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Yuzi Zhang Date 03/29/2018

Adaptive Bayesian Phase I Clinical Trial Designs for Estimating the Maximum Tolerated Doses for Two Drugs while Fully Utilizing all Toxicity Information

By

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Master of Science in Public Health

Biostatistics and Bioinformatics

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2016

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Abstract

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By Yuzi Zhang

Utilization of multiple drug treatment combinations is very common in contemporary medicine, especially in medical oncology. Therefore, we developed an Adaptive Bayesian Phase I clinical trial design entitled Escalation with Overdose Control (EWOC) using a Normalized Equivalent Toxicity Score (NETS) for estimating the Maximum Tolerated Dose (MTD) contour of two-drug combinations denoted (EWOC-NETS-COM). Using NETS as the primary endpoint in a clinical trial and assuming it follows the quasi-Bernoulli distribution treated as a quasi-continuous random variable in the logistic likelihood function. In addition, four parameters with explicit clinical meanings are re-parameterized to describe the association between NETS and the dosage levels of the two drugs (Dose-Toxicity Model). Non-informative priors are used while employing the Markov Chain Monte Carlo (MCMC) method to obtain realizations from a high-dimensional probability density, as well as to acquire estimation of four parameters in the Dose-Toxicity Model. Extensive simulations were conducted to evaluate the accuracy, safety, therapeutic effect, and trial efficiency of EWOC-NETS-COM under different scenarios using the EWOC as a reference. The results demonstrate that EWOC-NETS-COM not only estimates the MTD contour of multiple drugs more reliably but also provides a better therapeutic effect by reducing the probability of underdosing patient treatments while fully utilizing all toxicity information to improve trial efficiency.

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1. Introduction

Phase I clinical trials play an important role in cancer drug development. The main purposes of cancer Phase I trials are to determine cytotoxicity and understanding the biology of the drug [1]. Thus, estimation of the maximum tolerated dose (MTD) of a new single agent or the MTD contour for a combination of treatment levels with multiple agents is the primary purpose of a Phase I clinical trial. In general, there are two types of designs for finding MTDs for new agents. The two types of designs are referred to as rule based and model based. The most widely used rule based Phase I trial design is the 3+3 design. The Continual Reassessment Method (CRM) [2] is another popular design and is a model based design. The prior toxicity probability of each dose is pre-specified in a CRM design by using a one-parameter link function where the true toxicity probability can be estimated. During the trial, after enrolling a cohort of patients, the probability of toxicity at each dose level can be estimated through the posterior distribution of the model parameters. The allocation of the next cohort of patients is then determined as the dose whose toxicity probability is closest to the target toxicity level [3]. Escalation with Overdose Control (EWOC) proposed by Babb JS and colleagues [4] is another popular and widely used model based design for Phase I clinical trials.

Drug combination therapy has existed to treat cancer patients since the 1960s, producing a positive effect on reducing tumor resistance to therapy and improving tumor response [5]. Furthermore, drug combination therapy has become more and more common among Phase I cancer clinical trials for their benefits. However, most MTD estimation approaches are still designed only for a single agent drug. Novel methods for

estimating the MTD contour for combination of more than one drug are very desirable and should have a great impact on Phase I clinical trials.

Escalation with overdose control (EWOC) is a design based Adaptive Bayesian Phase I clinical trial design. EWOC aims to obtain estimates of the MTD for new agents while controlling the probability that a patient is overdosed. EWOC assumes the probability of a dose limiting toxicity (DLT) will increase as the dosage level is increased. We use here a logistic regression model with two parameters to describe the association toxicity probability and treatment agents' dose levels. During a Phase I trial, the EWOC design selects a dose level for the next patient so that the predicted probability that a selected dose level exceeds the MTD is less than or equal to pre-specified feasibility bound. To make an adaptation for drug combination therapy in contemporary medicine, more parameters can be added to the logistic regression model to define the relationship of the toxicity probability and the multiple drug dose levels. The interaction of multiple drugs can be taken into consideration here as well.

Moreover, the measurement of toxicity in cancer Phase I trials is usually treated as a binary outcome [4] based on the National Cancer Institute's (NCI) common toxicity criteria [6]. Typically, patients with grade 3 or 4 non-hematologic and grade 4 hematologic toxicities as well as grade 5 are considered suffering DLT. However, this will lead to underutilizing toxicity information because we discard partial drug toxicity data when converting the measurement of toxicity into a binary indicator of a DLT [7]. Some patients have multiple DLTs and those DLTs are not equally severe in real trials, for example, grade 4 more severe than a grade 3, but the indicator of DLT cannot reflect and distinguish this difference. Furthermore, dichotomizing would ignore a certain level

of toxicity information since indicators only depend on worst toxicity. Chen and colleagues proposed a Phase I trial design entitled Escalation with Overdose Control using a Normalized Equivalent Toxicity Score (EWOC-NETS), which can fully utilize all the toxicity information by treating toxicity outcome as a quasi-continuous variable. Furthermore, EWOC-NETS can outperform EWOC when estimating the MTD for a single agent [7].

In this thesis, we developed a Bayesian Adaptive Phase I clinical trial design entitled Escalation with Overdoing Control using a Normalized Equivalent Toxicity Score for estimating the MTD contour of two drug combinations (EWOC-NETS-COM) after taking into account all of the toxicity information collected from patients. In the new design EWOC-NETS-COM, four parameters proposed in EWOC for a two drug combination (EWOC-COM) [8] are used in the Dose -Toxicity Model, this model describes the association between the dosage of two drugs and NETS. These parameters in this model have an explicit practical meaning and are insensitive to vague prior distributions. Additionally, with these four parameters, the estimated MTD curve of the two-drug combinations lies on a Cartesian plane defined within the range of the drugs' dosage level [8]. The reference method be selected in this thesis is EWOC-COM, the Dose-Toxicity model in this design portrays the relationship between probability of DLT and dosage of two agents.

