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Escalation with Overdose Control using All Toxicities and Time to Event Toxicity Data in Cancer Phase I Clinical Trials

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Abstract

The primary purposes of Phase I cancer clinical trials are to determine the maximum tolerated dose (MTD) and the treatment schedule of a new drug. Phase I trials usually involve a small number of patients so that fully utilizing all toxicity information including time to event toxicity data is key to improving the trial efficiency and the accuracy of MTD estimation. Chen *et al.* [1] proposed a novel normalized equivalent toxicity score (NETS) system to fully utilize multiple toxicities per patient instead of a binary indicator of dose limiting toxicity (DLT). Cheung and Chappell [2] developed the time to toxicity event (TITE) approach to incorporate time to toxicity event data. Escalation with Overdose Control (EWOC) is an adaptive Bayesian Phase I design which can allow rapid dose escalation while controlling the probability of overdosing patients [3]. In this manuscript, we use EWOC as a framework and integrate it with the NETS system and the TITE approach to develop an advanced Phase I design entitled EWOC-NETS-TITE. We have conducted simulation studies to compare its operating characteristics using selected derived versions of EWOC because EWOC itself has already been extensively compared with common Phase I designs [3]. Simulation results demonstrate that EWOC-NETS-TITE can substantially improve the trial efficiency and accuracy of MTD determination as well as allow patients to be entered in a staggered fashion to significantly shorten trial duration. Moreover, user-friendly software for EWOC-NETS-TITE is under development.

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Keywords

Escalation with Overdose Control; Maximum Tolerated Dose; Multiple Toxicities; Quasi-continuous; Normalized Equivalent Toxicity Score; Toxicity Score System; Time to Toxicity Event; Phase I Clinical Trial

1. Introduction

Developing new anti-cancer drugs is a very complicated, extremely expensive and time-consuming process which includes: (1) the discovery of agents that demonstrate anti-tumor activity in preclinical models, (2) the evaluation of normal tissue toxicity, and (3) the confirmation of applicability in cancer patients in clinical trials. Phase I trials are conducted to seek a new drug's toxic effect on patients and to look for an optimal dose, called the maximum tolerated dose (MTD), which maximizes its therapeutic effect while maintaining a tolerable toxic effect [4]. The estimated MTD and the administered schedule of a new drug or treatment determined in a Phase I clinical trial will then be employed in Phase II and III clinical trials in which efficacy and therapeutic effects will be assessed.

Traditional cancer clinical trials begin with a Phase I study to test a new agent or treatment in cancer patients. There are two categories of designs for Phase I clinical trials; namely, rule-based and model-based designs. The standard 3+3 design is a popular rule based design, but it yields poor performance both in the accuracy of MTD and the therapeutic effect for patients [5, 6]. Adaptive and sequential designs have become increasingly popular in Phase I clinical trials [7]. In 1990, O'Quigley developed a Bayesian adaptive model-based design, the Continuous Reassessment Method (CRM), which significantly improves the accuracy of determining the MTD and provides better therapeutic effects for patients [8]. But CRM has been criticized for its high probability of exposing patients to over-toxic dosage [9]. As safety and ethical issues are of high priority when designing a Phase I trial due to limited information on patients' reactions to the drug, Babb et al. proposed another Bayesian approach, Escalation With Overdose Control (EWOC), to address this ethical concern by controlling the probability of overdosing patients during the dose escalation [3].

In both the EWOC and CRM designs, a binary indicator of dose limiting toxicity (DLT) (whether DLT occurs during the observation window of one cycle of therapy) is adopted to describe toxicity outcomes. In spite of its ease of application, there are unavoidable limitations in using DLT as a binary indicator [10, 11]. Patients often have multiple toxicities, but in this estimation of DLT, all other toxicities of each patient are ignored except the worst one. Moreover, even the grade of the worst toxicity is not fully utilized because the 5 grade levels are dichotomized into a binary indicator of DLT (Yes vs No). Chen and others have proposed a novel normalized equivalent toxicity scoring (NETS) system to utilize all toxicities and their grades of patients and demonstrated that it can substantially improve the accuracy of MTD and the trial efficiency [1, 12, 13].

In the current EWOC or CRM designs, some patients under treatment might not have completed the full assessment period and their toxicity outcomes, especially those late-onset toxicities, might not be fully available at the moment of dose assignment for a newly

arriving patient cohort. Usually, one way to solve the timeliness problem is to replicate dose levels when patients are accrued before the acquisition of new complete data. But this method will allocate the same dose level for several patients without any dose escalation and updating the estimate of MTD when the accrual rate is high. The newly recruited patients may also be accrued at a dose level recommended on the basis of all complete available information ignoring data from the patients not completed. In both scenarios, a high proportion of patients can be included at inefficient dose levels and this may lead to a poor estimate of the MTD because of the limited number of patients in a Phase I trial, the partially complete follow-up information and the partially available toxicities of the patients. An alternative option is to wait until all the toxicity responses of patients are available before making a decision on the dose assignment for newly arrived patient cohorts. However, this waiting time may significantly prolong the length of trials, especially when the evaluation window is long when compared to the arrival rate of patients. Furthermore, cancer patients in Phase I clinical trials cannot wait a long time to receive treatment as they usually have late stage cancers and have failed other standard treatments. The investigational drug is usually taken as their last resort. The need for a waiting period also complicates access of the patients to the Phase I trial and repeated accrual suspensions impose excessive administrative burdens and inconveniently long trial duration. Therefore, it is ideal to utilize the length of follow-up as well as those partially available toxicities of the uncompleted patients to determine dose assignment for staggered enrolled patients without a waiting period. In order to utilize the time to determine the DLT, Cheung and Chappell proposed a method called time to event (TITE) which uses weights to account for the percentage of follow-up times compared to the full observation window period [2]. Mauguén et al. have modified EWOC with the TITE method to take into account incomplete toxicity outcomes [14].

In order to fully utilize all toxicity information (frequency and grade) and the toxicity data of uncompleted patients as well as their follow-up time, we developed an advanced adaptive Phase I clinical trial design called EWOC-NETS-TITE which is an integration of the EWOC design, the NETS toxicity system, and the TITE method. The EWOC-NETS-TITE design is expected to produce several outstanding operating characteristics by: 1) addressing ethical concerns of over dosing patients; 2) improving the accuracy of the MTD; 3) increasing the efficiency of the trial; 4) fully utilizing incomplete patient data and follow-up time; 5) shortening the time length of trial; 6) improving therapeutic effectiveness for patients. Design operating characteristics are studied using extensive simulations and are compared with two different versions of EWOC by Babb et al [3], EWOC-NETS by Chen et al [12], and TITE-EWOC by Mauguén et al [14]. We are also developing user-friendly software for EWOC-NETS-TITE which will be freely available.

