing function of dose level. Since the distribution function is assumed to be logistic, we can write the model as:

$$P(DLT|Dose = x) = \frac{e^{\beta_0+\beta_1 x}}{1 + e^{\beta_0+\beta_1 x}} \tag{2}$$

The probability of the DLT at the minimum dose x_{min} is denoted by ρ_0, with y_i as a binary indicator for the DLT of the i^{th} patient. Utilizing all patient data, given by $D_n = \{(x_i, y_i), i = 1, ..., n\}$, the likelihood function of β_0, β_1 given D_n is:

$$L(\beta_0, \beta_1|D_n) = \prod_{i=1}^{n} logit^{-1}(\beta_0 + \beta_1 x_i)^{y_i}[1 - logit^{-1}(\beta_0 + \beta_1 x_i)]^{1-y_i} \tag{3}$$

Prior information is incorporated about β_0, β_1 through a prior probability density function $h(\beta_0, \beta_1)$. Using Bayes Theorem, the joint posterior distribution of (β_0, β_1) given the data D_k is then:

$$P(\beta_0, \beta_1|D_n) = \frac{L(\beta_0, \beta_1|D_n)h(\beta_0, \beta_1)}{\int\int L(x, y|D_n)h(x, y)dxdy} \tag{4}$$

We now must solve for our unknown parameters in terms of clinically meaningful terms. The marginal posterior distributions of the MTD can be derived with a basic transformation using ρ_0 and the MTD γ. The TTL is given by θ and can be modeled with the following equations:

$$logit(\rho_0) = \beta_0 + \beta_1 x_{min} \tag{5}$$

$$logit(\theta) = \beta_0 + \beta_1 \gamma \tag{6}$$

In equations (5) and (6), the probability of the DLT at the minimum dose ρ_0 and θ are written in terms of the minimum dose and MTD. These two equations can be solved simultaneously for the β coefficients, and can be expressed as:

$$f_1(\rho_0, \gamma) = \beta_0 = \frac{1}{\gamma - x_{min}}[\gamma logit(\rho_0) - x_{min} logit(\theta)] \tag{7}$$

$$f_2(\rho_0, \gamma) = \beta_1 = \frac{1}{\gamma - x_{min}}[logit(\theta) - logit(\rho_0)] \tag{8}$$

We can now easily interpret the β coefficients as they are now functions of the MTD γ, the pre-specified highest acceptable toxicity level θ, and the probability of the DLT at the lowest dose level ρ_0. Using these new parameterized terms, we can now write the joint posterior probability density function of (ρ_0, γ) given D_n using Bayes Theorem as follows:

$$P(\rho_0, \gamma | D_n) = \frac{L(f_1(\rho_0, \gamma), f_2(\rho_0, \gamma) | D_k) h(f_1(\rho_0, \gamma), f_2(\rho_0, \gamma)) f_2(\rho_0, \gamma)}{\int \int L(x, y | D_n) h(x, y) dx dy} \tag{9}$$

Utilizing this joint posterior probability density function, the marginal posterior PDF of the MTD γ given D_n as:

$$\pi(\gamma|D_n) = \int\int P(\rho_0, \gamma|D_n)d\rho_0 \tag{10}$$

To determine the MTD, we can integrate the marginal posterior PDF in (10) to obtain the marginal posterior CDF of the MTD given D_n:

$$\pi_k(z) = \int_{x_{min}}^{z} \pi(\gamma|D_n)d\gamma, x \in [x_{min}, x_{max}] \tag{11}$$

The escalation scheme for EWOC then is described using the following notation. There is an amount of data D_n after enrolling n patients in the trial, where y_i is the indicator for the DLT for the i^{th} patient. The prior distribution for ρ and γ is given by $h(\rho_0, \gamma)$ and bounded by $[0, \theta]$ and $[x_{min}, x_{max}]$. The first cohort of patients receive $x = x_{min}$ and if $y_1 = 0$ (absence of the DLT), then the i^{th} patient will receive the dose $x_n = \pi_{n-1}^{-1}(\alpha)$, where α is the feasibility bound. EWOC is constructed such that the minimum and first dose is assumed to be safe. Dose escalation will only proceed in the absence of the DLT. In the presence of the DLT, dose de-escalation following the posterior distribution of γ will be calculated for the next cohort of patients. Estimators of the final overall MTD include the mean, median, or mode of the marginal posterior PDF of the MTD.

2.2 NETS

Chen et. al. developed a novel toxicity score in order to quantitatively characterize each DLT experienced by a patient [10]. As described in the previous section, the

original methodology of EWOC only incorporated binary outcomes, which does not take into account the levels of the DLT. Using the NCI's guidelines for assessing the DLT, Chen developed the following score (NETS) [10].

$$S_i = \frac{1}{6}\left[G_{i,max} - 1 + \frac{exp\{\alpha + \beta(\sum_{j=1}^{J_i} \frac{w_{i,j}G_{i,j}}{G_{i,max}} - 1)\}}{1 + exp\{\alpha + \beta(\sum_{j=1}^{J_i} \frac{w_{i,j}G_{i,j}}{G_{i,max}} - 1)\}}\right] \tag{12}$$

The adjusted grade of the jth toxicity is given by $G_{i,j},\ j = 1, ..., J_i$ for the ith patient. The value of $G_{i,j}$ ranges from 0 to 6 and is defined based on the severity of the DLT defined by the NCI:

$$G_{i,j} = \begin{cases} 0, & \text{if Grade 0 Toxicity} \\ 1, & \text{if Grade 1 Toxicity} \\ 2, & \text{if Grade 2 Toxicity} \\ 3, & \text{if Grade 3 Toxicity non DLT} \\ 4, & \text{if Grade 4 Toxicity non DLT} \\ 5, & \text{if Grade 3 DLT} \\ 6, & \text{if Grade 4 DLT} \end{cases} \tag{13}$$

The score for toxicity S_i (NETS) defined in (12) is dependent on the toxic events observed $G_{i,j}$ and the maximum toxicity level $G_{i,max} = max(G_{i,j}, j = 1, ..., J_i)$. As seen in the equation, the maximum toxicity experienced is heavily weighted in the determination of S_i. The parameter $w_{i,j}$ is the correlation between the toxicities of i^{th} patient, and is usually predefined based on whether there is a belief that the agent can cause related symptoms. The weight is increased with decreasing correlation. In the event of complete independence between toxicities, the weight is set equal to 1.

The β parameter is a slope parameter that controls the rate of increase of S_i. If β is set equal to 0, then the equation is reduced to the event of only considering the most toxic event. The value of β is usually selected based on how much we value toxicities that are not the most toxic. The parameter α in (12) assesses the difference between the most toxic event and other toxic events. Chen has suggested that α be set to -2 for EWOC [10].

2.3 EWOC-NETS

In combining Escalation with Overdose Control (EWOC) with NETS to utilize all toxicity data available, we must redefine certain parameters. The target toxicity level (TTL) defined by θ is analogously defined to be a pre-specified target normalized equivalent toxicity score (TNETS). Therefore, the formal definition of TNETS is the score at which the MTD γ will converge. For consistency, we define θ to be TNETS in this section.

The estimate of θ is defined to be a summation of the mid-range NETS score m_l and the target probability corresponding to the maximum adjusted grade l toxicity (p_l). Therefore, $\hat{\theta}$ is defined as:

$$\hat{\theta} = \sum_{l=0}^{6} m_l p_l \tag{14}$$

Similar to EWOC from Section 2.1, we model toxicity in the form of a logistic model. Previously, EWOC modeled toxicity as a binary result. We can now model the NETS using a similar model:

$$S_i = F(\beta_0 + \beta_1 x_i) \tag{15}$$

where S_i is the corresponding NETS for the i^{th} patient and F is the specified distribution function, assumed to be logistic. Following EWOC, we can model S_i and dose level as follows:

$$logit(S_i|Dose = x_i) = \frac{logit(\rho_0)(\gamma - x_i) + logit(\hat{\theta})(x_i - x_{min})}{\gamma - x_{min}} \tag{16}$$

Analogous to EWOC, ρ_0 here is a measure of toxicity in terms of the NETS when a patient is treated at the minimum dose x_{min} and γ is the maximum tolerated dose corresponding to the target highest acceptable toxicity severity level in term of NETS, $\hat{\theta}$. In the construction of the likelihood function for ρ_0 and γ, we can consider NETS to be viewed as fractional events. Therefore, a quasi-Bernoulli likelihood can be constructed using a family of "quasi" probability distributions that can provide a simple way to incorporate NETS into parametric models. "Quasi" distributions that belong to linear exponential families exhibit quasi-maximum likelihood estimates that are strongly consistent. A quasi-Bernoulli likelihood was first implemented in the CRM and is also utilized here. Consider once again the data available D_n after observing n patients. The quasi-Bernoulli likelihood of (ρ_0, γ) given D_n is then given by:

$$\begin{aligned}\widetilde{L}(\rho_0, \gamma|D_k) = \prod_{i=1}^{n} &\Big[exp\Big\{\frac{logit(\rho_0)(\gamma - x_i) + logit(\hat{\theta})(x_i - x_{min})}{\gamma - x_{min}}\Big\}\Big]^{S_i} \\ &\times \Big[1 + exp\Big\{\frac{logit(\rho_0)(\gamma - x_i) + logit(\hat{\theta})(x_i - x_{min})}{\gamma - x_{min}}\Big\}\Big]^{1-S_i}\end{aligned} \tag{17}$$

where S_i is the NETS of the ith patient and is assumed to have a variance structure given by

$$Var(S_i) = \mu_{S_i|X_i}(1 - \mu_{S_i|X_i}) \tag{18}$$

where $\mu_{S_i|X_i}$ is the mean of generated scores conditional on dose level x_i for the i^{th} patient, assuming $S_1, ..., S_N$ are mutually independent. The quasi-maximum likelihood estimate from (17) is strongly consistent following the Bernoulli distribution. Therefore, this likelihood can be applied to update the posterior distribution of (γ, ρ_0).

The posterior distribution of γ can be constructed through sampling using the Metropolis-Hastings algorithm. Assume that $h(\gamma, \rho_0)$ be a prior distribution bounded by $[0, \theta] \times [x_{min}, x_{max}]$. The quasi-Bernoulli posterior distribution of (γ, ρ_0) given D_n following Bayes Theorem is then:

$$\widetilde{\pi}(\gamma, \rho_0|D_n) = \frac{\widetilde{L}(\rho_0, \gamma|D_n)h(\gamma, \rho_0)}{\int\int_{[0,\theta]\times[x_{min},x_{max}]} \widetilde{L}(\rho_0, \gamma|D_n)h(\gamma, \rho_0)d\rho_0 d\gamma} \tag{19}$$

The marginal posterior $\widetilde{\pi_n}(\gamma)$ can be updated using a MCMC sampler with a specific quantile level α.