Markov Chain Monte Carlo (MCMC) is a method comprising different algorithms to obtain realization from a high-dimensional probability density. Bayesian inference Using Gibbs Sampling (BUGS) is a program for analyzing Bayesian Graphical models via MCMC simulation. The principle of BUGS is drawing samples from the posterior

distributions for inference, it can directly called from R. Additionally, JAGS is a clone of BUGS, it is another Gibbs Sampler serving the same aim and function as BUGS and is developed as an R package [9]. In this thesis, we used existing R package 'rjags' to employ the MCMC method to generate a sequence of dependent samples from the posterior distribution of the parameters of interest in the model which are implemented in EWOC-COM design. The model specified in EWOC-NETS-COM has quasi-continuous outcome. NETS follows quasi-Bernoulli distribution instead of strict Bernoulli distribution, therefore JAGS cannot be used to generate dependent samples from posterior distribution of the parameters. The Metropolis-Hastings (M-H) algorithm is introduced to fix this problem. M-H algorithm belongs to the MCMC method, it is one of the most popular techniques used by statisticians today. Markov Chain is a model describing a sequence of events, in which the current event only be impacted the by previous event. M-H algorithm produces a Markov Chain whose members' limiting distribution is the target density we want [10]. At step i, an observation becomes the next value in the Markov chain with certain probability. This probability is determined by likelihood ratio and target density. Due to the property of NETS in EWOC-NETS-COM design, we used the M-H algorithm instead of existing package 'rjags' in R to obtain samplers from posterior distributions, based on the samplers gained from M-H algorithm we obtained an estimation of parameters involved in the Dose-Toxicity Model then constructed the estimated MTD curve.

This thesis is organized in four sections. Section 1 is the Introduction. In Section 2, we describe the Dose-Toxicity Model with four parameters in the EWOC-NETS-COM design. In Section 3, we present the results of the simulation studies based on the EWOC-

NETS-COM design for estimating the MTD curve for the two-drug combination. Also, we make comparisons between EWOC-NETS-COM and EWOC-COM by evaluating the accuracy, safety, therapeutic effect, and efficiency for Phase I clinical trials. The newly developed method is fully discussed in Section 4.

2. Methods

2.1 EWOC-NETS-COM Design for Drug Combinations

Dose-Toxicity Model:

$$S_i|\boldsymbol{x},\boldsymbol{y} = F(\mu + \beta x_i + \gamma y_i + \eta_1 x_i y_i) \tag{2.1}$$

$where\ S_i$ denotes a normalized equivalent toxicity score (NETS) in an EWOC-NETS design for a two-drug combination, x, y represented by a standardized dose level of agent A and a standardized dose level of agent B with ranges from 0 to 1, respectively. F is a specified cumulative distribution function and is called a tolerance distribution. In this thesis, we specify F is as a logistic function. Under the assumption that the parameters β, γ, η_1 are all greater than 0 assures that S_i will increase with the increase of the dosage level for one of the two agents while keeping the dosage level of the other agent fixed. Therefore, the Dose-Toxicity Model (2.1) will lie on the Cartesian plane defined by dose level x, y within the domain $[X_{min}, X_{max}] \times [Y_{min}, Y_{max}]$, where X_{min} and X_{max} represent the available minimum and maximum dosage levels of agent A; Y_{min} and Y_{max} represent the available minimum and maximum dosage level of agent B with $X_{min}, Y_{min} > 0$.

The MTD curve is defined by any dosage combination (x^*, y^*) that satisfies the following equations:

$$S_i|x^*, y^* = \tilde{\theta} \tag{2.2}$$

$$y^* = \frac{F^{-1}(\tilde{\theta}) - \mu - \beta x^*}{\gamma + \eta_1 x^*} \tag{2.3}$$

where $\tilde{\theta}$ represents the target normalized equivalent toxicity score which is a pre-specified value determined by clinicians. Equation (2.3) is the expression of the MTD curve.

In order to obtain a practical interpretation of the parameters in Model (2.1), reparametrization is introduced to Model (2.1) by replacing μ, β, γ with $\rho_{00}, \rho_{01}, \rho_{10}$ and keeping η_1 the same as in [8].

Reparametrization:

$$\begin{cases} \mu \\ \beta \\ \gamma \\ \eta_1 \end{cases} \rightarrow \begin{cases} \rho_{00} \\ \rho_{01} \\ \rho_{10} \\ \eta_1 \end{cases}$$

ρ_{00} is value of S when $x = X_{min}\ and\ y = Y_{min}$

ρ_{01} is value of S when $x = X_{min}\ and\ y = Y_{max}$

ρ_{10} is value of S when $x = X_{max}\ and\ y = Y_{min}$

η_1 is the interaction term

$$\begin{cases} \mu = F^{-1}(\rho_{00}) \\ \beta = F^{-1}(\rho_{10}) - F^{-1}(\rho_{00}) \\ \gamma = F^{-1}(\rho_{01}) - F^{-1}(\rho_{00}) \\ \eta_1 \end{cases} \tag{2.4}$$

where we assume agent A and agent B with standardized dosage levels ranging from 0 to 1

Then the MTD curve can be re-defined as:

$$y^* = \frac{F^{-1}(\tilde{\theta}) - F^{-1}(\rho_{00}) - (F^{-1}(\rho_{10}) - F^{-1}(\rho_{00}))x^*}{(F^{-1}(\rho_{01}) - F^{-1}(\rho_{00})) + \eta_1 x^*} \qquad (2.5)$$

$$logit(\tilde{\theta}) = \mu + \beta\Gamma_{A|B=0} \qquad logit(\tilde{\theta}) = \mu + \gamma\Gamma_{B|A=0}$$

$$\Gamma_{A|B=0} = \frac{logit(\tilde{\theta}) - logit(\rho_{00})}{logit(\rho_{10}) - logit(\rho_{00})} \qquad \Gamma_{B|A=0} = \frac{logit(\tilde{\theta}) - logit(\rho_{00})}{logit(\rho_{01}) - logit(\rho_{00})}$$

$$\Gamma_{A|B=y_i} = \frac{logit(\tilde{\theta}) - \mu - \gamma y_i}{\beta + \eta_1 y_i} \qquad \Gamma_{B|A=x_i} = \frac{logit(\tilde{\theta}) - \mu - \beta x_i}{\gamma + \eta_1 x_i}$$

where $\Gamma_{A|B=y_i}$ represents the MTD of agent A when agent B dosage level is y_i and $\Gamma_{B|A=x_i}$ represents the MTD of agent B when agent A dosage level is x_i

The primary purpose of a Phase I clinical trial is to estimate the MTD curve when we have combination treatments. Therefore, $\Gamma_{A|B=y_i}$ and $\Gamma_{B|A=x_i}$ are the parameters of most interest here and they can be calculated based on the parameters $\rho_{00}, \rho_{01}, \rho_{10}, \eta_1$.