The remainder of the manuscript is organized as follows. In Section 2, we briefly review the original EWOC methodology, the NETS toxicity scoring system, and the TITE approach. In Section 3.1, we present simulation studies to compare the operating characteristics of the new EWOC-NETS-TITE design with EWOC, EWOC-NETS, and TITE-EWOC, and in Section 3.2 we conduct sensitivity analyses to further investigate the properties of EWOC-NETS-TITE. We conclude with a brief discussion of our findings in Section 4.

2. Methodology of EWOC-NETS-TITE

Phase I clinical trials are usually small studies with limited toxicity information. Therefore, full utilization of all toxicity and time to toxicity data is essential to improve the trial efficiency and accuracy of MTD estimation. A novel normalized equivalent toxicity score (NETS) system has been proposed which can fully utilize multiple toxicities per patient instead of a binary indicator of dose limiting toxicity (DLT) [1, 12, 13]. The time to event (TITE) approach has been developed to incorporate time to toxicity data [2]. Escalation with Overdose Control (EWOC) is an adaptive Bayesian Phase I design which allows rapid dose escalation as well as control the probability of overdosing patients. It has been used to design a number of Phase I clinical trials [15-19]. In this manuscript, we use EWOC as a framework and integrate it with the NETS system and TITE approach to develop an advanced Phase I design entitled EWOC-NETS-TITE. This hybrid design can not only improve the trial efficiency and MTD accuracy substantially, but also allows patients to be entered in a staggered fashion to shorten trial time. The remainder of Section 2 will elaborate the theory of EWOC-NETS-TITE step by step.

2.1 Measurement of toxicity response

In EWOC-NETS-TITE, the toxicity response for each patient is not measured using a binary indicator of the DLT (0 or 1). Instead, a normalized equivalent toxicity score (NETS) is calculated for each patient based on all the toxicities the patient experiences according to the NETS system proposed by Chen et al [1, 12, 13]. Here we give a brief description of how NETS is calculated. Suppose there are N patients in the trial ($i=1$ to N) and each patient has J toxicities. The adjusted grade of the j^{th} toxicity $G_{i,j}$, $j=1, \dots, J_i$ of the i^{th} patient is defined as 0 for grade 0 toxicity, 1 for grade 1 toxicity, 2 for grade 2 toxicity, 3 for grade 3 non-DLT, 4 for grade 4 non-DLT, 5 for grade 3 DLT, and 6 for grade 4 DLT. Then the worst toxicity with the highest adjusted grade among all the toxicities of the i^{th} patient $G_{i,max}$ is defined as $G_{i,max} = \max(G_{i,j}, j=1, \dots, J_i)$. The NETS, S_i , for patient i is defined to be 0 if patient i has no toxicity, equals 1/60 if patient i has only one grade 1 toxicity, or is calculated from the equation (1) below:

$$S_i = \frac{1}{6} \left[G_{i,max} - 1 + \frac{\exp \left(-2 + \Delta * \left(\sum_{j=1}^{J_i} \frac{r_{i,j} G_{i,j}}{G_{i,max}} - 1 \right) \right)}{1 + \exp \left(-2 + \Delta * \left(\sum_{j=1}^{J_i} \frac{r_{i,j} G_{i,j}}{G_{i,max}} - 1 \right) \right)} \right] \quad (1)$$

The parameter $r_{i,j}$ represents the correlation of the j^{th} toxicity with other toxicities for the i^{th} patient. The slope parameter Δ represents the increasing “speed” of NETS due to additional toxicity besides the worst toxicity of the patient and it is recommended as a value in the range of 0.1 to 0.5 [1, 12]. From equation (1), S_i is equal to a weighted average of all toxicities experienced by patient i . S_i has been normalized to a range from 0 to 1 because the maximum possible value within the parenthesis is 6 and it is further divided by 6 according to the current toxicity grade classification criteria of NIH and the toxicity system proposed by Chen et al. [1, 12].

Like EWOC, a logistic function is employed to model the dose-toxicity relationship between the dose level, x_i , and the expectation of NETS S_i for the i^{th} patient, denoted by μ_{S_i}/x_i , as:

$$\mu_{s_i|x_i} = F(\beta_0 + \beta_1 x_i) = \frac{\exp(\beta_0 + \beta_1 x_i)}{1 + \exp(\beta_0 + \beta_1 x_i)} \quad (2)$$

$\mu_{s_i|x_i}$ can be interpreted as the average NETS (ANETS) for dose level X_i . F is a specified distribution function, called a tolerance distribution and $\beta_1 > 0$ implies that the average toxicity score ANETS monotonically increases with toxicity. Furthermore, we assume that the variance of NETS follows the pattern $\mu_{s_i|x_i}(1 - \mu_{s_i|x_i})$ under dose level x_i and $S_1, \dots, S_N$ are independent among different patients, so that quasi-Bernoulli likelihood can be used to make inference.

2.2 Definition of the MTD in terms of NETS

In EWOC, the MTD is defined as a specific dose associated with a certain desired probability of the DLT. But in EWOC-NETS-TITE, the MTD (γ) is redefined as a specific dose corresponding to a prespecified target normalized equivalent toxicity score (TNETS), $\tilde{\theta}$, defined below:

$$\tilde{\theta} = TNETS = ANETS|_{Dose=\gamma} \quad (3)$$

We assume γ has a uniform prior in this model. TNETS is determined by the target toxicity profile which relies heavily on clinician's input. Four related questions should be specified in order to define the target toxicity profile[1]. It consists of the proportion of patients who experience a DLT when treated at the MTD and the target probability that adjusted grade l toxicity is the expected worst toxicity when a patient is given the MTD. Then the target normalized equivalent toxicity score is calculated as below:

$$\tilde{\theta} = \sum_{l=0}^6 m_l \cdot p_l \quad (4)$$

where m_l is the mid-range of the NETS and p_l is the target probability according to the maximum adjusted grade l toxicity (see Table 2). For example, for a target probability of DLT of 33%, the corresponding TNETS, $\tilde{\theta}$, is calculated as 0.476 ($0.07 \cdot 0 + 0.15 \cdot 0.092 + 0.15 \cdot 0.250 + 0.15 \cdot 0.417 + 0.15 \cdot 0.583 + 0.165 \cdot 0.75 + 0.165 \cdot 0.917 = 0.476$) assuming equal probability for each subtype toxicity among the DLT and non-DLT toxicities, respectively.