2.4 EWOC-NETS with a Discrete Covariate

With the inclusion of a discrete covariate C to assess patient characteristics, the MTD's for each group could vary based on this covariate. We begin with the assumption that the MTD γ_1 for group 1 is different than the MTD γ_2 for group 2. The logistic model for this additional covariate modeling NETS and dose is:

$$\theta = F(\beta_0 + \beta_1\gamma_{max} + \delta) \tag{20}$$

where F is a logistic function and δ is an unknown parameter for the covariate. The MTD is solved such that the TNETS is equal to θ. Assume that ρ_1 is the average NETS (ANETS) for group 1 and ρ_2 be the ANETS for group 2. The model can then be rewritten as:

$$logit(\rho_1) = \beta_0 + \beta_1 x_{min} \tag{21}$$

$$logit(\rho_2) = \beta_0 + \beta_1 x_{min} + \delta \tag{22}$$

$$logit(\theta) = \beta_0 + \beta_1\gamma_2 + \delta \tag{23}$$

Similar to the reparameterization of EWOC and EWOC-NETS, the unknown parameters can be expressed in terms of γ, ρ_1, and ρ_2:

$$\beta_0 = logit(\rho_1) - \frac{logit(\theta) - logit(\rho_2)}{\gamma_2 - x_{min}} x_{min} \tag{24}$$

$$\beta_1 = \frac{logit(\theta) - logit(\rho_2)}{\gamma_2 - x_{min}} \tag{25}$$

$$\delta = logit(\rho_2) - logit(\rho_1) \tag{26}$$

$$\gamma_1 = \gamma_2 + \frac{\delta}{\beta_1} \tag{27}$$

The MTD for group 1 is given by γ_1 and is a function of γ_2 and the regression parameters. Utilizing these regression parameters, the model can now be set up to determine individual MTD's for each group of patients.

2.5 EWOC-NETS with a Continuous Covariate

For patient characteristics such as weight, age, and gene expression levels, a continuous covariate can be added into the model to determine if there are drastic differences in the MTD. The model is constructed similar to EWOC-NETS with discrete covariates, but the reparameterization of the unknown parameters is different. Given a continuous covariate Z that is hypothesized to increase when the MTD increases, the following equations are constructed:

$$logit(\theta) = \beta_0 + \beta_1\gamma_2 + \delta z_{max} \tag{28}$$

$$logit(\rho_1) = \beta_0 + \beta_1 x_{min} + \delta z_{min} \tag{29}$$

$$logit(\rho_2) = \beta_0 + \beta_1 x_{min} + \delta z_{max} \tag{30}$$

where z_{max} and z_{min} are the highest and lowest possible values for the specific covariate. We define γ_2 as the MTD at covariate level z_{max}. The variable ρ_1 then measures the toxicity level for patients receiving the lowest dose level at the smallest value for the covariate Z. Similarily, ρ_2 measures the toxicity level for patients receiving the lowest dose level at the highest value for Z. The reparametrization of the unknown parameters using equations (28)-(30) can then be shown to be:

$$\beta_0 = logit(\rho_1) - \frac{logit(\theta) - logit(\rho_2)}{\gamma_2 - x_{min}} x_{min} - \frac{logit(\rho_2) - logit(\rho_1)}{z_{max} - z_{min}} z_{max} \tag{31}$$

$$\beta_1 = \frac{logit(\theta) - logit(\rho_2)}{\gamma_2 - x_{min}} \tag{32}$$

$$\delta = \frac{logit(\rho_2) - logit(\rho_1)}{z_{max} - z_{min}} \tag{33}$$

Given a continuous covariate, the model can be constructed based on the toxicities at x_{min}, ρ_1 and ρ_2, and the covariate levels between z_{min} and z_{max}. Essentially, our model attempts to determine the MTD's for covariate values at z_{min} and z_{max}.

2.6 Simulation Settings and Methods

In order to assess the efficacy and accuracy of the newly developed models, we conduct simulation studies using EWOC-NETS as the framework to incorporate patient characteristics and biomarkers. In this thesis, three models will be considered, with the original EWOC-NETS framework as the baseline model. This original framework does not consider covariates in the estimation of the MTD, but patient covariate data are still used. Therefore, the posterior distribution of the MTD is the overall MTD, rather than subsets of MTD based on the covariates. The three models considered are: 1) model 1 is the original EWOC-NETS without covariates; 2) model 2 is EWOC-NETS plus a discrete covariate {C = 0, 1}; and 3) model 3 is EWOC-NETS plus a continuous covariate {Z $\sim$ (0,1)}:

$$\text{Model 1} : logit(\mu_{S_i|x_i}) = \beta_0 + \beta_1 X_i \tag{34}$$

$$\text{Model 2} : logit(\mu_{S_i|x_i,c_i}) = \beta_0 + \beta_1 X_i + \delta C_i \tag{35}$$

$$\text{Model 3} : logit(\mu_{S_i|x_i,z_i}) = \beta_0 + \beta_1 X_i + \delta Z_i \tag{36}$$

The reparameterization for $(\beta_0, \beta_1, \delta)$ are all different between the three models and are defined in the previous subsections. The advantage of EWOC-NETS with covariates is evaluated by comparing models 2 and 3 to model 1, and assessed using bias, standard error, and mean square error.

Comparisons between the three models will be evaluated under a total of 8 scenarios, 4 for the discrete case and 4 for the continuous case. In the discrete case, we define a covariate C that can either be 0 or 1, and thus creating two separate groups. We assume that group 1 is defined to be when C = 0 and is expected to have a lower MTD, γ_1. Group 2 is defined to be when C = 1 and is expected to have the higher MTD, γ_2. Therefore, in the calculation of ANETS, we expect ρ_2 to be lower than ρ_1. Specifically, we consider a continuous set of doses between $[0, 1]$, satisfying $x_{min} = 0$ and $x_{max} = 1$. Therefore, the values of γ_1 and γ_2 must between be $[0, 1]$. Specifically, we specify the true value of γ_2 to be 0.5 for all 4 scenarios. The true values of γ_1 are set to 0.27, 0.38, 0.44, and 0.5 for the four scenarios. The value of ρ_2 is set to .05 for all four scenarios. Using equations (24)-(26), ρ_1 is solved to be 0.163, 0.096, 0.0689, and 0.05 for the γ_1 values of 0.27, 0.38, 0.44, and 0.5, respectively. Since we also assume group 2 will have the higher MTD and is generally considered safer, we always enroll a patient with C = 1 to start the trial. Table 1 provides the details of the simulation study for EWOC-NETS with a discrete covariate.

Scenario	True Effect	MTD, C = 0	MTD, C = 1
1	Yes	0.27	0.50
2	Yes	0.38	0.50
3	Yes	0.44	0.50
4	No	0.50	0.50

Table 1: Scenarios for Discrete Covariate

In the model considering a continuous covariate Z, we follow the same scenarios described in the discrete covariate model. Specifically, we assume that MTD increases with respect to Z, where z_{max} is considered to be the highest value for the covariate and z_{min} is considered to be the lowest value for the covariate in the Phase I trial. Thus, z_{max} is analogous to γ_2 and z_{min} is analogous to γ_1 in the same way as the discrete case. The continuous covariate follows $Z \sim U(0, 1)$ and is randomly generated for each patient. Table 2 provides the details of the simulation study for EWOC-NETS

with a continuous covariate.

Scenario	True Effect	MTD, Z = 0	MTD, Z = 1
1	Yes	0.27	0.50
2	Yes	0.38	0.50
3	Yes	0.44	0.50
4	No	0.50	0.50

Table 2: Scenarios for Continuous Covariates

In each trial, we simulate 30 patients and provide a dose based on a constantly updated posterior distribution constructed from all previous data. The target NETS (TNETS), θ, is set to be 0.476 for all scenarios, analogous to a target toxicity level of 33%. The feasibility bound α is set to begin at 0.25, and increases by 0.05 up to a maximum of 0.5. The feasibility bound only increases if the current information on the MTD increases from the previous patient, and cannot exceed 0.5. The trial will always start with the lowest dose level, and the recommended dose level for the next patient is the α^{th} percentile of the marginal posterior distribution of the MTD, adjusting for the covariate.

Each scenario of each model is simulated 250 times and evaluated for its performance. Specifically, we are interested in the following 4 criteria: 1) whether the estimated MTD is a personalized MTD; 2) the measure of bias from the simulation; 3) the mean square error (MSE) of $\hat{\gamma}_2$ and $\hat{\gamma}_1$; and 4) the standard error of $\hat{\gamma}_2$ and $\hat{\gamma}_1$.

The marginal posterior distributions of $(\gamma_2, \rho_1, \rho_2)$ are constructed by direct sampling using the Metropolis-Hastings algorithm. The original sampling of EWOC is done in R using the RJAGS package. EWOC-NETS and EWOC-NETS with covariates are sampled from a user constructed MCMC sampler. We also specify non-informative prior distributions of $(\gamma_2, \rho_1, \rho_2)$, where $\gamma_2 \sim U(x_{min}, x_{min})$, $\rho_1 \sim U(0, \theta)$, and $\rho_2 \sim U(0, \theta)$. For each patient, we sample a total of 5,000 iterations with a burn in period of 1,000 iterations. The final posterior MTD is assumed to be the mean of the trials. We assess trace plots, histograms, and other diagnostic plots to assess the convergence of $(\gamma_2, \rho_1, \rho_2)$.

3 Results

In this section, we analyze the results of our simulation studies. We first assess the performance of Model 1, followed by Model 2 with a discrete covariate, and then Model 3 with a continuous covariate.

3.1 Discrete Covariate

The results of Model 1 are given in Table 3 with the overall mean MTD, bias, standard error, and MSE. In Model 1 of the first scenario, which has the largest true difference in MTD between the two groups, the mean MTD over a cohort of 30 patients is 0.355 over 250 simulations. The bias for group 2 (C = 1, true MTD = 0.50) is -.145, while the bias for group 1 (C = 0, true MTD = 0.27) is .085 in this first scenario. From this single scenario, we can see that the original EWOC-NETS produces a large bias in the overall MTD. Therefore, the bias is large in both directions for the first scenario.