2.2 Prior and Posterior Distribution of Parameters for EWOC-NETS-COM Design

In this thesis, vague prior distributions for $\rho_{00}, \rho_{01}, \rho_{10}, \eta_1$ are employed when estimating the MTD contour. Since our primary outcome S is a normalized equivalent toxicity score with range from 0 to 1 [7], we specify prior distributions of ρ_{01} and ρ_{10} as uniform distributions ranging from 0 to 1, and denote them by $\rho_{01} \sim Uniform(0,1)$ and $\rho_{10} \sim Uniform(0,1)$. In the Introduction section, we have assumed $\beta > 0, \gamma > 0, \eta_1 > 0$. According to its definition, the parameter, ρ_{00}, is restricted within the range from 0 to the minimum between ρ_{01} and ρ_{10} instead of from 0 to 1 denoted as: $\rho_{00} \sim Uniform(0, \min(\rho_{01}, \rho_{10}))$. Also, a vague prior $Uniform(0,100)$ is specified for the interaction term, η_1, which assures us that the two drugs have positive impact on each other. In Model (2.1), the NETS score S could be treated as a fractional event with values

in the range between 0 to 1 [7]. S is a quasi-continuous toxicity score which follows a quasi-Bernoulli distribution and is incorporated into parametric Model (2.1). As presented in publications [11, 12], quasi-maximum likelihood estimates (QMLEs) are strongly consistent while the quasi-distribution belongs to the linear exponential family. The quasi-Bernoulli likelihood of parametric Model (2.1) is expressed below as:

$$L(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1 | D_n)$$

$$= \prod_{i=1}^{n} \left(logit^{-1}(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1; x_i, y_i)\right)^{S_i} \tag{2.6}$$

$$\times (1 - logit^{-1}(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1; x_i, y_i))^{1-S_i}$$

where $D_n = \{(x_i, y_i, S_i), i = 1, 2, \dots, n\}$ is the data set including the dosage levels of agents A and B, and $NETS$ for n patients who have been enrolled into a trial. S_i can be computed using methods proposed by Chen and colleagues [13] in real trials.

Based on Bayesian inference, the posterior density functions for those four parameters can be expressed below as:

$$\pi(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1 | D_n) = K(D_n) L(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1 | D_n)\, \pi(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1)$$

where $K(D_n)$ is scale term which only depends on data we collected; $\pi(\rho_{00}, \rho_{01}, \rho_{10}, \eta)$ is a joint prior density function.

$$K(D_n)$$

$$= \int\int\int\int_{\rho_{00}, \rho_{01}, \rho_{10}, \eta_1} L(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1 | D_n)\, \pi(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1)\, d\rho_{00} d\rho_{01} d\rho_{10} d\eta_1$$

$$\pi(\rho_{00}, \rho_{01}, \rho_{10}, \eta_1) = \pi(\rho_{00} | \rho_{01}, \rho_{10}) \pi(\rho_{01}) \pi(\rho_{10}) \pi(\eta_1)$$

Since the likelihood of parametric Model (2.1) is a quasi-Bernoulli likelihood and the joint posterior density function does not have a closed form, Markov Chain Monte Carlo

(MCMC) is utilized to estimate the marginal posterior distribution of the parameters in Model (2.1). The parameters $\Gamma_{A|B=y_i}$ and $\Gamma_{B|A=x_i}$ are estimated based on dependent samplers from posterior distribution of the parameters $\rho_{00}, \rho_{01}, \rho_{10}, \eta_1$ by using MCMC. In the MCMC procedure, we only keep the last 5,000 samples to estimate the marginal posterior distribution of those parameters.

2.3 EWOC-COM Design for Drug Combinations

Dose-Toxicity Model:

$$\Pr(Z_i = 1|\boldsymbol{x}, \boldsymbol{y}) = F(\beta_0 + \beta_1 x_i + \beta_2 y_i + \eta_2 x_i y_i) \quad (2.7)$$

where Z_i is the primary outcome of a trial and $Z_i = 1$ when a patient has DLT, $Z_i = 0$ otherwise and the probability of $Z_i = 1$ is transformed outcome at certain dosage levels; x, y represent the same information as described in an EWOC-NETS-COM design; and F is a logistic function. As in an EWOC-COM design, we assume all parameters to be greater than 0 in order to ensure that probability of a DLT at certain drug combination dosage levels will monotonically increase with the increase of the dosage level of one of agent while keeping the dosage level for the other agent the same. The domain for Model (2.7) will be defined as $[X_{min}, X_{max}] \times [Y_{min}, Y_{max}]$, where X_{min}, X_{max} represent available minimum and maximum dosage level of agent A, respectively; Y_{min}, Y_{max} represent respectively the available minimum and maximum dosage level of agent B with $X_{min}, Y_{min} > 0$.

The target probability for the DLT θ is defined as any dosage combination (x^*, y^*) satisfying the following condition:

$$\Pr(Z_i = 1|x^*, y^*) = \theta \quad (2.8)$$

The MTD curve can be further described by the following expression:

$$y^* = \frac{F^{-1}(\theta) - \beta_0 - \beta_1 x^*}{\beta_2 + \eta_2 x^*} \tag{2.9}$$

The same reparameterization will be performed as in EWOC-NETS-COM

Reparameterization:

$$\begin{cases} \beta_0 \\ \beta_1 \\ \beta_2 \\ \eta_2 \end{cases} \rightarrow \begin{cases} \rho_{00}{}' \\ \rho_{01}{}' \\ \rho_{10}{}' \\ \eta_2 \end{cases}$$

$$logit(\rho_{00}{}') = \beta_0 + \beta_1 X_{min} + \beta_2 Y_{min} + \eta_2 X_{min} Y_{min}$$

$$logit(\rho_{01}{}') = \beta_0 + \beta_1 X_{min} + \beta_2 Y_{max} + \eta_2 X_{min} Y_{max}$$

$$logit(\rho_{10}{}') = \beta_0 + \beta_1 X_{max} + \beta_2 Y_{min} + \eta_2 X_{max} Y_{min}$$

η_2 is interaction term same as before

$$\begin{cases} \beta_0 = logit(\rho_{00}{}') \\ \beta_1 = logit(\rho_{10}{}') - logit(\rho_{00}{}') \\ \beta_2 = logit(\rho_{01}{}') - logit(\rho_{00}{}') \\ \eta_2 \end{cases} \tag{2.10}$$

After reparameterization, the MTD curve is formulated below as:

$$y^* = \frac{logit(\theta) - logit(\rho_{00}{}') - (logit(\rho_{10}{}') - logit(\rho_{00}{}'))x^*}{(logit(\rho_{01}{}') - logit(\rho_{00}{}')) + \eta_2 x^*} \tag{2.11}$$

2.4 Prior and Posterior Distribution for Parameters of EWOC Design

In the EWOC-COM design, the prior distribution of parameters is based upon the same assumption as EWOC-NETS-COM. However there exist some differences such as the probability of the DLT is a continuous variable based on the binary outcome and the likelihood of the parameters is Bernoulli likelihood. Based on a Bayesian rule, the posterior joint distribution is below as:

$$\pi(\rho_{00}', \rho_{01}', \rho_{10}', \eta_2)$$

$$\propto \prod_{i=1}^{n} (\Pr(Z_i = 1|x, y))^{z_i} (1 - \Pr(Z_i = 1|x, y))^{1-z_i} \pi(\rho_{00}')\pi(\rho_{01}')\pi(\rho_{10}')\pi(\eta_2) \quad (2.12)$$

In the computation, JAGS is introduced in Introduction section and is used to estimate posterior distribution of these parameters in Model (2.7).