2.3 Re-parameterization using parameters with clinical interpretation

The parameters β_0 and β_1 in the above dose-toxicity relationship model have no clear clinical interpretation in EWOC-NETS-TITE. Therefore, the logistic dose-toxicity relationship model is re-parameterized using parameters with clinical interpretations: MTD ($g=g$), NETS (ρ) at the starting dose ($X_{\min}$), and the TNETS (θ) as below:

$$\tilde{\theta} = \frac{\exp(\beta_0 + \beta_1 \gamma)}{1 + \exp(\beta_0 + \beta_1 \gamma)} \quad (5)$$

$$\rho_0 = \frac{\exp(\beta_0 + \beta_1 x_{\min})}{1 + \exp(\beta_0 + \beta_1 x_{\min})} \quad (6)$$

The two original parameters β_0 and β_1 can be written as follows:

$$\beta_0 = \frac{x_{\min} \cdot \text{logit}(\tilde{\theta}) - \gamma \cdot \text{logit}(\rho_0)}{x_{\min} - \gamma} \quad (7)$$

$$\beta_1 = \frac{\text{logit}(\rho_0) - \text{logit}(\tilde{\theta})}{x_{\min} - \gamma} \quad (8)$$

By substituting equation (7) and (8) into equation (2), we obtain the relationship between the dose, x_i , and the NETS, S_i of patient i in terms of γ, ρ_0 and θ as below:

$$\text{logit}(\mu_{S_i|x_i}) = \frac{(\gamma - x_i) \cdot \text{logit}(\rho_0) - (x_i - x_{\min}) \cdot \text{logit}(\tilde{\theta})}{\gamma - x_{\min}} \quad (9)$$

2.4 Utilization of uncompleted toxicity responses

Assume T is the predefined observation window and u_i is the actual duration of assessment for i^{th} patient when a new patient cohort enters the trial and the decision of new dose level is made. The $w(u_i; T)$ is a function used to estimate the weight, w_i , for the NETS, S_i , based on the observed toxicities of patient i at the correct cut off moment. The function $w(u_i; T)$ is defined as below:

$$w(u_i; T) = w_i = \begin{cases} \frac{u_i}{T} & \text{if } u_i < T \\ 1 & \text{if } u_i \geq T \end{cases} \quad (10)$$

where w_i can be viewed as the proportion of the actual duration of assessment for the i^{th} patient given the predefined observation window T . Our weight function is somewhat different from the TITE approach proposed by Cheng et al [2] in which w_i is 1 when a DLT occurs regardless of the actual duration of assessment. In our EWOC-NETS-TITE, all toxicities observed during the whole predefined observation window will be used to calculate the NETS for that patient, thus occurrence of the first DLT should not be considered as the completed observation for that patient.

In EWOC-NETS-TITE, early NETS should be given less weight because it would be dangerous to escalate dose level based on the limited data collected at an early stage of the trial. Assigning less weight to the early observed NETS can reduce the contribution of this component to the whole quasi-likelihood function and reduce the risk of overdosing patients at an early stage. As the follow up time increases, the similarity between the accumulated data up to that time point and the final data at the end of observation window will increase, increasing confidence in the accumulating data. Therefore, early NETS scores should be given less weight than late NETS scores from accumulated data.

2.5 Weighted quasi-Bernoulli likelihood

To adapt to the modification in the measurement of toxicity response in term of NETS and to fully utilize all of the partial NETS from the patients before completion of the predefined observation window, a weighted quasi-Bernoulli likelihood function [10, 12, 20-22] is used in EWOC-NETS-TITE as below:

$$L(\rho_0, \gamma | D_N) = \prod_{i=1}^N c_i \cdot [w_i \cdot F(\rho_0, \gamma, x_i)]^{s_i} [1 - w_i \cdot F(\rho_0, \gamma, x_i)]^{1-s_i} = \prod_{i=1}^N c_i \cdot g(s_i) \quad (11)$$

where $g(s_i) = [w_i \cdot F(\rho_0, \gamma, x_i)]^{s_i} [1 - w_i \cdot F(\rho_0, \gamma, x_i)]^{1-s_i}$, D_N is all accumulated data after the N patients, S_i is the observed NETS for the i^{th} patient, and c_i depends on w_i , ρ_i , γ and x_i satisfying $\int_0^1 c_i \cdot g(s_i) ds_i = 1$. With expansions and transformations, the above likelihood function can be re-written as below:

$$\begin{aligned} L(\rho_0, \gamma | D_N) &= \prod_{i=1}^N w_i^{s_i} \cdot \frac{\ln \left[\left\{ 1 - w_i \exp \left(\frac{\text{logit}(\rho_0) \cdot (\gamma - x_i) + \text{logit}(\tilde{\theta}) \cdot (x_i - x_{\min})}{\gamma - x_{\min}} \right) \right\}^{-1} - 1 \right]}{(2w_i - 1) \cdot \exp \left(\frac{\text{logit}(\rho_0) \cdot (\gamma - x_i) + \text{logit}(\tilde{\theta}) \cdot (x_i - x_{\min})}{\gamma - x_{\min}} \right) - 1} \\ &\quad \times \left[\exp \left(\frac{\text{logit}(\rho_0) \cdot (\gamma - x_i) + \text{logit}(\tilde{\theta}) \cdot (x_i - x_{\min})}{\gamma - x_{\min}} \right) \right]^{s_i} \\ &\quad \times \left[1 + (1 - w_i) \cdot \exp \left(\frac{\text{logit}(\rho_0) \cdot (\gamma - x_i) + \text{logit}(\tilde{\theta}) \cdot (x_i - x_{\min})}{\gamma - x_{\min}} \right) \right]^{1-s_i} \end{aligned} \quad (12)$$