In scenarios 2 and 3 for Model 1 where the MTD of group 1 is closer to the MTD of group 2, the overall mean MTD from the simulation study increases. However, this MTD is still an overall mean and does not distinguish between the two groups (Figure 3). In scenario 4 where both group 1 and 2 have a true MTD of 0.5, indicating that the covariate has no real effect, we can see that EWOC-NETS quite accurately estimates the true MTD. In addition, the MSE for both groups is largest when the two MTD's are vastly different, indicating that Model 1 is much less robust when there is a large true difference. Standard errors are relatively similar for all scenarios, suggesting that no scenario was heavily influenced by error or convergence.

Scenario	Mean	SE	Bias, C=0	MSE, C=0	Bias, C=1	MSE, C=1
1	0.355	0.053	0.085	0.010	-0.145	0.024
2	0.446	0.051	0.066	0.007	-0.054	0.005
3	0.485	0.055	0.045	0.005	-0.015	0.003
4	0.518	0.062	0.018	0.004	0.018	0.004

Table 3: Simulation Results of Model 1, No Discrete Covariate Considerations

In Model 2 where we consider the effect of the discrete covariate, simulation results show two separate MTD's, one for group 1 and another for group 2. In scenario 1, Model 2 is able to accurately estimate the MTD of group 1 (C = 0, true MTD = 0.27), with an estimate of .241 (Table 4). The bias of scenario 1 for this group is -.029, indicating that this model correctly identified a unique MTD for this group. For group 2 (C = 1, true MTD = 0.50) in scenario 1, the MTD was estimated to be 0.439, also indicating an close estimate of the true MTD for group 1 (Table 5). In general, while Model 2 does not precisely estimate the MTD's for each group (all with varying biases), the model is able to correctly identify the scenarios where the covariate has a true effect (scenarios 1, 2, & 3). Standard errors for both groups decrease from scenarios 1 to 4, suggesting that the point estimate of the MTD is more precise in the latter scenarios. From the simulation results under a discrete covariate, Model 2 is more robust and accurate in estimating the true MTD compared to Model 1.

Table 6 gives the overdosing rates for Model 1 and Model 2. In general, Model 2 is much less likely to overdose patients from the true MTD. While the overdosing rates for scenarios 3 and 4 appear to be rather high, this is actually due to the continuous dose levels, where doses given to patients were only slightly larger than the true MTD. Table 7 gives the average NETS between Model 1 and 2, with subjects in Model 2 having expected NETS compared to Model 1 ($\theta = .476$).

Scenario	True Value	Mean	SE	Bias	MSE
1	0.27	0.241	0.064	-0.029	0.005
2	0.38	0.371	0.061	-0.009	0.004
3	0.44	0.459	0.059	0.019	0.004
4	0.50	0.527	0.056	0.027	0.004

Table 4: Simulation Results of Model 2 for Group 1, C = 0

Scenario	True Value	Mean	SE	Bias	MSE
1	0.50	0.439	0.061	-0.061	0.007
2	0.50	0.460	0.056	-0.040	0.005
3	0.50	0.484	0.053	-0.016	0.003
4	0.50	0.492	0.049	-0.008	0.003

Table 5: Simulation Results of Model 2 for Group 2, C = 1

Scenario	Model 1	Model 2
1	0.368	0.167
2	0.417	0.309
3	0.455	0.395
4	0.495	0.485

Table 6: Overdosing Rates between Model 1 and Model 2

Scenario	Model 1	Model 2
1	0.573	0.497
2	0.524	0.480
3	0.489	0.472
4	0.471	0.462

Table 7: Average Nets between Model 1 and Model 2

3.2 Continuous Covariate

Under a continuous covariate Z, simulation results for Model 1 that does not consider the value of the covariate in the likelihood function is given in Figure 1. In this figure, all four scenarios described earlier are plotted to show the relationship between MTD and Z under Model 1. This relationship is constructed with all data points from 250 simulations, and fitted in R using the Lowess function for a polynomial fit. In general, we do not see a monotonically increasing relationship between MTD and Z as we would expect. In scenarios 2-4, the relationship seems to increase and decrease randomly with respect to the covariate Z. The four lines indicate that there is no obvious pattern in the relationship between MTD and Z. Table 8 gives the results of Model 1 for $Z = 0$ when the covariate is at its minimum value, and for $Z = 1$ when the covariate is at its maximum value. Overall, the mean MTD ranges from 0.341 to 0.515 for scenarios 1 to 4. Standard errors are consistent among the four scenarios and range from 0.053 to 0.60. Both the bias and MSE decrease from scenario 1 to scenario 4, suggesting that Model 1 is only accurate when the two groups (Z = 0, Z = 1) have equal MTDs. In the event of personalized medicine in scenarios 1, 2 and 3, Model 1 is unable to identify a difference in the MTDs.

Scenario	Mean	SE	Bias, Z=0	MSE, Z=0	Bias, Z=1	MSE, Z=1
1	0.381	0.055	0.111	0.008	-0.119	0.028
2	0.435	0.057	0.056	0.006	-0.065	0.007
3	0.469	0.053	0.029	0.004	-0.031	0.004
4	0.515	0.060	0.015	0.004	0.015	0.004

Table 8: Simulation Results of Model 1, No Continuous Covariate Considerations

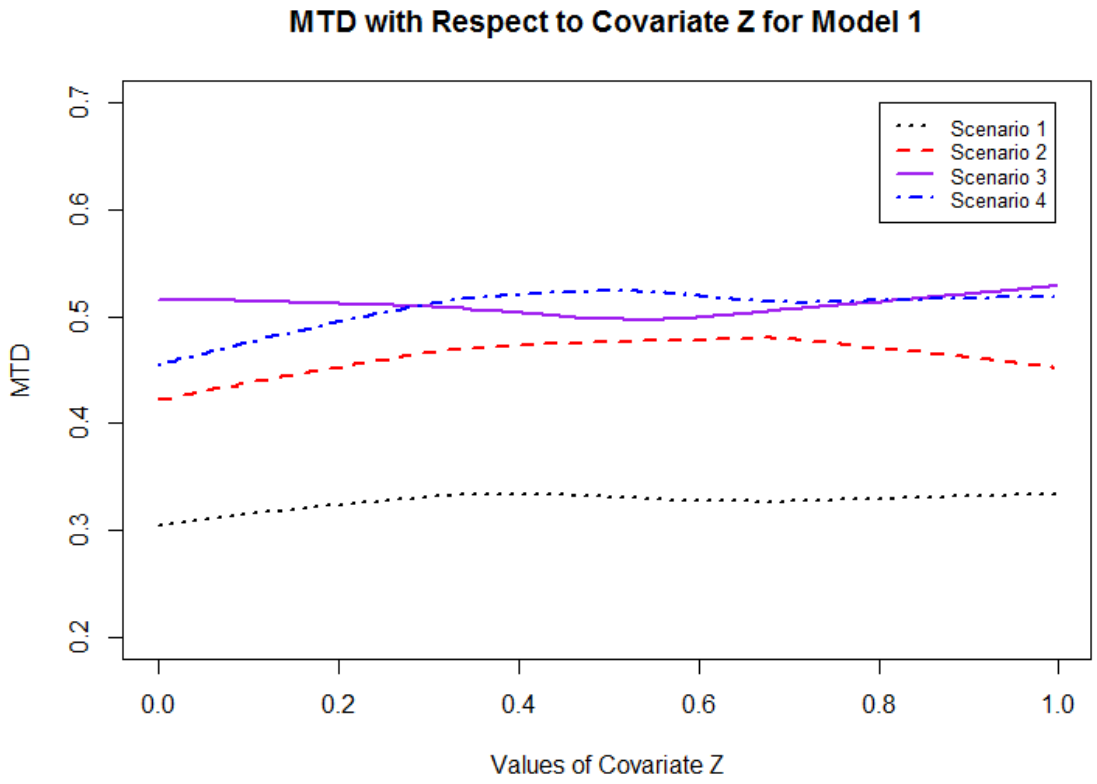

Figure 1: Relationship between MTD and Z under Model 1

The results of Model 3 with a continuous covariate are given in Figure 2. Similar to the previous figure, the four lines estimate the relationship between MTD and Z for all four scenarios. In scenario 1, there is an obvious increase in MTD with respect to Z, which is the expected result. Scenarios 2 and 3 also show a monotonically increasing relationship between MTD and Z. In scenario 4 under a null effect in the covariate, we see that the overall fit is completely constant with no change in slope. Comparing Figures 1 and 2, the MTD changes drastically under Model 3 compared to the MTD under Model 1.