2.5 Trial Design

2.5.1 Pre-stopping Rule

The trial will stop before the total sample size (N patients) is achieved if three dose levels are assigned close enough to each other when measured by certain pre-specified criteria. If the dosage level is visualized by points that lie on a Cartesian plane, then the Euclidian distance between points measures how close are the dosage levels. To be more specific, we stop enrolling patients to a trial if the average of Euclidian distances between each other divided by the average of Euclidian distances between points of dosage levels to the origin is less than a certain value decided by clinicians before the trial begins. The condition can be represented by following equation:

$$\frac{\left|\left|\boldsymbol{\kappa_i} - \boldsymbol{\kappa_{i+2}}\right|\right| + \left|\left|\boldsymbol{\kappa_i} - \boldsymbol{\kappa_{i+4}}\right|\right| + \left|\left|\boldsymbol{\kappa_{i+2}} - \boldsymbol{\kappa_{i+4}}\right|\right|}{\left|\left|\boldsymbol{\kappa_i}\right|\right| + \left|\left|\boldsymbol{\kappa_{i+2}}\right|\right| + \left|\left|\boldsymbol{\kappa_{i+4}}\right|\right|} < \sigma \quad (2.13)$$

where $\boldsymbol{\kappa_i}$ represents a vector of dosage levels for i-th patient, $\forall i = 1 \ldots N$ and σ is constant specified before the trial starts. $\sigma = 0.05$ is used in this thesis.

2.5.2 Procedure for a Trial

For EWOC-COM and EWOC-NETS-COM trial designs, the dosage levels for agent A and for agent B are within the intervals $[X_{min}, X_{max}]$, $[Y_{min}, Y_{max}]$, respectively. Then

a univariate escalation scheme is used to increase alternately the dose level for one agent for each new cohort of two patients. A feasibility bound, denoted by α, in these EWOC-NETS-COM and EWOC-COM trial designs, sets an initial value of α= 0.25. Then when each new patient cohort is enrolled the value is increased in increments of 0.05 until α reaches 0.5. The only difference between those two designs is the type of outcome variable: EWOC-COM with a binary outcome, EWOC-NETS-COM with a quasi-continuous outcome. A detailed algorithm for implementing the EWOC-NETS-COM design is described as follows:

1. First two patients in first cohort will receive the same minimum dose levels of agent A and agent B

$$(x_1, y_1) = (x_2, y_2) = (X_{min}, Y_{min})\ D_2 = ((x_1, y_1, S_1), (x_2, y_2, S_2))$$

2. In the second cohort, the third patient will be treated under dose levels (x_3, y_3), x_3 is α-th percentile of marginal posterior distribution $\pi(\Gamma_{A|B=y_1}|D_2)$, and $y_3 = y_1$. The fourth patient will receive dose levels (x_4, y_4), in which y_4 is α-th percentile of marginal posterior distribution $\pi(\Gamma_{B|A=x_1}|D_2)$, and $x_4 = x_2$
3. Starting from the third cohort, the design will take one of the following 4 choices:

   (1). If k-th patient is jth patient in ith cohort, i is even and j is odd,

   then $y_k = y_{k-2}, x_k = \alpha$-th percentile of marginal posterior distribution $\pi(\Gamma_{A|B=y_{k-2}}|D_{2i-2})$

   (2). If k-th patient is jth patient in ith cohort, i is even and j is even,

   then $x_k = x_{k-2}, y_k = \alpha$-th percentile of marginal posterior distribution $\pi(\Gamma_{B|A=x_{k-2}}|D_{2i-2})$

   (3). If k-th patient is jth patient in ith cohort, i is odd and j is even,

then $y_k = y_{k-2}, x_k = \alpha$-th percentile of marginal posterior distribution $\pi(\Gamma_{A|B=y_{k-2}}|D_{2i-2})$

(4). If k-th patient is jth patient in ith cohort, i is odd and j is odd,

then $x_k = x_{k-2}, y_k = \alpha$-th percentile of marginal posterior distribution $\pi(\Gamma_{B|A=x_{k-2}}|D_{2i-2})$

To restrict α-th percentile of the marginal posterior distribution $\pi(\Gamma_{B|A=x}|D)$ and $\pi(\Gamma_{B|A=x}|D)$ between 0 and 1, the MCMC sampler is truncated within the range from 0 to 1.

4. Repeat step 3, until the fixed target sample size (N) patients has been recruited into the trial or the pre-trial stopping rule has been achieved.

The EWOC-COM design uses the same set of algorithmic procedures except using the probability of a DLT instead of NETS.

3. Simulation Studies

To assess the performance of the EWOC-NETS-COM design for drug combinations, simulation studies were conducted to compare EWOC-NETS-COM and EWOC-COM under different scenarios. Their performances are evaluated in terms of the MTD accuracy, therapeutic effect, trial safety, and trial efficiency.

3.1 Simulation Setup and Scenarios

In the EWOC-COM design, the target probability of a DLT is set as 33% and the equivalent corresponding target NETS (TNETS) of the EWOC-NETS-COM design is 0.476 under an "ideal" scenario as described in the original publication of Chen and colleagues [13]. Among all simulation scenarios, the logistic function is used as link