2.6 Overdosing control

Using $h(\rho_0, \gamma)$ to denote the prior distribution on $[0, \tilde{\theta}] \times [X_{\min}, X_{\max}]$, then the posterior distribution of (ρ_0, γ) is:

$$\pi(\rho_0, \gamma | D_i) = \frac{L(\rho_0, \gamma | D_i) \cdot h(\rho_0, \gamma)}{\iint_{[0, \tilde{\theta}] \times [X_{\min}, X_{\max}]} L(\rho_0, \gamma | D_i) h(\rho_0, \gamma) d\rho_0 d\gamma} \quad (13)$$

Thus, $\pi_i(\gamma)$ is the marginal posterior c.d.f. of γ given D_i and is defined as follows:

$$\pi_i(\gamma) = Pr(MTD \leq \gamma | D_i) \quad (14)$$

The $\pi_i(\gamma)$ will be updated based on all available data using Markov Chain Monte Carlo (MCMC) framework when the next dose level is determined. The Metropolis-Hastings algorithm is implemented in the MCMC. Dose levels are selected between $X_{\min}$ and $X_{\max}$, which represent the minimum and maximum doses anticipated in the trial, respectively. Then the EWOC-NETS-TITE method can be described as follows: The first patient receives the dose $x_1 = X_{\min}$ and $\pi_1(\gamma)$ is updated based on accumulated data at the moment of decision

of the new dose level. Given the accumulated data of the i^{th} patients, D_i , then $(i + 1)^{th}$ patient receives the dose

$$x_{i+1} = \pi_i^{-1}(\alpha) \quad (15)$$

where the posterior probability of exceeding the MTD is equal to the feasibility bound α . The trial continues until the pre-specified maximum number of patients have been enrolled, treated, and completed their observation of toxicity response. Then the MTD is the mean or median of the marginal posterior c.d.f. of γ .

3. Simulation Study

Extensive simulation studies were conducted to evaluate the performance of our proposed hybrid Phase I EWOC-NETS-TITE design. The two major aims of the simulation studies are to demonstrate that: (1) incorporation of the NETS system in EWOC increases the accuracy of MTD estimation and therapeutic effectiveness; (2) incorporation of the TITE approach in EWOC-NETS eliminates the waiting period and reduces the trial length time while maintaining the advantages of EWOC-NETS.

3.1 Simulation plan

EWOC, which is the framework design used to develop EWOC-NETS-TITE, has been extensively compared with other major Phase I designs, such as CRM, and the standard 3+3 design. Therefore, in this manuscript EWOC-NETS-TITE is compared only to a series of designs derived from the EWOC method, including original EWOC waiting for the completion of observation (EWOC-W), EWOC not waiting for the completion of observation and omitting incomplete observations (EWOC-NW), EWOC-NETS waiting for the completion of observation (EWOC-NETS-W), EWOC-NETS not waiting for the completion of observation and omitting incomplete observations (EWOC-NETS-NW), and TITE-EWOC. Performance was measured with regard to three major aspects: the proportion of trials recommending a given dose level as the correct MTD, the trial duration, and the therapeutic effectiveness for patients.

3.2 Simulation setup

The simulation studies were conducted under three scenarios: the target-scenario, the under-toxic-scenario, and the over-toxic-scenario (Table 1). These scenarios were partly adopted from Chen *et al.* [1, 12]. Although all 3 scenarios have the same profile in terms of probability of a DLT across 6 different dose levels, their exact toxicity profiles are different. The ANETS for each dose level is calculated in the same way as for TNETS in equation (4) but varies according to the exact toxicity profile across the 3 scenarios. In the target-scenario, an equal ratio is assumed for all non-DLT toxicities, and both DLT toxicities, respectively, as in the target toxicity profile used to calculate the TNETS. Therefore, the DLT probability and ANETS match well in measuring the overall toxicity severity for each dose level. The toxicity profiles of the 2 other scenarios deviate from that of the target-scenario. Skewed toward the lower toxicity grades, in the under-toxic-scenario each dose level is less toxic than the corresponding one in the target-scenario. In contrast, in the over-toxic-scenario, the toxicity profile is skewed toward higher toxicity grades with larger

ANETS values so that each dose level is more toxic than the corresponding one in the target-scenario.

We assumed that γ and ρ are independent and uniformly distributed in the interval $[0,7] \times [0, \text{TNETS}]$ (the prior distribution). And we select the largest pre-specified dose level or feasible dosage which is less than or equal to the α^{th} (feasibility bound) quartile from MTD's(γ) posterior distribution as the dose level for the next patient. Since we used uninformative prior, the result were not be sensitive to prior specification. If some informative prior is used given some previous information about the drug, it will of course accelerate the convergence of the posterior distribution and the performance of results will be even better.

The assessment time window can vary from several days to several months and was set as up to 28 days in the simulation studies, consistent with common clinical trials observation time (usually four weeks or one month). Time and events were simulated using an exponential distribution so that half of the events happened in half of the observation window for EWOC and EWOC-NETS designs. We also assumed that multiple events within the same patient were independent. The inter-patient arrival time followed an exponential distribution with mean 7, 28, or 100 days in different simulations, respectively. Various sample sizes (15, 30, or 60 patients) and cohort sizes (1 or 3 patients per cohort) were used for each design in the comparison of the accuracy of MTD estimation, therapeutic effectiveness, and trial duration for different designs. The trial length was further compared between different designs under various mean inter-patient arrival times (7, 28, 100 days). For designs EWOC-W, EWOC-NW, and TITE-EWOC, which use the probability of DLT as the target toxicity level, the MTD was defined as the dose with expected 33% DLT and the true MTD in each scenario was the dose level with probability of DLT closest to 33%. For the other designs, EWOC-NETS-W, EWOC-NETS-NW, and EWOC-NETS-TITE, which use the NETS system instead of the probability of DLT, the estimated MTD is the dose with TNETS of 0.476, 0.410, or 0.555 and true MTD in each scenario was one of the 6 dose levels with ANETS closest to the pre-specified TNETS (Table 2). We used the MCMC sampling method to simulate the posterior distributions of all parameters of interest. A replicate of 1,000 trials was conducted for each scenario. The 1000 iterations are used as burn-in period and the next 4000 iterations are used as MCMC sample. Figure 1 shows that after 4000 iterations, the posterior distributions of γ and ρ become uni-modal shape curves which can provide more information to make inferences of γ and ρ by their posterior medians. The trace plot and autocorrelation graphs, which are not included in the paper due to space limits, show that the Markov Chain and the posterior distributions converge after 4000 draws using MCMC. Therefore, although not a direct proof of the correctness of the quasi-likelihood function, the trace plots, histograms, and autocorrelation graphs of two key parameters demonstrate that the quasi-likelihood function of EWOC-NETS-TITE converges and works well when used to produce posterior samples. Due to space limitations, its advanced operation characteristics will not be investigated here but will be reported elsewhere.