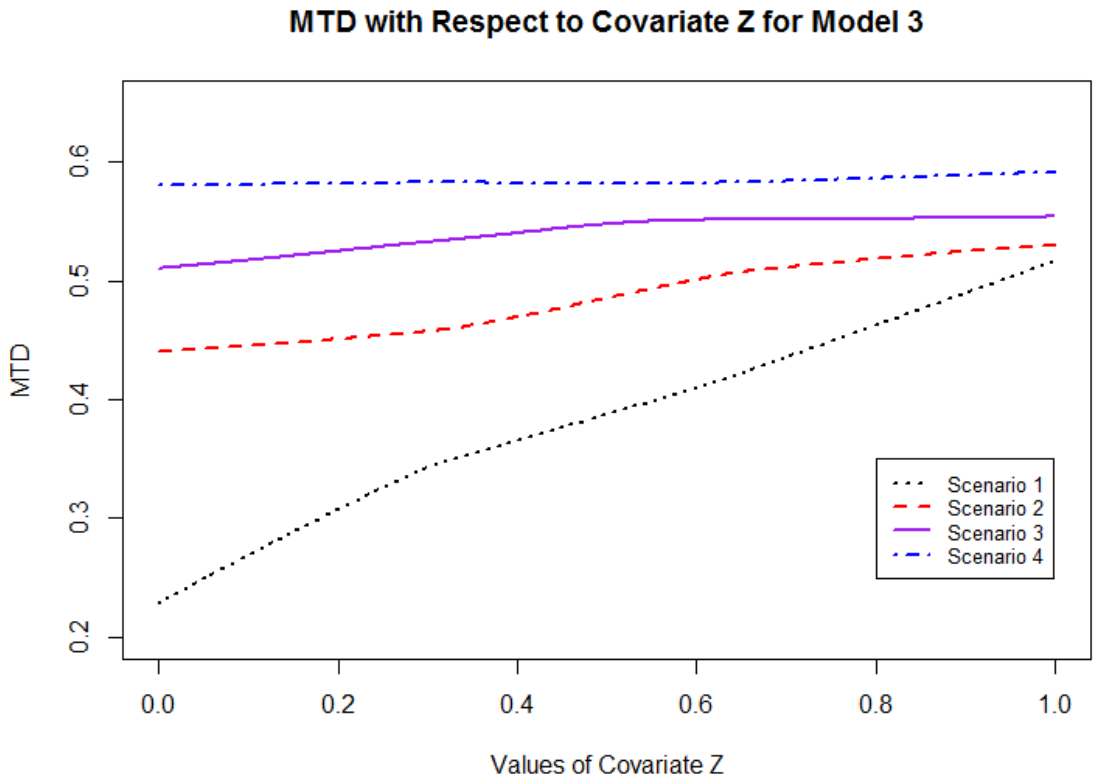

Figure 2: Relationship between MTD and Z under Model 3

Tables 9 and 10 estimates the MTD values when $Z = 0$ at the minimum covariate value and $Z = 1$ at the maximum covariate value. Theoretical values of the MTD are given in Table 1. In the most extreme scenario where the true MTD of the smallest covariate value (Z = 0) and the largest covariate value (Z = 1) are extremely different, the estimates are .276 and .498.Both of these estimates are extremely close to their true values, with biases of 0.006 and -0.002. Estimates of the MTD in scenarios 1-3 under Model 3 determine a personalized MTD as expected. Under scenario 4, Model 3 estimates the two MTD's to be 0.541, while the true MTD is 0.5. This estimate is actually less accurate than Model 1 with the original EWOC-NETS, but is still extremely close to the true values. Standard errors for all four scenarios are relatively similar at around 0.05. The mean squared errors are all low and consistent among the scenarios, suggesting that the performance of Model 3 under all 4 scenarios is

consistent. Comparing the tables to Figure 2, the values at $Z = 0$ and $Z = 1$ do not exactly match due to the polynomial fit. However, the monotonically increasing pattern presented in the figure indicates the presence of a personalized MTD.

Scenario	True Value	Mean	SE	Bias	MSE
1	0.27	0.276	0.058	0.006	0.003
2	0.38	0.399	0.057	0.019	0.004
3	0.44	0.467	0.049	0.027	0.003
4	0.50	0.541	0.049	0.041	0.004

Table 9: Simulation Results of Model 3 γ_1 (Z=0)

Scenario	True Value	Mean	SE	Bias	MSE
1	0.50	0.498	0.058	-0.002	0.003
2	0.50	0.515	0.057	0.015	0.003
3	0.50	0.525	0.049	0.025	0.003
4	0.50	0.541	0.049	0.041	0.004

Table 10: Simulation Results of Model 3 for γ_2 (Z=1)

Under Model 1, the average NETS are high in scenarios 1 and 2, up to 60% and 53%, respectively. In scenarios 3 and 4, the average NETS return to expected rates at 49% and 46%, respectively (Table 11) . These ANETS values also indicate that Model 1 does not accurately estimate the MTD in scenarios 1 and 2. The ANETS values for Model 3 are much closer to what we would expect, with all 4 scenarios having rates that are very close to $\theta = 0.476$. All 4 scenarios also have ANETS values less than θ under Model 3, while the ANETS values of Model 1 under certain scenarios are much higher than the safety limit.

Scenario	Model 1	Model 3
1	0.601	0.447
2	0.530	0.465
3	0.498	0.467
4	0.465	0.463

Table 11: Average NETS between Model 1 and Model 3

4 Discussion

In Model 1, only one overall MTD is given for each scenario for both discrete and continuous covariates. In the continuous setting, it is impossible to give an estimate of both γ_1 and γ_2 for Model 1 due to the continuous nature of the covariate. In the discrete case for Model 1, it is actually possible to provide two MTD estimates, one for γ_1 (C = 0) and one for γ_2 (C = 1). However, only one estimate is given because there is no substantial difference in MTD between the two groups from Model 1 (Figure 3). In all scenarios, the MTD's in Figure 3 between the two groups have relatively similar medians and distributions. Therefore, for both the discrete and continuous scenarios under Model 1, we only report an overall MTD.

The overall MTD's from Model 1 in the discrete and continuous case are relatively similar in the four scenarios. Since the range of values for all covariates are between 0 and 1, both scenarios under Model 1 attempt to model a mid-point value of the covariates (Z $\sim$ 0.5, C $\sim$ 0.5). Therefore, the overall MTD's between the two covariates are similar since the covariate values are similar.

In Model 2 for Group 1, estimated mean MTD's are very close to the true value and is successfully identified as a personalized MTD. For Group 2 where the true MTD for all scenarios is 0.5, the estimated MTD is further away depending on the true MTD of Group 1. For scenario 1, we see that the estimated MTD is much less than scenario 4, even though the true MTD is 0.5 for both scenarios (Table 5). This is caused by the equations for β_0, β_1, and δ given by (24)-(26). Since these equations contain both γ_1 and γ_2, the lower γ_2 for Group 1 causes the estimated $\hat{\gamma_2}$ to be lower. When the two MTD's are close, then both groups have very accurate MTD estmates. If the MTD for group 1 was higher than group 2, we would expect the estimated MTD's for group 2 to be higher than the true values.

In assessing overdosing rates, both Model's 2 and 3 have lower rates than Model 1, suggesting that Model's 2 and 3 are safer for patients. While some overdosing rates appear to be high, an analysis of the simulated data shows that many patients receive doses very close to the true MTD (+/- 0.05). This is caused by the nature of the continuous dose levels and the original design of EWOC, where the model rapidly escalates to the estimated MTD with recommended dose levels around that value. In assessing average NETS, Model's 2 and 3 also have lower rates than Model 1, suggesting that these patients are receiving less severe toxicities and therefore less toxic doses. All average NETS for models 2 and 3 are close to the true value $\theta = 0.476$. Overall, this results in a lower MTD estimate in Model's 2 and 3 compared to Model 1.

Overall, although Model's 2 and 3 are not entirely precise in estimating the true MTD for both groups, they are both much closer than the estimated MTD in Model 1. Larger discrepancies are seen when the true MTD's are vastly different between the two patient groups. From Model 1, we also see that overdosing rates and average NETS are higher than expected when the MTD's are different between the two groups. In Model's 2 and 3, overdosing and average NETS are consistent with expected values and overdose control. We conclude that our developed methods are able to identify the scenarios that have personalized MTD consistently, while the original EWOC-NETS cannot be incorporated with patient distinct covariates.