function F, sample size is fixed as 40, and target percent of a DLT θ is 0.33 in the EWOC-COM design, TNETS $\tilde{\theta}$ is 0.476 in the EWOC-NETS-COM design. In the simulations, NETS are generated from Model (2.1) after adding some random effect. Dose level assigned to each patient is computed from α-th percentile of the posterior distribution of the parameters $\Gamma_{A|B=y}$ and $\Gamma_{B|A=x}$, where α is a feasibility bound with a pre-specified value. The α will increase at increments of 0.05 per new patient cohort until reaching the maximum value of 0.5. Simulation results are presented by plotting estimate curves across the four different scenarios. The estimates of the MTD accuracy, trial safety and efficiency are summarized in tables. Scenario 1 corresponds to a situation where both drugs are extremely safe for patients and have weak synergy. Scenario 2 corresponds to a situation where the MTD for agent A is in the agent A dose level interval when agent B is at the minimum dose level, but the MTD for agent B is slightly out of the range for the agent B dose level while agent A is at the minimum dose level and they have a medium level of synergy. Scenario 2 means agent B is safer than agent A. The Scenario 3, is the opposite of Scenario 2. In Scenario 3, the agent A is safer than agent B, also there is a medium level of synergy between two agents. The last scenario is similar to Scenario 2 except that the two agents strongly interact. In all scenarios, the priors of those four parameters are vague as we described in Section 2. All four different scenario set-ups are summarized in *Table 1* for both the EWOC-COM and the EWOC-NETS-COM designs. Within each scenario, 100 trials are simulated for both the EWOC-COM and the EWOC-NETS-COM designs. The MTD curve is obtained from estimates of those four parameters used in the reparameterization for the EWOC-COM and the EWOC-NETS-COM designs. For making direct comparisons between two designs, we

rescale the parameters in Model (2.1) so that the true MTD curve in both designs is the exactly same. Additionally, in the EWOC-NETS-COM design, patients be counted as DLT when their corresponding NETS is greater than 0.476. Through this procedure percent of DLT across 100 simulations is computed. Comparative results of the MTD accuracy, trial safety and efficiency between the two designs are summarized in tables and plots in the Appendix.

3.2 Performance Criteria for Trial Designs

For each scenario, the formulas to get estimates of the MTD curves for the EWOC-NETS-COM design and the EWOC-COM design are expressed below.

For the EWOC-NETS-COM design,

$$y^* = \frac{logit(\tilde{\theta}) - logit(\widehat{\rho_{00}}) - (logit(\widehat{\rho_{10}}) - logit(\widehat{\rho_{00}}))x^*}{(logit(\widehat{\rho_{10}}) - logit(\widehat{\rho_{00}})) + \widehat{\eta_1}x^*} \qquad (3.1)$$

where $\widehat{\rho_{00}}, \widehat{\rho_{10}}, \widehat{\rho_{10}}, and\ \widehat{\eta_1}$ are respectively the average of estimates from the corresponding parameters among 100 simulated trials. Each estimate from a single trial is the median of its posterior distribution obtained from the MCMC procedure,

For the EWOC-COM design,

$$y^* = \frac{logit(\theta) - logit(\widehat{\rho_{00}}') - (logit(\widehat{\rho_{10}}') - logit(\widehat{\rho_{00}}'))x^*}{(logit(\widehat{\rho_{10}}') - logit(\widehat{\rho_{00}}')) + \widehat{\eta_2}x^*} \qquad (3.2)$$

where $\widehat{\rho_{00}}', \widehat{\rho_{10}}', \widehat{\rho_{10}}', and\ \widehat{\eta_2}$ are respectively the average of estimates from the corresponding parameters among 100 simulated trials. Each estimate from a single trial is the median of the posterior distribution obtained from the MCMC procedure.

One trial performance measure is safety which can be assessed by percent of DLTs among all patients and all trials. Another measure is MTD accuracy, which is evaluated by three criteria. The measurements for the first criteria are bias, standard error

(SE) and mean squared error (MSE) of the relevant parameters in Dose-Toxicity Model. For the second criteria, we select some points from the true MTD curve, find the point on the estimated curve that has the minimum distance from true MTD curve, and then compute the average of those minimum distances. This measurement is called pointwise average relative minimum distance between true MTD curve and estimated MTD curve denoted ($\overline{d_{(x,y)}}$). Pointwise bias between the true curve and the estimated curve can be expressed by $\overline{d_{(x,y)}}$[6,10]. The calculation formula is as below:

$$d^{j}_{(x,y)} = sign(y' - y) \times \min\left(\sqrt{(x-a)^2 + (y-b)^2}\right) \tag{3.3}$$

$$\overline{d_{(x,y)}} = \frac{1}{M}\sum_{j=1}^{n} d^{j}_{(x,y)} \tag{3.4}$$

The (x, y) denote the points that have be selected from the true MTD curve. The y' is calculated by plugging x into the estimated MTD curve, (a, b) is the point on the estimated curve and M represents the number of trials we have. The last measurement criteria of the MTD accuracy is the pointwise percent of trials that have minimum distance from a selected location (x, y) on the true curve to the estimated curve that is no more than 20% of the distance between (x, y) and origin [8, 14]. This measurement can be computed based on the equation below:

$$\frac{1}{n}\sum_{j=1}^{n} I\left(\left|d^{j}_{(x,y)}\right| < p\Delta(x,y)\right) \tag{3.5}$$

where $\Delta(x, y)$ is the distance between (x, y) and origin, $p = 0.2$ is selected. This measurement also could as criteria for therapeutic effect because therapeutic effect is achieved by reducing the probability of patients be treated far away from target dosage levels.

The final trial criteria measurement is the trial efficiency. Average sample size after conducting the pre-stopping rule could reflect trial efficiency. Smaller average sample size yields better trial efficiency.

4. Results

Figure 1 shows plots of the estimated MTD curve and the true MTD curve under four scenarios for the EWOC-NETS-COM design. The red solid lines represent estimated MTD curves obtained from Model (2.1), the black solid lines represent the true MTD curves defined by parameters that are summarized in *Table 1*. As shown in *Figure 1*, the estimated MTD curve is extremely close to true MTD curve especially under S4. Under S2 and S3, the estimated curves are also close to the true curves except near the edges of curves. But the estimated MTD curve under S1 is far away from the true curve, as considered in detail in the Discussion section.

Figure 2 represents the estimated MTD curves and the true MTD curves for the EWOC-COM design. From *Figure 1* and *Figure 2* we can see that estimated curves obtained from Model (2.1) are closer to the true curve than estimated curves computed from Model (2.7) under S2 and S3. Estimated curves for both designs nearly overlay the true curve under S4. The estimated MTD curve for S1 under both trial designs is far from the true MTD curve since there is no toxicity information under this scenario.