3.3 Simulation results

The simulation results are presented as 3 major parts. The first part is the comparison of the accuracy of MTD estimation using our EWOC-NETS-TITE (cohort size 1) with other two-stage designs including EWOC-NETS-W (wait, cohort size 1), EWOC-NETS-NW (no wait, cohort size 1), TITE-EWOC (cohort size 1), EWOC-W (wait, cohort size 1) and EWOC-NW (wait, cohort size 1). The second part further compares the therapeutic effectiveness in terms of treated patient distribution across different dose levels. The third part compares the durations of simulated trials using different designs and different sample sizes.

3.3.1 MTD accuracy—Table 3 gives the percent of each dose level in the trial that is recommended as the MTD for each design under each scenario. First, we will look at the difference in the MTD accuracy between two groups of designs stratified by whether the NETS system is used. In the target-scenario, EWOC-NETS-TITE (54.5%), EWOC-NETS-NW (44.7%), and EWOC-NETS-W (55.5%) have higher percentages of MTD recommendation compared to EWOC-TITE (41.3%), EWOC-NW (40.90%), and EWOC-W (43.70%), respectively. The absolute difference in these proportions can be as high as 13.2%. This suggests that the designs treating the toxicity response as a quasi-continuous variable and fully utilizing all toxicity information substantially improve the accuracy of MTD estimation compared with designs treating toxicity response as a binary indicator of DLT under the various scenarios. When the same TNETS (0.476) is used to determine the MTD, the approximate correct MTDs are dose levels 3, 4, and 2 under the target-scenario, the under-toxic-scenario, and the over-toxic-scenario, respectively. EWOC-NETS-TITE, EWOC-NETS-W, and EWOC-NETS-NW can “recognize” the deviation of toxicity profile and correctly estimate dose levels 3, 4, and 2 under the target-scenario, the under-toxic-scenario, and the over-toxic-scenario, respectively. The simulation results for EWOC-TITE, EWOC-NW, and EWOC-W are the same in the 3 different scenarios so that their simulation results for the under-toxic-scenario and over-toxic-scenario are not repeated in Table 3. EWOCW, EWOC-NW, and EWOC-TITE can detect a traditional MTD corresponding to a TTL, such as 33%. But if investigators want to consider not only DLT events but also non-DLT events for the MTD, the EWOC-W, EWOC-NW and EWOC-TITE designs are limited by only using the binary DLT. Meanwhile, through our extensive simulations, after using NETS instead of a binary DLT, EWOC-NETS-W, EWOC-NETS-TITE, and EWOC-NETS-NW can detect the MTD with different toxicity profiles consisting of both DLT and non-DLT events. Moreover, through the comparison when TTL=33% and TNETS=0.476, EWOC-NETS-W, EWOC-NETS-NW, and EWOC-NETS-TITE estimate the MTDs more accurately because of fully utilizing all toxicity events. However, the direct relationship between TTL and TNETS warrants further study. When EWOC-NETS-TITE, EWOC-NETS-NW, and EWOC-NETS-W target dose level 3 as the true MTD by adjusting the TNETS to be 0.41 in the under-toxic-scenario and 0.555 in the over-toxic-scenario, EWOC-NETS-TITE (53.4% or 59.2%), EWOC-NETS-NW (55.4% or 53.4%), and EWOC-NETS-W (61% or 65.6%) still have a higher percentage of correct MTDs compared to EWOC-TITE (35.5%), EWOC-NW (33.7%), and EWOC-W (46%), respectively.

Secondly, we look at the differences in the accuracy of MTD estimation between three groups of designs stratified by whether TITE, no-waiting for complete data (NW), or

waiting for complete data (W) is used. TITE outperforms NW in all corresponding comparisons (EWOC-NETS-TITE vs EWOC-NETS-NW and EWOC-TITE vs EWOC-NW) under all 3 scenarios (Table 3). These simulation results demonstrate that TITE can improve the accuracy of MTD determination by fully utilizing the partial complete data compared with NW which ignores incomplete data during the new dose level decision. It is obvious that the method W has better MTD accuracy than both TITE and NW because the method W requires one to wait for the data of all enrolled patients to be complete and fully utilizes them in the new dose level decision, but at the substantial cost of a much prolonged trial duration (Tables 4 and 5).

Finally, we rank the accuracy of MTD estimation of our proposed hybrid design with EWOC-W, EWOC-NW, EWOC-NETS-W, EWOC-NETS-NW, and EWOC-TITE. Without doubt, EWOC-NETS-W has the overall highest accuracy as it waits and uses complete data at the cost of prolonged trial length, followed closely by our proposed hybrid design — EWOC-NETS-TITE. If expressed as an inequality, the overall accuracy of MTD estimation is: EWOC-NETS-W > EWOC-NETS-TITE > EWOC-NETS-NW > EWOC-W > EWOC-TITE > EWOCNW. The NETS system improves the MTD accuracy by fully utilizing all available toxicity information and TITE can help by fully utilizing the partially complete data without the waiting period. Therefore, EWOC-NETS-TITE is the best choice because it renders the best performance in terms of the MTD accuracy without any waiting period.

In this study, only 3 scenarios were selected in the simulations studies to briefly demonstrate that the advantages of NETS were kept in the EWOC-NETS-TITE because the main purpose of this paper is to further incorporate the TITE approach into EWOC-NETS to allow flexible patient enrollment and utilize partially completed data at the moment of decision on new dose level. For full investigation of the property of NETS, please refer to the extensive simulation studies comparing EWOC-NETS and the original EWOC under many different scenarios in the two previous papers of Chen et al. [1, 12]. Simulation results comparing MTD detection rates for binary endpoints and composite endpoints are linked, but are a bit difficult interpretation. The direct transformation between them warrants further study.