5 Bibliography

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6 Appendix

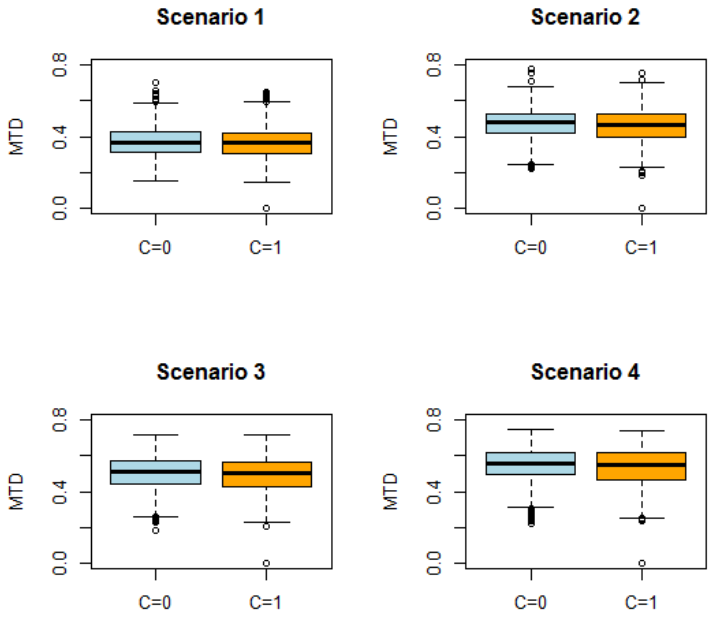

Figure 3: MTD Distribution with no Discrete Covariate Consideration

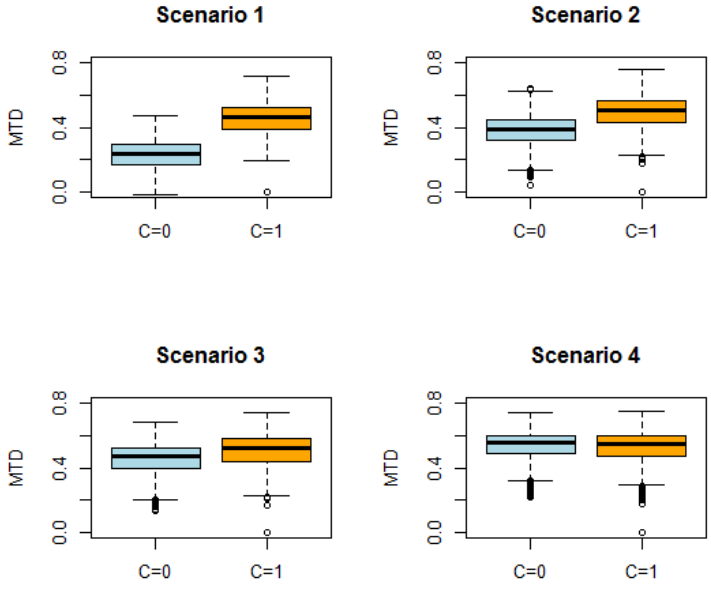

Figure 4: MTD Distribution with Discrete Covariate Consideration

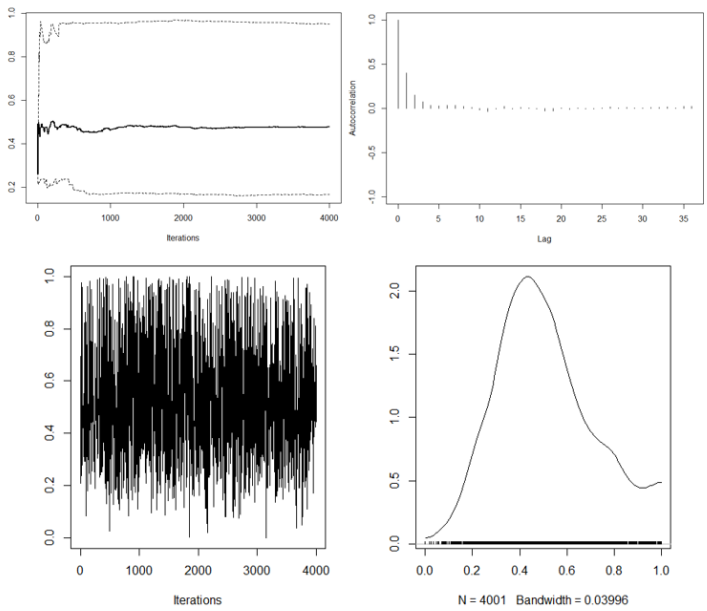

Figure 5: Sample Diagnostic Plots Assessing the Convergence of the MCMC Sample

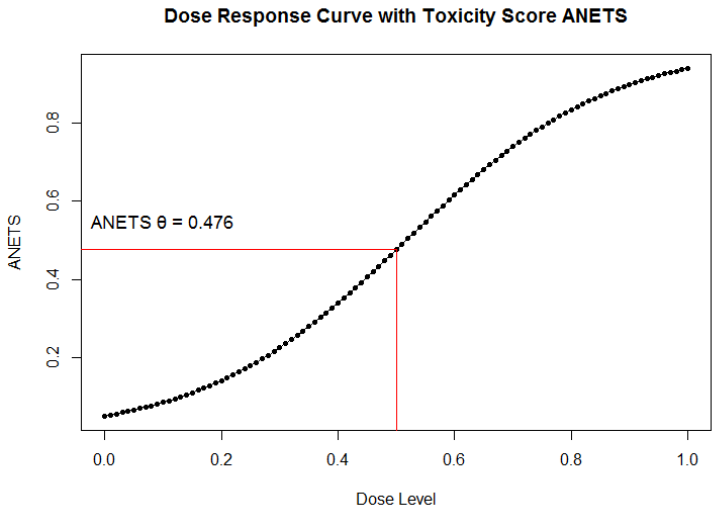

Figure 6: Average NETS with Respect to Dose Level using a Logistic Model

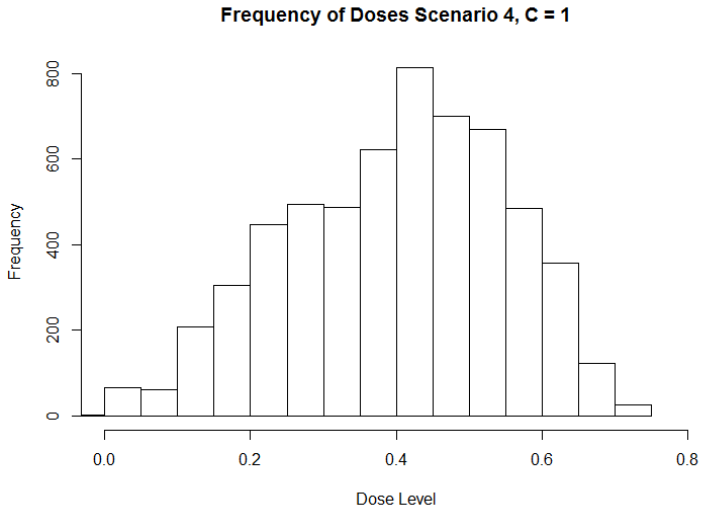

Figure 7: Dose Level Frequencies for Scenario 4, C = 1

Original EWOC with JAGS

```
install.packages('rjags')
library(rjags)

#Model for JAGS (Bayesian Methods Book)

model="model{
for (i in 1:N){

tox[i]~dbern(p[i])
logit(p[i])<- (1/(gamma - Xmin))*(gamma*logit(rho0)-
    Xmin*logit(theta)+(logit(theta)-logit(rho0))*X[i])
}

gamma ~ dunif(Xmin,Xmax)
rho0 ~ dunif(0,theta)
}"

#Function for logit
logit<-function(p) {
  return(log(p/(1-p)))
}

#Input Parameters (Varying)
doses = seq(140,425,10) #Dose levels (discrete)
Xmin = 140
Xmax = 425
gam_mtd = 160          #prior MTD
rho = .05              #probability of DLT at Xmin
theta = 1/3            #target toxicity level TTL

#B0 and B1 in logistic model
b0=1/(gam_mtd-Xmin)*(gam_mtd*logit(rho)-Xmin*logit(theta))
b1=1/(gam_mtd-Xmin)*(logit(theta)-logit(rho))

prob_dose<-1-(exp(-(b0+b1*doses))/(1+exp(-(b0+b1*doses))))


#Beginning of JAGS

subjects = 30
nsims = 10
finaldata=list()
varying_a = T

for (i in 1:nsims){
  alpha = .25              #alpha value
  for (j in 1:subjects) {

    if (j == 1) {
      data=list(tox=c(0),X=c(140),Xmin=140,Xmax=425,theta=theta,N=1)
       initialize =list(rho0=rho,gamma=gam_mtd)
      N.sim<-jags.model(textConnection(model),data=data,inits=initialize,quiet=T)
```

```
    out <- coda.samples(model=N.sim,variable.names=c('gamma','tox','rho0'), n.iter=5000)
    gamma.next <- as.numeric(quantile(unlist(out[1][1001:5000,1]),alpha))
    gamma.next1 <- findInterval(gamma.next,doses)

    data$tox <- c(data$tox, NA)
    data$X <- c(data$X, doses[gamma.next1])
    data$N <- data$N + 1

    if (varying_a == T & doses[gamma.next1] != Xmin) {
      alpha = alpha + .05
    }
  }

  else {

  N.simall <- jags.model(textConnection(model),data=data,inits=initialize,quiet=T)
      #simulate Missing Patient

  out1 <- coda.samples(model=N.simall,variable.names=c('gamma','tox','rho0'), n.iter=5000)
  prob.tox <- mean(unlist(out1[1][1001:5000,j+2]))

  tox.sim <- sample(c(0,1),1,replace=T,prob=c(1-prob.tox,prob.tox))
  data$tox[is.na(data$tox)] <- tox.sim

  N.simall1<- jags.model(textConnection(model),data=data,inits=initialize,quiet=T)
      #simulate actual data
  out2 <- coda.samples(model=N.simall1,variable.names=c('gamma','tox','rho0'), n.iter=5000)
  gamma.mtd <- as.numeric(quantile(unlist(out2[1][1001:5000,1]),alpha))
  gamma.mtd1 <- findInterval(gamma.mtd, doses)

  data$tox <- c(data$tox, NA)
  data$X <- c(data$X, doses[gamma.mtd1])
  data$N <- data$N + 1

  if (varying_a == T & alpha<.45 & doses[gamma.mtd1] > data$X[j]) {
    alpha = alpha + .05
  }
  }
 }
 data$tox<-head(data$tox,-1)
 data$X<-head(data$X,-1)
 finaldata [[ i ]] <- data
}

mtd<-list()

for (i in 1:nsims) {
 mtd[[i ]] <- finaldata[[i ]]$X
}

finalmtd<-mean(unlist(mtd))
```