Table 2 gives the average percentage of a DLT across four different scenarios of the EWOC-NETS-COM and the EWOC-COM designs. The average percent of a DLT in the EWOC-NETS-COM design varies from 0.00% to 26.36% across scenarios 1 to 4. In the EWOC-COM design, it varies from 0.17% to 28.65% across scenarios 1 to 4. The simulation results in *Table 2* shows that, both designs could satisfy the purpose of

Escalation with Overdose Controls since all probabilities of DLT under both design across four different scenarios are lower than the target probability of DLT it is 33%. *Table 2* presents the summary of bias, standard error (SE) and MSE of the estimators of interest for $\Gamma_{A|B=0}$ and $\Gamma_{B|A=0}$. These two parameters represent the MTD of a single agent when the other agent is at the minimum dose level. Based on the results in *Table 2*, the EWOC-NETS-COM design yields a smaller SE although it yields a higher bias compared to the EWOC-COM. The reason why bias calculated from EWOC-NETS-COM is higher is discussed in the Discussion section. After the trade-off between bias and SE, the EWOC-NETS-COM design gives lower MSE for both parameters than EWOC-COM design. This result supports the conclusion that estimated curve from the EWOC-NETS-COM design provides more stable estimation of the MTD curve. In addition, *Table 2* also gives average sample sizes under all scenarios that are measurements of trial efficiency. The EWOC-NETS-COM yielded smaller average sample sizes compared to the EWOC-COM design under the majority scenarios except S2. Under S2, the two-averaged sample size are very close. Making comparisons between the EWOC-NETS-COM and the EWOC-COM supports the conclusion that the EWOC-NETS-COM has better trial efficiency in some sense.

Figure 3 presents plots of pointwise average relative minimum distances from the true MTD curves to the estimated MTD curves called pointwise bias under S1 to S4. Under S2 and S3, the pointwise bias detracts from 0 at the edges of the true MTD curve for both designs. Under the EWOC-NETS-COM design, the average pointwise bias of the center part of the true MTD curve is slightly closer to 0. For S4, the pointwise bias is similar under both designs and for both are negligible.

Figure 4 shows plots of the second measure of trial efficiency that is the pointwise percent of the MTD recommendation for the tolerance p to be 0.2. It is clear in the plots that the EWOC-NETS-COM will always results in an MTD estimated within 20% of the true combination of the MTD under scenario 2 to scenario 4. Whereas, the results from the EWOC-NETS-COM design are better than results from the EWOC-COM design.

5. Discussion

Application of the Bayesian Adaptive Design for the MTD curve estimation of drug combinations has been studied by several investigator groups[8, 13]. The normalized equivalent toxicity score was introduced into cancer Phase I clinical trials in 2010, has been shown to improve the trial efficiency and the MTD accuracy when estimating the MTD for single drugs. In addition, the EWOC-NETS design has been implemented in several cancer Phase I clinical trials [13, 15]. In this thesis, we employ the EWOC-NETS as a framework to estimate the MTD contour of two-drug combinations (EWOC-NETS-COM) and demonstrate that the EWOC-NETS-COM design under different simulation scenarios has superior performance on trial efficiency and precision of estimating the MTD contour. This result is consistent with some previous study results in regard to comparison of the performance between the EWOC-NETS and the EWOC designs [7] [13, 16]. Equally important, the model used for estimating the MTD contour can be extended into multiple drug combinations in the future. In summary, this thesis has extended EWOC-NETS, which incorporates equivalent toxicity score systems fully by utilizing all toxicity information instead of binary outcomes for the EWOC design. The simulation results demonstrate that the EWOC-NETS-COM can improve the accuracy of the MTD contour and trial efficiency, as well as preventing under dosage in too many

patients in cancer Phase I clinical trials, while also addressing the ethical concerns of patient safety.

In this thesis, I found that the new method has some weaknesses and needs to be improved through future work. The first weakness is that, since the NETS follows quasi-Bernoulli distribution, it is not a strict Bernoulli distribution. This leads to the bias of parameters is larger than estimations from EWOC-COM design. This situation is shown in *Table 2* and *Figure 3*, especially in Scenario 1; the reason why bias in the EWOC-NETS-COM design much larger than EWOC-COM design is that, Scenario 1 is an extreme case in which both drugs are very safe and no DLT occurs means no information about toxicity. Naturally, it is hard to make inferences based on such limited information. The second weakness is that, under the framework of EWOC-NETS-COM design, it is hard to incorporate preliminary information about a single drug. It is clearly that toxicity information about a single drug is valuable and could provide a guide when we conduct trials with two-drug combinations. In addition, at the end of trial, the novel method provides a curve of two-drug combinations, which means any combinations as long as it satisfies the estimated MTD curve is a possible dosage combination for the following Phase II and Phase III designs. I did not provide any method to assess the efficiency of those possible combinations. Based on my studies, it is impossible to distinguish those dosage combinations, and in real trials this may be inconvenient for the following stage of clinical trials. In the future, it is desirable to develop criteria to assess the efficiency of those dosage combinations lie on estimated MTD curves.

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8. Appendix

Table 1 Simulation Scenario Set-up

	Scenario 1 (S1)			
	(Both drugs are extremely safe with low level interaction)			
	ρ_{00}	ρ_{01}	ρ_{10}	η
EWOC-COM	$1\,X10^{-7}$	3×10^{-6}	3×10^{-6}	10
EWOC-NETS-COM	1.84×10^{-7}	5.51×10^{-6}	5.51×10^{-6}	10
	Scenario 2 (S2)			
	(Agent A more toxic than Agent B with median level interaction)			
	ρ_{00}	ρ_{01}	ρ_{10}	η
EWOC-COM	0.01	0.2	0.9	20
EWOC-NETS-COM	0.0183	0.316	0.943	20
	Scenario 3 (S3)			
	(Agent B more toxic than Agent A with median level interaction)			
	ρ_{00}	ρ_{01}	ρ_{10}	η
EWOC-COM	0.001	0.6	0.1	10
EWOC-NETS-COM	0.00184	0.735	0.0183	10
	Scenario 4 (S4)			
	(Agent A more toxic than Agent B with median level interaction)			
	ρ_{00}	ρ_{01}	ρ_{10}	η
EWOC-COM	0.01	0.2	0.9	100
EWOC-NETS-COM	0.0183	0.316	0.943	100

Dosage level of Agent A represented by x in Dose-Toxicity Model
Dosage level of Agent B represented by y in Dose-Toxicity Model

Table 2 Simulation Results from the EWOC-COM and the EWOC-NETS-COM Designs under Different Scenarios