3.3.2 Trial duration—Trial duration is the second major point of interest and key motivation for proposing this hybrid EWOC-NETS-TITE design. Tables 4 and 5 illustrate the trial durations using different sample sizes and different mean arrival times, respectively. We can consider the nature of EWOC-NETS-TITE, EWOC-TITE, EWOC-NETS-NW, and EWOC-NW to be similar with respect to trial duration. All four designs allow newly recruited patients to enter the trial in a staggered manner and be treated immediately without waiting. The use of the TITE approach or NW method can effectively reduce the trial duration by about 70% compared to the method W when the observation window is 28 days and the inter-patient arrival time is 7 days (Table 4). There is little difference between designs using the TITE approach compared to those using the NW method, suggesting that trial length depends mainly on the patient accrual pattern and whether the waiting period is implemented. However, it is not affected by the approach to deal with data. No obvious difference in trial length is observed between the designs with NETS and corresponding designs without using the NETS system so that the NETS system does not affect patient

enrollment and has no impact on trial duration. The reduction in the trial length increases as the sample size of the Phase I clinical trial increases, but the change is not obvious as suggested from the simulation results with different sample sizes (15, 30, and 60) (Table 3).

The reduction in trial duration for designs using the TITE or NW approach decreases from about 70% to 0.2% as the inter-patient arrival time increases from 7 days to 28 days, given the fixed observation window of 28 days. The trial durations of all designs are almost the same when the patient arrival time interval increases to 100 days and the observation window is still 28 days. This result is reasonable because almost all previous patients will finish their observation before enrollment of new patients, and waiting thus is not an issue anymore when the inter-patient arrival time is longer than the observation window. On the other hand, there is no penalty in terms of trial duration for using EWOC-NETS-TITE when no waiting is required. But in practical Phase I clinical trials, it is more common that inter-patient arrival time is much shorter than the observation period and waiting is required most of the time. Therefore, the use of EWOC-NETS-TITE is robust under all scenarios.

EWOC-NETS-TITE is proposed to deal with a long observation window in relation to rapid patient accrual rate (short inter patient arrival time). In the simulation study, we used an observation window of 28 days as an example under different patient accrual rates, such as 7, 28, 100 days for inter-patient arrival time (Table 5). However, this does not mean that EWOC-NETS-TITE is proposed only for a short observation window, such as 28 days. Instead, EWOC-NETS-TITE can be applied to any length of observation window, such as 6 months or even longer. Actually, the RELATIVE RATIO between the observation window and patient accrual rate is a more comprehensive measurement and matters more than the absolute length of the observation window. The percentage of reduction in length of trial increases as the relative ratio between the observation window and patient accrual rate (Table 5) increase. Of course, given the same percentage of reduction in the length of trial, the absolute reduction in the number of days increases with the length of observation window. Therefore, the observation window and the assessment time of the composite endpoint are of equal importance in EWOC-NETS-TITE as in TITE-CRM with binary endpoint DLT.

3.3.3 Therapeutic effectiveness—Another factor in evaluating model performance is the percentage of patients treated at each dose level. Considering that the guiding principle in Phase I clinical trials is to treat as many patients as possible at therapeutic dose levels in order to avoid exposures at lower dose levels, the results shown were promising in that most patients were treated at the target dose levels. Overall, the designs using the NETS system, EWOC-NETS-TITE, EWOC-NETS-NW, and EWOC-NETS-W, tend to treat a higher percentage of patients at dose levels around the MTD (± 1 dose level) under all scenarios compared to EWOC-TITE, EWOC-NW, and EWOC-W, respectively (Table 6). This suggests that NETS can help to improve therapeutic effectiveness by fully utilizing all toxicity information in making better new dose level decisions. The designs with the TITE approach, EWOC-NETS-TITE and EWOC-TITE, are more aggressive in treating a higher percentage of patients above the true MTD than the other designs with the NW or the W method, respectively. This can be explained by the fact that the TITE approach more aggressively uses partially complete data for the new dose level decision, especially at the

early stage of Phase I clinical trials with little data available. The method W is more conservative than the method NW as it waits for completion of all patients and fully utilizes all complete data. The differences between TITE, NW, and W decrease substantially as the mean inter-patient arrival time increases and become minor when the mean inter-patient arrival time is equal to 14 and 21 days (data not shown).

4. Conclusion and Discussion

Compared to EWOC, we demonstrate that EWOC-NETS-TITE has better precision in the estimation of MTD by fully utilizing toxicity information with the NETS system and partially complete data with the TITE approach while shortening the trial duration by removing the waiting period.

Currently, only a very small proportion of investigational agents eventually progress to gain approval for clinical use, making the clinical trials process highly resource-intensive. Accurate MTD determination is one of the crucial factors affecting the eventual fate of an agent in a confirmative Phase III clinical trial. The objective of this study was to develop a leading design which can estimate the MTD accurately and timely with small sample size. Simulation studies show that the EWOC-NETS-TITE dose-allocation method can consequentially increase the accuracy of MTD estimation, improve therapeutic effectiveness, decrease the overall trial duration, increase trial efficiency and control the probability of overdosing.

The improved accuracy of MTD determination and increased therapeutic effectiveness are mainly accredited to the full utilization of toxicity information with the NETS system and partially complete data with the TITE approach while shortening the trial duration by removing the waiting period. While a binary indicator of DLT as the toxicity response of a patient is simple and convenient to use in a Phase I clinical trial, it discards a lot of toxicity information which is valuable, especially in a Phase I clinical trial with a very small sample size. The downsides of using a binary indicator of the DLT have been discussed extensively in other publications [1, 10, 12]. Statistically, the power and efficiency improve as the amount of data utilized increases. The NETS system is designed to improve the MTD accuracy and trial efficiency by fully utilizing more data. Incorporation of the NETS system enables full utilization of the multiple toxicities of patients as well as their ordinal toxicity grades. The utilization of incomplete data with the TITE approach in the process of a new dose level decision also contributes to the improvement in the precision of MTD determination. Many approaches have been proposed to utilize incomplete data when deciding the dose level for newly accrued patients. The TITE approach uses a weight based on the follow-up time to take into account differentially the data for subjects who have not experienced toxicity thus far. The TITE approach has been demonstrated to work successfully in the CRM and EWOC methods to shorten trial duration significantly without shortening the estimation period. Further discussion on the methodology of the TITE approach can be found in other publications [14, 19]. In our hybrid design, the TITE approach has been adopted with a slight modification to be compatible with the NETS system. As a result, the hybrid design is dynamic in the sense that patients can enter the trial at any time and the dose allocated to a patient makes use of all the information available at

the time the patient enters the trial. On the other hand, when the toxicity observation period is relatively short given very slow patient accrual rate, the benefit of using the TITE method diminishes. As evidenced by the simulation study, the added TITE feature in EWOC-NETS-TITE can reduce the waiting time length, better utilize partial data, and save trial costs without sacrificing the accuracy of MTD estimation. These advantages warrant the complexity of including TITE. Overall, EWOC-NETS-TITE has the same theoretical and practical advantages as the original TITE-CRM to justify the complexity caused by the incorporation of the TITE approach in EWOC-NETS in real clinical trial.