EWOC NETS No Discrete (Model 1, No Discrete Covariate)

```
library(truncnorm)

#Likelihood function, no covariate
lik<-function(simdata,rho0,gamma){
  alpha<-1/(gamma-simdata$Xmin)*(gamma*logit(rho0)-simdata$Xmin*logit(simdata$theta))
  beta<-1/(gamma-simdata$Xmin)*(logit(simdata$theta)-logit(rho0))
  s<-simdata$S
  x<-simdata$X
  p<-1/(1+exp(-(alpha+beta*x)))
   likli <-p^(s)*(1-p)^(1-s)
   totlik<-prod(likli)
  return (totlik)
}

#Posterior distribution
post.up<-function(simdata,Xmin,Xmax,theta,it,init.rho0,init.gamma){
  gamma.s<-rep(0,it)
  rho0.s<-rep(0,it)
  gamma.s[1]<-init.gamma
  rho0.s[1]<-init.rho0
  for(i in 2:it){
    gamma.s[i]=gamma.up(simdata,Xmin,Xmax,theta,it,rho0.s[i-1],gamma.s[i-1])
    rho0.s[i]=rho.up(simdata,Xmin,Xmax,theta,it,rho0.s[i-1],gamma.s[i])
  }
   pst.list <-list(gamma.s,rho0.s)
  return( pst.list )
}

#updating of rho
rho.up<-function(simdata,Xmin,Xmax,theta,it,oldrho0,gamma.u){
  rho.new<-runif(1,0,theta)
  lik.new<-lik(simdata,rho.new,gamma.u)
   lik.old <-lik(simdata,oldrho0,gamma.u)
  ratio<-lik.new/lik.old
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y=rho.new
  }else{
    test<-runif(1)
    if(test<ratio){
      y<-rho.new
    }
    else{
      y<-oldrho0
    }
  }
  return(y)
}

#updating of gamma
gamma.up<-function(simdata,Xmin,Xmax,theta,it,rho0.u,oldgamma){
  gamma.new<-runif(1,Xmin,Xmax)
```

```
  lik.new<-lik(simdata,rho0.u,gamma.new)
  lik.old <-lik(simdata,rho0.u,oldgamma)
  ratio<-lik.new/lik.old
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-gamma.new
  }else{
    test<-runif(1)
    if(test<ratio){
      y<-gamma.new
    }
    else{
      y=oldgamma
    }
  }
  return(y)
}

logit<-function(p) {
  return(log(p/(1-p)))
}

Xmin<-0 #Minimum dose level
Xmax<-1 #Maximum dose level
gamma_max<-0.5 #True MTD for Group 2
rho1<-c(0.16355,0.09455,0.06894,0.05) #Toxicity at Xmin for Group 1
rho2<-c(.05) #Toxicity at Xmin for Group 2
theta<-0.476 #TNETS
gammaa<-c(.32,.43,.49,.55) #Threshold Dose level

mean<-rep(NA,4)
se<-rep(NA,4)
biasgroup2<-rep(NA,4)
biasgroup1<-rep(NA,4)
msegroup2<-rep(NA,4)
msegroup1<-rep(NA,4)
mtdavg<-rep(NA,4)
lnetavg<-rep(NA,4)
finalgam0<-list()
finalgam1<-list()


for (p in 1:4){
  #Parameter estimates for ANETS for Group 2
  b0.2<-logit(rho1[p])-Xmin*(logit(theta)-logit(rho2))/
  (gamma_max-Xmin)
  b1.2<-(logit(theta)-logit(rho2))/(gamma_max-Xmin)
  delta.2<-logit(rho2)-logit(rho1[p])
  gamma_0<-gamma_max+delta.2/b1.2

  #Parameter estimates for ANETS for Group 1
  b0.1<-logit(rho1[p])-Xmin*(logit(theta)-logit(rho2))/
  (gamma_0-Xmin)
  b1.1<-(logit(theta)-logit(rho2))/(gamma_0-Xmin)
```

```
delta.1<-logit(rho2)-logit(rho1[p])

#Priors for rho and gamma
gamma<-0.8
rho<-0.8

#Number of patients
N<-30

#Number of simulations
Nsim<-2

t.table<-NULL
r.table<-NULL
res<-c()
MTDover0<-c()
MTDover1<-c()
MTDover<-c()
LNETS<-c()
gam0<-list()
gam1<-list()

#For each scenario (4 total)
for (n in 1:Nsim){
  alpha<-0.25
  nextdose<-rep(NA,N)
  nextgamma<-rep(NA,N)

  #Starting data: NETS = .341, Dose = 0, Z = 1, Gamma = 0
  simdata<-list(S=c(0.341),X=c(0),Xmin=Xmin,theta=theta,N=1,Z=c(1),Gamma=c(0))

  #FOr each Patient (30 total)
  for (i in 1:N){
    print(c(p,n,i))
    if ((i!=1)&(alpha<0.45)){
      alpha<-alpha+0.05
    }

    out1<-post.up(simdata,Xmin,Xmax,theta,5000,rho,gamma)
    nextgamma[i]<-quantile(out1[[1]][1000:5000], prob=alpha)
    simdata$Z<-c(simdata$Z,sample(c(0,1),1,prob=c(0.5,0.5)))
    nextdose[i]<-nextgamma[i]

    #ANETS calculation and NETS score generated using truncated normal
    if (simdata$Z[i+1] == 0) {
      ANETS<-exp(b0.1+b1.1*nextdose[i]+delta.1*simdata$Z[i+1])/
        (1+exp(b0.1+b1.1*nextdose[i]+delta.1*simdata$Z[i+1]))
    }
    else {
      ANETS<-exp(b0.2+b1.2*nextdose[i]+delta.2*simdata$Z[i+1])/
        (1+exp(b0.2+b1.2*nextdose[i]+delta.2*simdata$Z[i+1]))
    }
    NETS<-rtruncnorm(1,a=0,b=1,mean=ANETS,sd=sqrt(ANETS*(1-ANETS)))
```

```
    simdata$X<-c(simdata$X,nextdose[i])
    simdata$N<-simdata$N+1
    simdata$S<-c(simdata$S,NETS)
    simdata$Gamma<-c(simdata$Gamma,nextgamma[i])
  }


  sim.list <-list(simdata,Nsim.n=n,size=simdata$N,patientId=1:simdata$N)
  t.list =data.frame(sim.list) [1:( simdata$N-1),]
  r.list =data.frame(sim.list) [simdata$N,]

 a<-which(t.list$Z==0)
 aa<-which(t.list$Z==1)
  t.lista <-t.list[a,]
  t.listaa <-t.list[aa,]

 #MTD of each Simulation, and performance
 res[n]<-mean(t.list$Gamma)
 #Overdosing rate
 MTDover[n] <- sum(t.list$X>(gammaa[p]+.05))/30
 #Average NETS
 LNETS[n]<-sum(t.list$S>.526)/30
 #MTD DATA
 gam0[[n]]<-t.lista$X
 gam1[[n]]<-t.listaa$X
}
mtdover<-MTDover
lnets<-LNETS
mtdavg[p]<-mean(mtdover)
lnetavg[p]<-mean(lnets)

finalgam0[[p]]<-gam0
finalgam1[[p]]<-gam1

#Overall result
r<-res
mean[p]<-mean(r)
se[p]<-sd(r)
biasgroup2[p]<-mean[p]-gamma_max
biasgroup1[p]<-mean[p]-gamma_0
msegroup2[p]<-mean((r-gamma_max)^2)
msegroup1[p]<-mean((r-gamma_0)^2)

}
(result<-round(cbind(mean,se,biasgroup2,msegroup2,biasgroup1,msegroup1),3))

library(coda)
ite=5000;burnin=1000
names(out1)<-c("gamma","rho")
out2<-mcmc(data.frame(out1)[burnin:ite,])
xyplot(out2)
acfplot(out2)
densplot(out2)
```

```
traceplot(out2)
```

EWOC NETS with Discrete Covariate (Model 2)

```
#Likelihood function including discrete  covariate
lik<-function(simdata,rho1,rho2,gamma){
  alpha<-logit(rho1)-simdata$Xmin*(logit(simdata$theta)-logit(rho2))/
  (gamma-simdata$Xmin)
  beta<-(logit(simdata$theta)-logit(rho2))/(gamma-simdata$Xmin)
  delta<-logit(rho2)-logit(rho1)
  s<-simdata$S
  x<-simdata$X
  z<-simdata$Z
  p<-exp(alpha+beta*x+delta*z)/(1+exp(alpha+beta*x+delta*z))
   likli <-p^(s)*(1-p)^(1-s)
   totlik <-prod(likli)
  return( totlik )
}

#Posterior Distribution
post.up<-function(simdata,Xmin,Xmax,theta,it,init.rho1,init.rho2,init.gamma){

  gamma.s<-rep(0,it)
  rho1.s<-rep(0,it)
  rho2.s<-rep(0,it)

  gamma.s[1]<-init.gamma
  rho1.s[1]<-init.rho1
  rho2.s[1]<-init.rho2

  for(i in 2:it){

    gamma.s[i]=gamma.up(simdata,Xmin,Xmax,theta,it,rho1.s[i-1],rho2.s[i-1],gamma.s[i-1])
    rho1.s[i]=rho1.up(simdata,Xmin,Xmax,theta,it,rho1.s[i-1],rho2.s[i],gamma.s[i])
    rho2.s[i]=rho2.up(simdata,Xmin,Xmax,theta,it,rho1.s[i],rho2.s[i-1],gamma.s[i])

  }
   pst.list <-list(gamma.s,rho1.s,rho2.s)
  return( pst.list )
}

#Updating of gamma
gamma.up<-function(simdata,Xmin,Xmax,theta,it,rho1.u,rho2.u,oldgamma){
  gamma.new<-runif(1,Xmin,Xmax)
  lik.new<-lik(simdata,rho1.u,rho2.u,gamma.new)
   lik.old <-lik(simdata,rho1.u,rho2.u,oldgamma)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-gamma.new
  }
  if(ratio<1){
```

```
    test<-runif(1)
    if(test<ratio){
      y<-gamma.new
    }
    if(test>ratio){
      y=oldgamma
    }
  }
  return(y)
}

#updating of rho1
rho1.up<-function(simdata,Xmin,Xmax,theta,it,oldrho1,rho2.u,gamma.u){
  rho1.new<-runif(1,0,theta)
  lik.new<-lik(simdata,rho1.new,rho2.u,gamma.u)
  lik.old <-lik(simdata,oldrho1,rho2.u,gamma.u)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-rho1.new
  }
  if(ratio<1){
    test<-runif(1)
    if(test<ratio){
      y<-rho1.new
    }
    if(test>ratio){
      y<-oldrho1
    }
  }
  return(y)
}

#updating of rho2
rho2.up<-function(simdata,Xmin,Xmax,theta,it,rho1.u,oldrho2,gamma.u){
  rho2.new<-runif(1,0,theta)
  lik.new<-lik(simdata,rho1.u,rho2.new,gamma.u)
  lik.old <-lik(simdata,rho1.u,oldrho2,gamma.u)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-rho2.new
  }
  if(ratio<1){
    test<-runif(1)
    if(test<ratio){
      y<-rho2.new
    }
    if(test>ratio){
      y<-oldrho2
    }
  }
```

```
  return(y)
}


logit<-function(p){return(log(p/(1-p)))}

Xmin<-0 #Minimum dose level
Xmax<-1 #Maximum dose level
gamma_r<-0.5 #True MTD for Group 2
rho1_r<-c(0.16355,0.09455,0.06894,0.05) #Toxicity at Xmin for Group 1
rho2_r<-c(.05) #Toxicity at Xmin for Group 2
theta<-0.476 #TNETS
gammaa<-c(.55,.43,.49,.32)


mean0<-rep(NA,4)
mean1<-rep(NA,4)
bias0<-rep(NA,4)
bias1<-rep(NA,4)
se0<-rep(NA,4)
se1<-rep(NA,4)
mse0<-rep(NA,4)
mse1<-rep(NA,4)
mtdavg<-rep(NA,4)
lnetavg<-rep(NA,4)
finalgam0<-list()
finalgam1<-list()


for (rr in c(1:length(rho1_r))){
  #Parameter estimates for ANETS for Group 2
  alpha_r<-logit(rho1_r[rr])-Xmin*(logit(theta)-logit(rho2_r))/
  (gamma_r-Xmin)
  beta_r<-(logit(theta)-logit(rho2_r))/(gamma_r-Xmin)
  delta_r<-logit(rho2_r)-logit(rho1_r[rr])
  gamma0_r<-gamma_r+delta_r/beta_r

  #Parameter estimates for ANETS for Group 1
  alpha_r0<-logit(rho1_r[rr])-Xmin*(logit(theta)-logit(rho2_r))/
  (gamma0_r-Xmin)
  beta_r0<-(logit(theta)-logit(rho2_r))/(gamma0_r-Xmin)
  delta_r0<-logit(rho2_r)-logit(rho1_r[rr])

  gamma<-0.2
  rho1<-1
  rho2<-1
  N<-30
  sim<-2
  t.table<-NULL
  r.table<-NULL
  res0<-c()
  res1<-c()
  MTDover0<-c()
```

```
MTDover1<-c()
MTDover<-c()
LNETS<-c()
gam0<-list()
gam1<-list()

for (k in 1:sim){
  fb<-0.25
  ew.nextdose<-rep(NA,N)
  next_gamma<-rep(NA,N)
  next_gamma0<-rep(NA,N)

  #Starting data: NETS = .341, Dose = 0, Z = 1, Gamma = 0
  simdata<-list(S=c(0.341),X=c(0),Xmin=Xmin,theta=theta,N=1,Z=c(1),G=c(0),G0=c(0))


  for (i in 1:N){
    print(c(rr,k,i))
    if((i!=1)&(fb<0.45)){
      fb<-fb+0.05
    }

    #Likelihood and Data
    out1<-post.up(simdata,Xmin,Xmax,theta,5000,rho1,rho2,gamma)

    #Gamma of Group 2
    next_gamma[i]<-quantile(out1[[1]][1000:5000],prob=fb)

    #Gamma of Group 1
    next_gamma0[i]<-next_gamma[i]+delta_r/beta_r


    #Covariate Data
    simdata$Z<-c(simdata$Z,sample(c(0,1),1,replace=TRUE,prob=c(0.5,0.5)))
    if (simdata$Z[i+1]==1){
      nextdose<-next_gamma[i]
    }
    if (simdata$Z[i+1]==0){
      nextdose<-next_gamma0[i]
    }

    #Next dose based on group of patient
    ew.nextdose[i]<-nextdose

    #ANETS calculation and NETS calculation
    if (simdata$Z[i+1] == 0) {
      ANETS<-exp(alpha_r0+beta_r0*ew.nextdose[i]+delta_r0*simdata$Z[i+1])
      /(1+exp(alpha_r0+beta_r0*ew.nextdose[i]+delta_r0*simdata$Z[i+1]))
    }
    else {
      ANETS<-exp(alpha_r+beta_r*ew.nextdose[i]+delta_r*simdata$Z[i+1])
      /(1+exp(alpha_r+beta_r*ew.nextdose[i]+delta_r*simdata$Z[i+1]))
    }
    nets<-rtruncnorm(1,a=0,b=1,mean=ANETS,sd=sqrt(ANETS*(1-ANETS)))
```

```
      simdata$X<-c(simdata$X,ew.nextdose[i])
      simdata$N<-simdata$N+1
      simdata$S<-c(simdata$S,nets)
      simdata$G<-c(simdata$G,next_gamma[i])
      simdata$G0<-c(simdata$G0,next_gamma0[i])
    }
    sim.list <-list(simdata,sim.n=k,size=simdata$N,patientId=1:simdata$N)
     t.list =data.frame(sim.list) [1:( simdata$N-1),]
     r.list =data.frame(sim.list) [simdata$N,]
    a<-which(t.list$Z==0)
    aa<-which(t.list$Z==1)
     t.lista <-t.list[a,]
     t.listaa <-t.list[aa,]

    #MTD's of each group
    res0[k]<-mean(t.list$G0)
    res1[k]<-mean(t.list$G)

    #Overdosing rates
    MTDover0[k] <- sum(t.lista$X>gammaa[rr])
    MTDover1[k] <- sum(t.listaa$X>.55)
    MTDover[k] <-(MTDover0[k] + MTDover1[k])/30
    #Average NETS
    LNETS[k]<-sum(t.list$S>.526)/30
    #MTD data
    gam0[[k]]<-t.lista$X
    gam1[[k]]<-t.listaa$X


  }

  mtdover<-MTDover
   lnets<-LNETS
  mtdavg[rr]<-mean(mtdover)
  lnetavg[rr]<-mean(lnets)

  finalgam0[[rr]]<-gam0
  finalgam1[[rr]]<-gam1

  r0<-res0
  r1<-res1
  mean0[rr]<-mean(r0)
  mean1[rr]<-mean(r1)
  se0[rr]<-sd(r0)
  se1[rr]<-sd(r1)
  bias0[rr]<-m0[rr]-gamma0_r
  bias1[rr]<-m1[rr]-gamma_r
  mse0[rr]<-mean((r0-gamma0_r)^2)
  mse1[rr]<-mean((r1-gamma_r)^2)
}
(result<-round(cbind(m1,bias1,se1,mse1,m0,bias0,se0,mse0),3))
```