EWOC-NETS-COM						
	Estimation of the MTD				Average Sample Size	Average Pr(DLT) (%)
	Parameters	Bias	SE	MSE		
S1	$\Gamma_{A\|B=0}$	-2.397	0.097	5.756	29.28	0.00
	$\Gamma_{B\|A=0}$	-2.173	0.163	4.750		
S2	$\Gamma_{A\|B=0}$	0.296	0.019	0.088	22.22	15.41
	$\Gamma_{B\|A=0}$	-0.072	0.036	0.007		
S3	$\Gamma_{A\|B=0}$	-1.170	0.019	1.368	23.28	18.10
	$\Gamma_{B\|A=0}$	0.260	0.019	0.068		
S4	$\Gamma_{A\|B=0}$	0.154	0.009	0.024	16.06	26.36
	$\Gamma_{B\|A=0}$	-0.353	0.044	0.127		
EWOC-COM						
	Estimation of the MTD				Average Sample Size	Average Pr(DLT) (%)
	Parameters	Bias	SE	MSE		
S1	$\Gamma_{A\|B=0}$	0.413	3.156	10.134	33.68	1.41
	$\Gamma_{B\|A=0}$	-0.437	1.686	3.033		
S2	$\Gamma_{A\|B=0}$	0.411	0.305	0.262	20.23	0.17
	$\Gamma_{B\|A=0}$	0.414	0.756	0.743		
S3	$\Gamma_{A\|B=0}$	-0.197	0.858	0.775	24.82	14.98
	$\Gamma_{B\|A=0}$	0.299	0.370	0.227		
S4	$\Gamma_{A\|B=0}$	0.153	0.140	0.043	21.25	28.65
	$\Gamma_{B\|A=0}$	-0.059	0.409	0.170		

Figure 1 True and Estimated MTD Curves for the EWOC-NETS-COM Designs under Different Scenarios

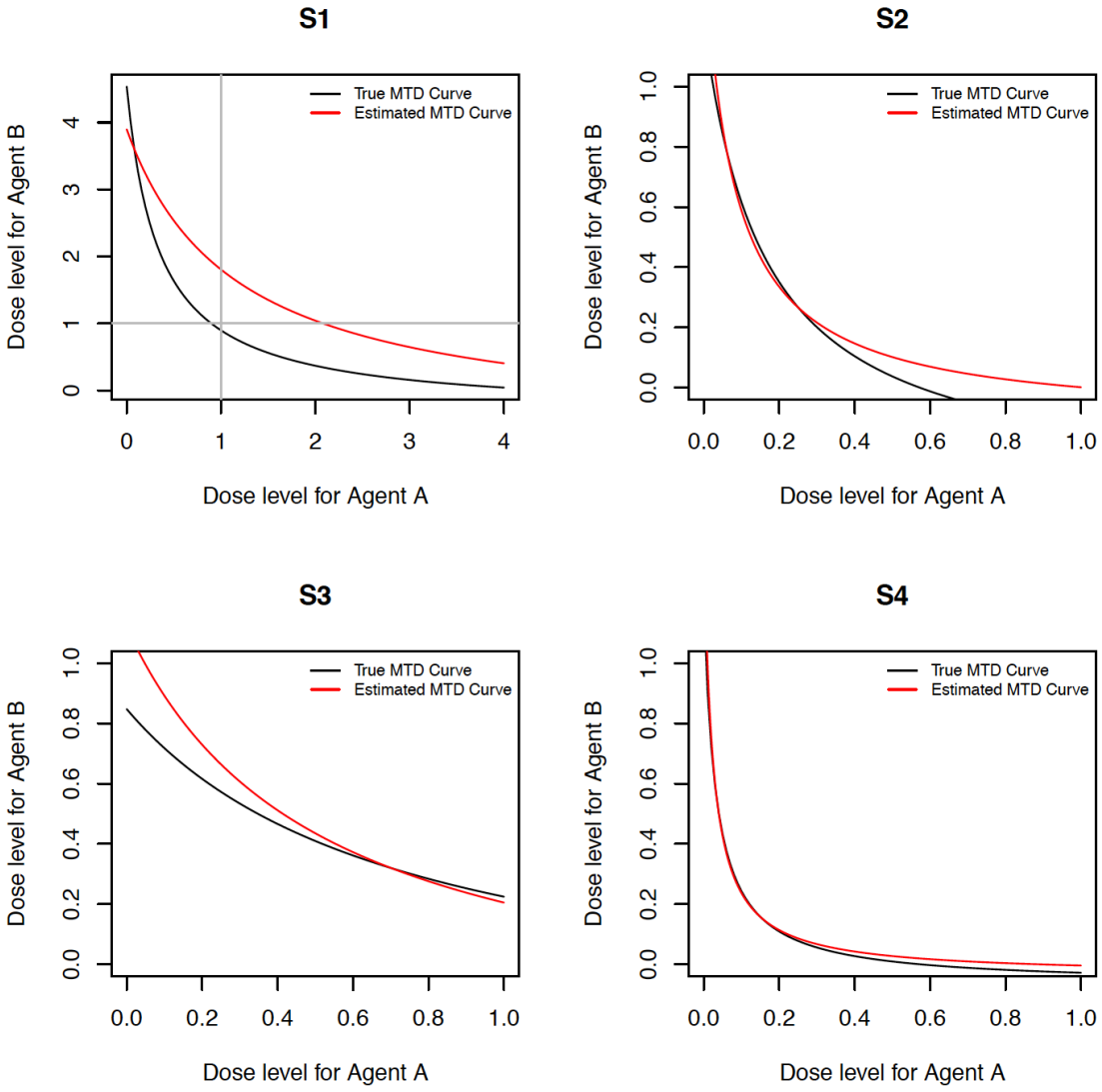

Figure 2 True and Estimated MTD Curves for the EWOC-COM Designs under Different Scenarios