The EWOC algorithm is adopted as a framework for the hybrid design because of its outstanding performance in MTD estimation and attractive overdosing control characteristics. The hybrid design is essentially an extension of the original EWOC design so that the operating characteristics of EWOC have been retained in EWOC-NETS-TITE. A detailed discussion of the methodology and the operating characteristics of EWOC can be found in previous publications [3, 23-25]. With the additional integration of the NETS system and the TITE approach using a weighted quasi-Bernoulli likelihood, the hybrid design can further improve its performance in terms of MTD estimation, therapeutic effectiveness, shortening the trial duration and allowing flexibility in patient accrual.

In summary, we have successfully integrated the toxicity scoring system of Chen et al. [1, 12] and the TITE approach of Cheung and Chappell [2] with EWOC [3] to develop the EWOC-NETS-TITE design. This treats the toxicity response as a quasi-continuous variable instead of a binary indicator of DLT and fully utilizes all toxicity information and incomplete data while eliminating a waiting period. Simulation studies demonstrate that EWOC-NETS-TITE can: (1) address ethical concerns of overdosing patients; (2) have better accuracy of estimating the MTD; (3) have higher trial efficiency; (4) fully utilize the data of uncompleted patients and follow-up time; (5) shorten the trial duration without a waiting period for any patients; (6) provide better therapeutic effectiveness for patients. A trial using EWOC-NETS-TITE may require quite some extra effort, but its usage will likely gain additional advantages. Therefore, this hybrid design will be of practical use in the field of Phase I clinical trials. A user-friendly software program for EWOC-NETS-TITE is under development.

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Figure 1.

Marginal posterior distribution for MTD γ, ρ , under TNETS=0.476, after 30 patients recruited into the trial

Table 1

Probability that Adjusted Grade / Toxicity Is the Worst When a Patient Is Treated at a Given Dose Level

	The “worst” toxicity / Maximum adjusted grade		Dose level					
			1	2	3	4	5	6
Target Scenario	0	0	0.110	0.090	0.070	0.050	0.030	0.010
	1	1	0.200	0.160	0.150	0.120	0.100	0.050
	2	2	0.200	0.170	0.150	0.130	0.100	0.060
	3 non DLT	3	0.200	0.170	0.150	0.130	0.100	0.060
	4 non DLT	4	0.210	0.170	0.150	0.130	0.110	0.060
	3 DLT	5	0.040	0.120	0.165	0.220	0.280	0.380
	4 DLT	6	0.040	0.120	0.165	0.220	0.280	0.380
	Probability of DLTs for the dose		0.080	0.240	0.330	0.440	0.560	0.760
	ANETS for the dose		0.341	0.427	0.476	0.540	0.607	0.713
Under-toxicity scenario	0	0	0.110	0.090	0.070	0.050	0.030	0.010
	1	1	0.324	0.268	0.240	0.204	0.164	0.092
	2	2	0.243	0.201	0.180	0.153	0.123	0.069
	3 non DLT	3	0.162	0.134	0.120	0.102	0.082	0.046
	4 non DLT	4	0.081	0.067	0.060	0.051	0.041	0.023
	3 DLT	5	0.060	0.160	0.220	0.300	0.370	0.510
	4 DLT	6	0.020	0.080	0.110	0.140	0.190	0.250
	Probability of DLTs for the dose		0.080	0.240	0.330	0.440	0.560	0.760
	ANETS for the dose		0.269	0.363	0.410	0.483	0.556	0.670
Over-toxicity scenario	0	0	0.110	0.090	0.070	0.050	0.030	0.010
	1	1	0.324	0.067	0.060	0.051	0.041	0.023
	2	2	0.243	0.134	0.100	0.102	0.082	0.046
	3 non DLT	3	0.162	0.201	0.100	0.153	0.123	0.069
	4 non DLT	4	0.081	0.268	0.340	0.204	0.164	0.092
	3 DLT	5	0.060	0.080	0.110	0.140	0.190	0.250
	4 DLT	6	0.020	0.160	0.220	0.300	0.370	0.510
	Probability of DLTs for the dose		0.080	0.240	0.330	0.440	0.560	0.760
	ANETS for the dose		0.269	0.486	0.555	0.593	0.653	0.751

Table 2

Mid-range of NETS and Probability of Most Severe Toxicity under Five Scenarios

Most severe toxicity	Maximum adjusted grade	Range of NETS	Mid-range NETS (m_1)	Target toxicity profile for MTD in different scenarios (p_i)		
				Ideal Scenario	Under-toxic Scenario	Over-toxic Scenario
Grade 0	0	0	0	0.070	0.07	0.07
Grade 1	1	[1/60 – 1/6)	0.092	0.150	0.24	0.06
Grade 2	2	[1/6 – 1/3)	0.25	0.150	0.18	0.10
Grade 3 non DLT	3	[1/3 – 1/2)	0.417	0.150	0.12	0.10
Grade 4 non DLT	4	[1/2 – 2/3)	0.583	0.150	0.06	0.34
Grade 3 DLT	5	[2/3 – 5/6)	0.75	0.165	0.22	0.11
Grade 4 DLT	6	[5/6 – 1)	0.917	0.165	0.11	0.22
TNETS for each scenario				0.476	0.410	0.555

Table 3Percent of Trials Recommending a Dose Level as the MTD under Different Scenarios^{*}