EWOC NETS no Continuous (Model 1, no Continuous)

```
lik<−function(simdata,rho0,gamma){
  alpha<−1/(gamma−simdata$Xmin)∗(gamma∗logit(rho0)−simdata$Xmin∗logit(simdata$theta))
  beta<−1/(gamma−simdata$Xmin)∗(logit(simdata$theta)−logit(rho0))
  s<−simdata$S
  x<−simdata$X
  p<−1/(1+exp(−(alpha+beta∗x)))
   likli <−pˆ(s)∗(1−p)ˆ(1−s)
   totlik<−prod(likli)
  return  ( totlik )
}

post.up<−function(simdata,Xmin,Xmax,theta,it,init.rho0,init.gamma){
  gamma.s<−rep(0,it)
  rho0.s<−rep(0,it)
  gamma.s[1]<−init.gamma
  rho0.s [1] <−init.rho0
  for ( i  in  2: it ){
    gamma.s[i]=gamma.up(simdata,Xmin,Xmax,theta,it,rho0.s[i−1],gamma.s[i−1])
    rho0.s [ i]=rho.up(simdata,Xmin,Xmax,theta,it,rho0.s[i−1],gamma.s[i])
  }
   pst.list <−list(gamma.s,rho0.s)
  return( pst.list )
}

rho.up<−function(simdata,Xmin,Xmax,theta,it,oldrho0,gamma.u){
  rho.new<−runif(1,0,theta)
  lik.new<−lik(simdata,rho.new,gamma.u)
   lik.old <−lik(simdata,oldrho0,gamma.u)
  ratio<−lik.new/lik.old
  if ( ratio==”NaN”) ratio<−1
  if ( ratio>=1){
    y=rho.new
  }else{
    test<−runif(1)
    if ( test<ratio){
      y<−rho.new
    }
    else{
      y<−oldrho0
    }
  }
  return(y)
}

gamma.up<−function(simdata,Xmin,Xmax,theta,it,rho0.u,oldgamma){
  gamma.new<−runif(1,Xmin,Xmax)
  lik.new<−lik(simdata,rho0.u,gamma.new)
   lik.old <−lik(simdata,rho0.u,oldgamma)
  ratio<−lik.new/lik.old
  if ( ratio==”NaN”) ratio<−1
  if ( ratio>=1){
```

```
    y<-gamma.new
  }else{
    test<-runif(1)
    if(test<ratio){
      y<-gamma.new
    }
    else{
      y=oldgamma
    }
  }
  return(y)
}

logit<-function(p) {
  return(log(p/(1-p)))
}

Xmin<-0 #Minimum dose level
Xmax<-1 #Maximum dose level
Zmin<-0 #Minimum covariate value
Zmax<-1 #Maximum covariate value
gamma_max<-0.5 #True MTD for Group 2
rho1<-c(0.16355,0.09455,0.06894,0.05) #Toxicity at Xmin for Group 1
rho2<-c(.05) #Toxicity at Xmin for Group 2
theta<-0.476 #TNETS
gammaa<-c(.32,.43,.49,.55)


mean<-rep(NA,4)
se<-rep(NA,4)
biasgroup2<-rep(NA,4)
biasgroup1<-rep(NA,4)
msegroup2<-rep(NA,4)
msegroup1<-rep(NA,4)
mtdavg<-rep(NA,4)
lnetavg<-rep(NA,4)
finalgam0<-list()
finalgam1<-list()

for (p in 1:4){
  #Parameter estimates for ANETS for Group 2
  b0.2<-logit(rho1[p])-Xmin*(logit(theta)-logit(rho2))/
  (gamma_max-Xmin)-Zmax*(logit(rho2)-logit(rho1[p]))/(Zmax-Zmin)
  b1.2<-(logit(theta)-logit(rho2))/(gamma_max-Xmin)
  delta.2<-(logit(rho2)-logit(rho1[p]))/(Zmax-Zmin)
  gamma_0<-gamma_max+delta.2/b1.2


  #Parameter estimates for ANETS for Group 1
  b0.1<-logit(rho1[p])-Xmin*(logit(theta)-logit(rho2))/
  (gamma_0-Xmin)-Zmax*(logit(rho2)-logit(rho1[p]))/(Zmax-Zmin)
  b1.1<-(logit(theta)-logit(rho2))/(gamma_0-Xmin)
  delta.1<-(logit(rho2)-logit(rho1[p]))/(Zmax-Zmin)
```

```
#Priors for rho and gamma
gamma<-0.8
rho<-0.8

#Number of patients
N<-30

#Number of simulations
Nsim<-2

t.table<-NULL
r.table<-NULL
res<-c()
MTDover0<-c()
MTDover1<-c()
MTDover<-c()
LNETS<-c()
gam0<-list()
gam1<-list()

#For each scenario (4 total)
for (n in 1:Nsim){
  alpha<-0.25
  nextdose<-rep(NA,N)
  nextgamma<-rep(NA,N)

  #Starting data: NETS = .341, Dose = 0, Z = 1, Gamma = 0
  simdata<-list(S=c(0.341),X=c(0),Xmin=Xmin,theta=theta,N=1,Z=c(1),Gamma=c(0))

  #FOr each Patient (30 total)
  for (i in 1:N){
    print(c(p,n,i))
    if((i!=1)&(alpha<0.45)){
      alpha<-alpha+0.05
    }

    simdata$Z<-c(simdata$Z,runif(1,Zmin,Zmax))
    out1<-post.up(simdata,Xmin,Xmax,theta,5000,rho,gamma)
    nextgamma[i]<-quantile(out1[[1]][1000:5000], prob=alpha)
    nextdose[i]<-nextgamma[i]

    ANETS<-exp(b0.2+b1.2*nextdose[i]+delta.2*simdata$Z[i+1])/
       (1+exp(b0.2+b1.2*nextdose[i]+delta.2*simdata$Z[i+1]))

    NETS<-rtruncnorm(1,a=0,b=1,mean=ANETS,sd=sqrt(ANETS*(1-ANETS)))


    simdata$X<-c(simdata$X,nextdose[i])
    simdata$N<-simdata$N+1
    simdata$S<-c(simdata$S,NETS)
    simdata$Gamma<-c(simdata$Gamma,nextgamma[i])
  }
```

```
    sim.list <−list(simdata,Nsim.n=n,size=simdata$N,patientId=1:simdata$N)
    t.list =data.frame(sim.list) [1:( simdata$N−1),]
    r.list =data.frame(sim.list) [simdata$N,]

   #MTD of each Simulation
   res [n]<−mean(t.list$Gamma)
   MTDover[n] <− sum(t.list$X>(gammaa[p]+.05))/30
   LNETS[n]<−sum(t.list$S>.526)/30
  }

  mtdover<−MTDover
  lnets<−LNETS
  mtdavg[p]<−mean(mtdover)
  lnetavg[p]<−mean(lnets)


  #Overall result
  r<−res
  mean[p]<−mean(r)
  se[p]<−sd(r)
  biasgroup2[p]<−mean[p]−gamma_max
  biasgroup1[p]<−mean[p]−gamma_0
  msegroup2[p]<−mean((r−gamma_max)^2)
  msegroup1[p]<−mean((r−gamma_0)^2)

}
(result<−round(cbind(mean,se,biasgroup2,msegroup2,biasgroup1,msegroup1),3))
```