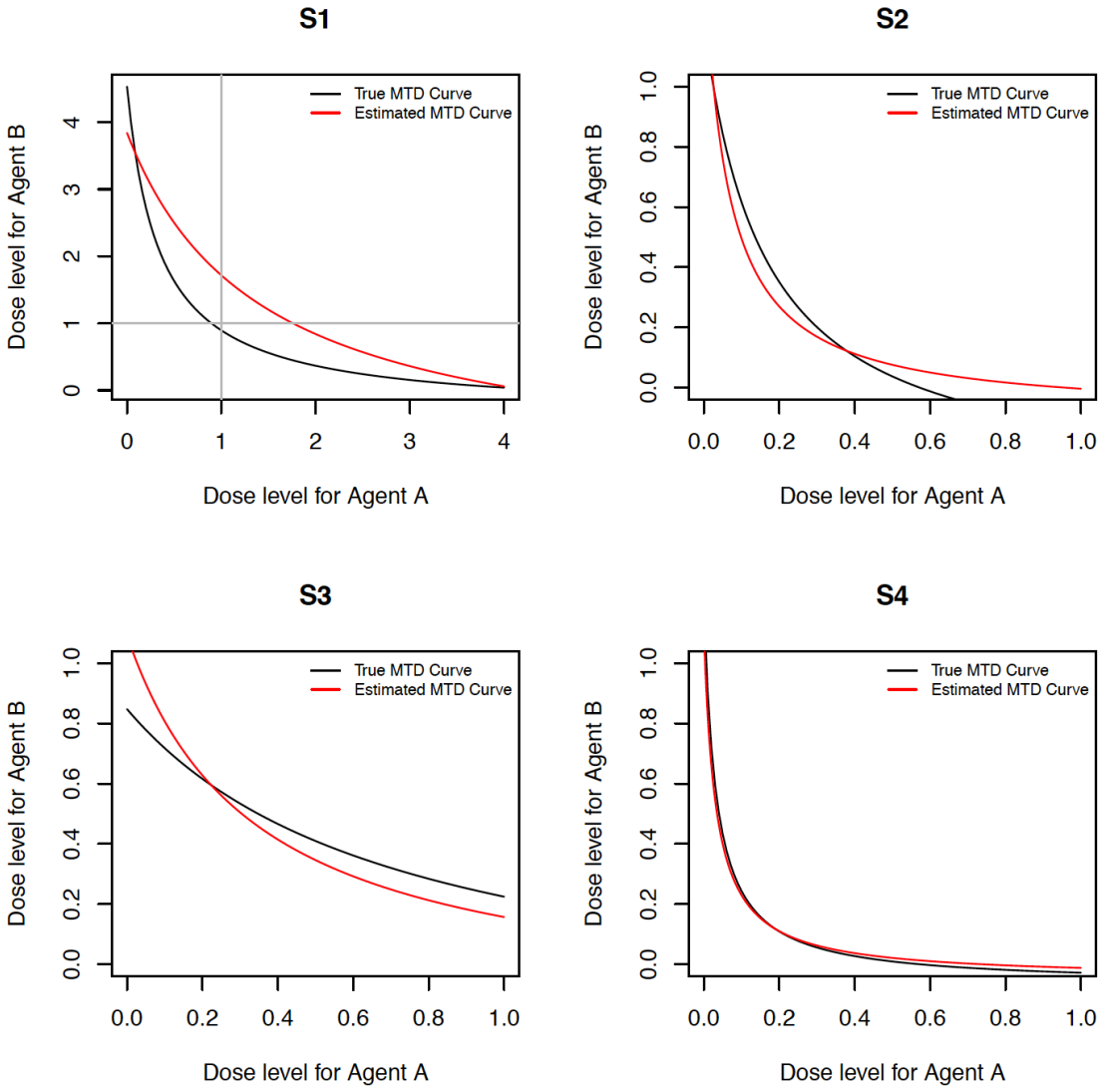

Figure 3 Pointwise Average Relative Minimum Distance from the True MTD Curve to Estimated Curve for EWOC-COM and for EWOC-NETS-COM Designs under Different Scenarios

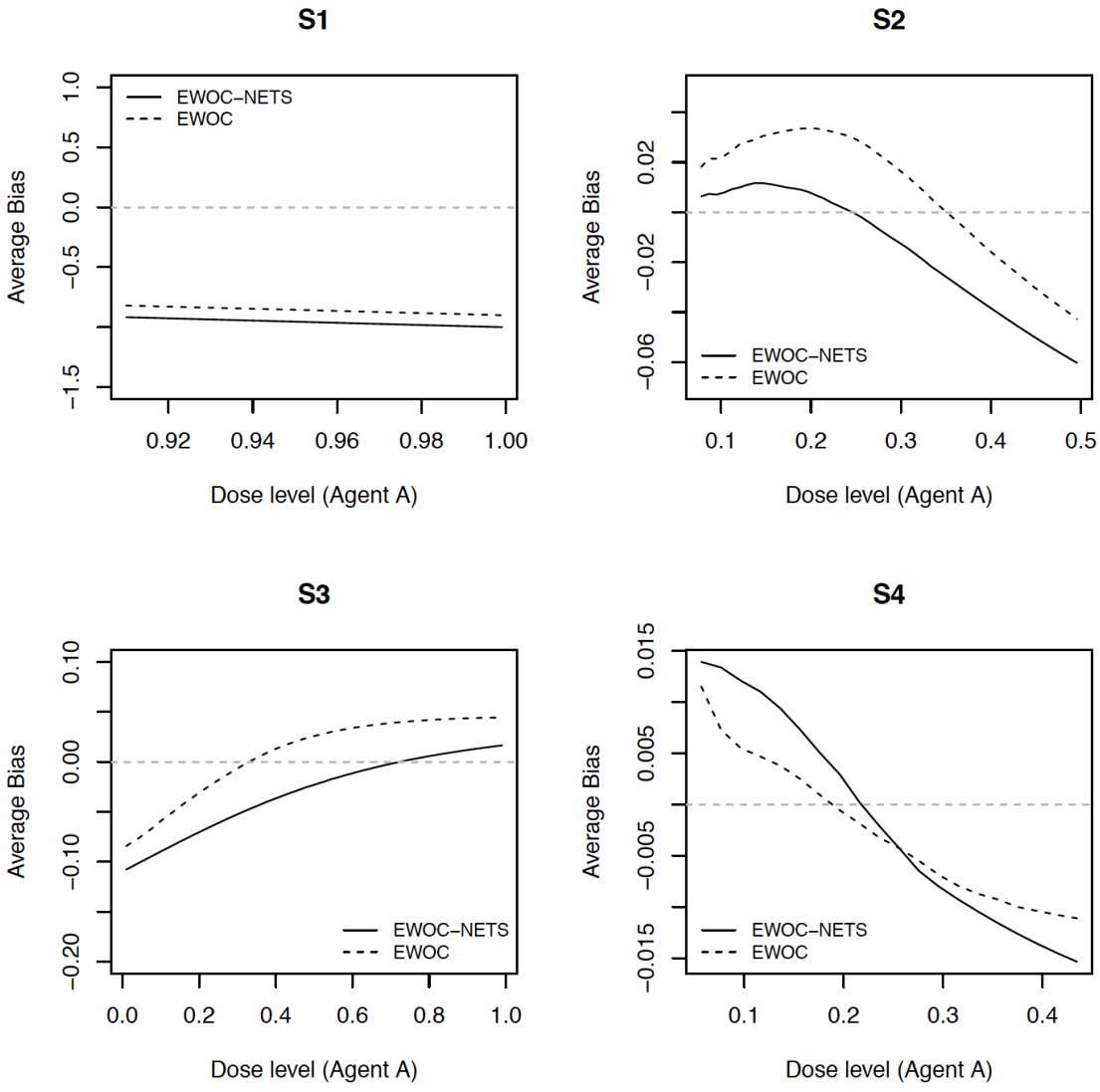

Figure 4 Pointwise Percent of MTD Recommendation for p=0.2 for EWOC-COM and for EWOC-NETS-COM Designs under Different Scenarios