Scenarios	Designs	Dose Level					
		1	2	3	4	5	6
Target Scenario	EWOC-NETS-TITE (TNETS=0.476)	1.10	17.30	<u>54.50</u>	26.70	0.40	0.00
	EWOC-NETS –NW (TNETS=0.476)	0.30	8.10	<u>44.70</u>	41.40	5.50	0.00
	EWOC-NETS –W (TNETS=0.476)	1.40	19.60	<u>55.50</u>	22.60	0.90	0.00
	EWOC-TITE (TTL=33%)	4.50	25.60	<u>41.30</u>	25.60	2.90	0.10
	EWOC-NW (TTL=33%)	2.90	26.70	<u>40.90</u>	25.70	3.70	0.10
	EWOC-W (TTL=33%)	7.30	29.70	<u>43.70</u>	17.80	1.50	0.00
Under-Toxicity Scenario	EWOC-NETS-TITE (TNETS=0.476)	0.30	18.40	<u>62.60</u>	18.70	0.00	0.00
	EWOC-NETS –NW (TNETS=0.476)	0.00	6.90	<u>53.30</u>	39.40	0.40	0.00
	EWOC-NETS –W (TNETS=0.476)	0.20	17.20	<u>63.30</u>	19.30	0.00	0.00
	EWOC-NETS-TITE (TNETS=0.41)	1.10	17.60	<u>53.60</u>	27.00	0.70	0.00
	EWOC-NETS –NW (TNETS=0.41)	0.30	12.00	<u>48.20</u>	36.90	2.60	0.10
	EWOC-NETS –W (TNETS=0.41)	1.90	21.50	<u>55.40</u>	20.30	0.90	0.00
Over-Toxicity Scenario	EWOC-NETS-TITE (TNETS=0.476)	5.50	<u>57.90</u>	32.20	4.30	0.10	0.00
	EWOC-NETS –NW (TNETS=0.476)	0.90	<u>31.90</u>	49.60	17.00	0.60	0.00
	EWOC-NETS –W (TNETS=0.476)	7.80	<u>58.20</u>	29.90	4.00	0.10	0.00
	EWOC-NETS-TITE (TNETS=0.555)	0.30	14.90	<u>52.30</u>	31.10	1.40	0.00
	EWOC-NETS –NW (TNETS=0.555)	0.00	4.10	<u>31.30</u>	55.00	9.60	0.10
	EWOC-NETS –W (TNETS=0.555)	0.50	15.70	<u>54.40</u>	27.50	1.90	0.00

^{*} : The sample size is 30, observation window is 28 days, and mean inter-patient arrival time is 7 days, the bond numbers underlined are the numbers for the true MTD dose level for the specific design in that scenario.

Table 4

Duration of Simulated Trial (days) and Percentage Change (%) Compared to EWOC-W by Different Sample Size^{*}.

Design of Phase I Trials	Sample Size		
	15	30	60
EWOC-NETS-TITE	139 (−67.5%)	254 (−70.0%)	477 (−71.7%)
EWOC-NETS −NW	141 (−67.1%)	249 (−70.6%)	476 (−71.8%)
EWOC-NETS −W	425 (−0.7%)	850 (−0.2%)	1676 (−0.7%)
EWOC-TITE	138 (−67.8%)	261 (−69.2%)	469 (−62.2%)
EWOC −NW	141 (−67.1%)	265 (−68.7%)	467 (−72.3%)
EWOC −W (Reference group)	428	848	1688

* : Observation window is 28 days and mean inter-patient arrival time is 7 days

Table 5

Duration of Simulated Trial (days) and Percentage Change (%) Compared to EWOC-W by Mean Inter-Patient Arrival Time ^{*}.

Design of Phase I Trials	Mean Inter-Patient Arrival Time		
	7	28	100
EWOC-NETS-TITE	254 (−70.0%)	882 (−9.9%)	2,999 (−0.2%)
EWOC-NETS −NW	254 (−70.0%)	875 (−10.6%)	3,000 (−0.2%)
EWOC-NETS −W	852 (−0.05%)	1000 (−2%)	2900 (−3.5%)
EWOC-TITE	260 (−69.3%)	877 (−10.4%)	3,000 (−0.2%)
EWOC −NW	258 (−69.6%)	876 (−10.5%)	2999 (−0.2%)
EWOC −W (Reference group)	848	979	3005

* : Observation window is 28 days and sample size is 30

Table 6Percent of Patients Treated at Each Dose Level under Different Scenarios^{*}

Scenarios	Designs	Dose Level					
		1	2	3	4	5	6
Target Scenario	EWOC-NETS-TITE (TNETS=0.476)	6.91	19.86	<u>49.40</u>	23.35	0.49	0.00
	EWOC-NETS –NW (TNETS=0.476)	5.64	7.72	<u>28.90</u>	46.49	11.24	0.01
	EWOC-NETS –W (TNETS=0.476)	7.04	21.66	<u>45.49</u>	25.05	0.76	0.00
	EWOC-TITE (TTL=33%)	10.34	22.00	<u>33.91</u>	27.96	5.76	0.03
	EWOC –NW (TNETS=33%)	5.90	19.36	<u>31.73</u>	31.03	11.84	0.14
	EWOC –W (TNETS=33%)	10.98	26.13	<u>36.77</u>	22.55	3.57	0.00
Under-Toxicity Scenario	EWOC-NETS-TITE (TNETS=0.476)	4.32	9.58	22.52	<u>50.78</u>	12.75	0.00
	EWOC-NETS –NW (TNETS=0.476)	4.28	4.65	9.62	<u>39.15</u>	41.20	1.10
	EWOC-NETS –W (TNETS=0.476)	4.57	7.86	21.48	<u>51.49</u>	14.60	0.01
	EWOC-NETS-TITE (TNETS=0.41)	6.02	20.70	<u>47.67</u>	24.78	0.85	0.00
	EWOC-NETS –NW (TNETS=0.41)	4.97	10.06	<u>31.20</u>	45.32	8.44	0.00
	EWOC-NETS –W (TNETS=0.41)	7.21	22.59	<u>45.41</u>	24.02	0.75	0.00
Over-Toxicity Scenario	EWOC-NETS-TITE (TNETS=0.476)	6.74	<u>42.14</u>	43.52	7.51	0.08	0.00
	EWOC-NETS –NW (TNETS=0.476)	4.02	<u>16.93</u>	37.96	35.19	5.90	0.01
	EWOC-NETS –W (TNETS=0.476)	7.95	<u>43.31</u>	40.29	8.32	0.13	0.00
	EWOC-NETS-TITE (TNETS=0.555)	3.88	21.60	<u>47.00</u>	27.39	1.13	0.00
	EWOC-NETS –NW (TNETS=0.555)	3.37	5.92	<u>20.95</u>	49.21	20.47	0.08
	EWOC-NETS –W (TNETS=0.555)	4.21	19.67	<u>47.04</u>	27.38	1.71	0.00

^{*} : The sample size is 30, observation window is 28 days, and mean inter-patient arrival time is 7 days, the bond numbers underlined are the numbers for the true MTD dose level for the specific design in that scenario.