EWOC NETS with Continuous Covariate (Model 3)

```
lik<−function(simdata,rho1,rho2,gamma){
  alpha<−logit(rho2)−(simdata$Xmin∗(logit(simdata$theta)−logit(rho2)))/
  (gamma−simdata$Xmin)−(simdata$Zmax∗(logit(rho2)−logit(rho1)))/(simdata$Zmax−simdata$Zmin)
  beta<−(logit(simdata$theta)−logit(rho2))/(gamma−simdata$Xmin)
  delta<−(logit(rho2)−logit(rho1))/(simdata$Zmax−simdata$Zmin)
  s<−simdata$S
  x<−simdata$X
  z<−simdata$Z
  p<−exp(alpha+beta∗x+delta∗z)/(1+exp(alpha+beta∗x+delta∗z))
   likli <−p^(s)∗(1−p)^(1−s)
   totlik <−prod(likli)
  return( totlik )
}

post.up<−function(simdata,Xmin,Xmax,theta,it,init.rho1,init.rho2,init.gamma){

  gamma.s<−rep(0,it)
  rho1.s<−rep(0,it)
  rho2.s<−rep(0,it)

  gamma.s[1]<−init.gamma
  rho1.s[1]<−init.rho1
  rho2.s[1]<−init.rho2
```

```
  for(i in 2:it){

    gamma.s[i]=gamma.up(simdata,Xmin,Xmax,theta,it,rho1.s[i-1],rho2.s[i-1],gamma.s[i-1])
    rho1.s[i]=rho1.up(simdata,Xmin,Xmax,theta,it,rho1.s[i-1],rho2.s[i-1],gamma.s[i])
    rho2.s[i]=rho2.up(simdata,Xmin,Xmax,theta,it,rho1.s[i],rho2.s[i-1],gamma.s[i])

  }
   pst.list <-list(gamma.s,rho1.s,rho2.s)
  return( pst.list )
}

gamma.up<-function(simdata,Xmin,Xmax,theta,it,rho1.u,rho2.u,oldgamma){
  gamma.new<-runif(1,Xmin,Xmax)
  lik.new<-lik(simdata,rho1.u,rho2.u,gamma.new)
   lik.old <-lik(simdata,rho1.u,rho2.u,oldgamma)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-gamma.new
  }
  if(ratio<1){
    test<-runif(1)
    if(test<ratio){
      y<-gamma.new
    }
    if(test>ratio){
      y=oldgamma
    }
  }
  return(y)
}

rho1.up<-function(simdata,Xmin,Xmax,theta,it,oldrho1,rho2.u,gamma.u){
  rho1.new<-runif(1,0,theta)
  lik.new<-lik(simdata,rho1.new,rho2.u,gamma.u)
   lik.old <-lik(simdata,oldrho1,rho2.u,gamma.u)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-rho1.new
  }
  if(ratio<1){
    test<-runif(1)
    if(test<ratio){
      y<-rho1.new
    }
    if(test>ratio){
      y<-oldrho1
    }
  }
  return(y)
```

```
}


rho2.up<-function(simdata,Xmin,Xmax,theta,it,rho1.u,oldrho2,gamma.u){
  rho2.new<-runif(1,0,theta)
  lik.new<-lik(simdata,rho1.u,rho2.new,gamma.u)
   lik.old <-lik(simdata,rho1.u,oldrho2,gamma.u)
  ratio<-lik.new/lik.old
  #if(length(ratio)==0) ratio=1
  if(ratio=="NaN") ratio<-1
  if(ratio>=1){
    y<-rho2.new
  }
  if(ratio<1){
    test<-runif(1)
    if(test<ratio){
      y<-rho2.new
    }
    if(test>ratio){
      y<-oldrho2
    }
  }
  return(y)
}

logit<-function(p){return(log(p/(1-p)))}

Xmin<-0 #Minimum dose level
Xmax<-1 #Maximum dose level
gamma_r<-0.5 #True MTD for Group 2
rho1_r<-c(.16355,0.09455,0.06894,0.05) #Toxicity at Xmin for Group 1
rho2_r<-c(.05) #Toxicity at Xmin for Group 2
theta<-0.476 #TNETS
Zmin<-0
Zmax<-1


m0<-rep(NA,4)
m1<-rep(NA,4)
bias0<-rep(NA,4)
bias1<-rep(NA,4)
se0<-rep(NA,4)
se1<-rep(NA,4)
mse0<-rep(NA,4)
mse1<-rep(NA,4)
lnetavg<-rep(NA,4)
totaldat<-list()
totaldatZ<-list()


for (rr in c(1:4)){
  alpha_r<-logit(rho2_r)-(Xmin*(logit(theta)-logit(rho2_r))/
  (gamma_r-Xmin))-(Zmax*(logit(rho2_r)-logit(rho1_r[rr]))/(Zmax-Zmin))
  beta_r<-(logit(theta)-logit(rho2_r))/(gamma_r-Xmin)
```

```
delta_r<-(logit(rho2_r)-logit(rho1_r[rr]))/(Zmax-Zmin)
gamma0_r<-gamma_r+delta_r/beta_r

gamma<-1
rho1<-0.8
rho2<-0.7
N<-30
sim<-2
t.table<-NULL
r.table<-NULL
res0<-c()
res1<-c()
LNETS<-c()
dat<-list()
datZ<-list()

for (k in 1:sim){
  fb<-0.25
  ew.nextdose<-rep(NA,N)
  next_gamma<-rep(NA,N)
  next_gamma0<-rep(NA,N)
  next_gammak<-rep(NA,N)

  #We start the treatment from the patient with the highest Z value, i.e. the oldest patient
  simdata<-list(S=c(0.341),X=c(0),Xmin=Xmin,Zmin=Zmin,Zmax=Zmax,theta=theta,N=1,Z=c(0),G=c(0),G0

  for (i in 1:N){
    print(c(rr,k,i))
    if ((i!=1)&(fb<0.45)){
      fb<-fb+0.05
    }

    out1<-post.up(simdata,Xmin,Xmax,theta,5000,rho1,rho2,gamma)
    next_gamma[i]<-quantile(out1[[1]][1000:5000], prob=fb)

    simdata$Z<-c(simdata$Z,runif(1,Zmin,Zmax))
    next_gamma0[i]<-next_gamma[i]+delta_r/beta_r
    next_gammak[i]<-next_gamma[i]+(delta_r/beta_r)*(Zmax-simdata$Z[i+1])
    ew.nextdose[i]<-next_gammak[i]

    ANETS<-exp(alpha_r+beta_r*ew.nextdose[i]+delta_r*simdata$Z[i+1])/
    (1+exp(alpha_r+beta_r*ew.nextdose[i]+delta_r*simdata$Z[i+1]))
    nets<-rtruncnorm(1,a=0,b=1,mean=ANETS,sd=sqrt(ANETS*(1-ANETS)))

    simdata$X<-c(simdata$X,ew.nextdose[i])
    simdata$N<-simdata$N+1
    simdata$S<-c(simdata$S,nets)
    simdata$G<-c(simdata$G,next_gamma[i])
    simdata$G0<-c(simdata$G0,next_gamma0[i])

  }
  sim.list<-list(simdata,sim.n=k,size=simdata$N,patientId=1:simdata$N)
  t.list=data.frame(sim.list)[1:(simdata$N-1),]
  r.list=data.frame(sim.list)[simdata$N,]
```

```
    res0[k]<-mean(t.list$G0)
    res1[k]<-mean(t.list$G)

    LNETS[k]<-sum(t.list$S>.526)/30
    dat[[k]]<-t.list$X
    datZ[[k]]<-t.list$Z

  }

  totaldat[[rr]]<-unlist(dat)
  totaldatZ[[rr]]<-unlist(datZ)
  lnets<-LNETS
  lnetavg[rr]<-mean(lnets)

  r0<-res0
  r1<-res1
  m0[rr]<-mean(r0)
  m1[rr]<-mean(r1)
  se0[rr]<-sd(r0)
  se1[rr]<-sd(r1)
  bias0[rr]<-m0[rr]-gamma0_r
  bias1[rr]<-m1[rr]-gamma_r
  mse0[rr]<-mean((r0-gamma0_r)^2)
  mse1[rr]<-mean((r1-gamma_r)^2)
}

(result<-round(cbind(m1,bias1,se1,mse1,m0,bias0,se0,mse0),3))
```

Plots for Model 3

```
plot(unlist(fdatZ[[1]]),unlist(fdat[[1]]),type='n',xlab='Values of Covariate
    Z',ylab='MTD',ylim = c(.2,.7))
lines(lowess(unlist(fdatZ[[1]]),unlist(fdat[[1]])),lwd=2,lty=3)
lines(lowess(unlist(fdatZ[[2]]),unlist(fdat[[2]])),lwd=2,lty=2,col='red')
lines(lowess(unlist(fdatZ[[3]]),unlist(fdat[[3]])),lwd=2,col='purple')
lines(lowess(unlist(fdatZ[[4]]),unlist(fdat[[4]])),lwd=2,lty=4,col='blue')
legend(.8,.7,c("Scenario 1","Scenario 2","Scenario 3","Scenario
    4"),cex=.8,col=c("black","red","purple","blue"),lwd=2,lty=c(3,2,1,4))
title('MTD with Respect to Covariate Z for Model 1')


plot(unlist(fdatZ[[2]]),unlist(fdat[[2]]),type='n',xlab='Values of Covariate
    Z',ylab='MTD',ylim=c(.2,.65))
lines(lowess(unlist(fdatZ[[1]]),unlist(fdat[[1]])),lwd=2,lty=3)
lines(lowess(unlist(fdatZ[[2]]),unlist(fdat[[2]])),lty=2,col='red',lwd=2)
lines(lowess(unlist(fdatZ[[3]]),unlist(fdat[[3]])),lwd=2,col='purple')
lines(lowess(unlist(fdatZ[[4]]),unlist(fdat[[4]])),lwd=2,col='blue',lty=4)
legend(.8,.35,c('Scenario 1','Scenario 2', 'Scenario 3','Scenario
    4'),cex=.8,col=c('black','red','purple','blue'),lwd=2,lty=c(3,2,1,4))
title('MTD with Respect to Covariate Z for Model 3')
```