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Youyun Zheng 4/8/2018

Interactive Software for Dose Calculation and Simulation of Phase I Cancer Clinical Trial Using EWOC-NETS Design

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
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Abstract

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Phase I clinical trials signify the first stage experimentation of a new drug in human use. Because cancer patients who respond poorly to conventional treatment usually resort to experimental treatment options such as phase I cancer clinical trials, additional concerns arise in the design of such trials. A combination of accuracy of Maximum Tolerated Dose (MTD) prediction and rapidity of dose escalation is required to maximize the therapeutic effect and minimize the toxic effect for enrolled patients. It is with such considerations that Escalation With Overdose Control – Normalized Equivalent Toxicity Score (EWOC-NETS) was created. Incorporating Bayesian statistics and a novel quasi-continuous toxicity grading system, EWOC-NETS has been shown to outperform various rule-based and adaptive models. However, due to its statistical complexity, it is exceedingly difficult to implement. Because of that, its usage in clinical settings has been significantly hindered. Here, we introduce a user-friendly, standalone software that enables both MTD calculation during trial progress and trial simulations. Our software enables clinicians to both implement and simulate EWOC-NETS clinical trials. It is our hope that the prevalent usage of EWOC-NETS resulting from the development of our software can facilitate and catalyze the efforts in cancer drug development worldwide.

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Abstract

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Introduction

Project Objective and Goals

Before entry to commercial market, novel therapeutics must be examined in clinical trials to assess not only their efficacy but also potential adverse events (AE). Phase I clinical trials signify the first stage experimentation of a new drug in human use. Followed by Phase II and III, its main purpose involves toxicity-testing and dose-finding [1]. Accordingly, traditional Phase I clinical trials for many diseases requires recruitment of healthy human subjects so as to minimize potential risks for studied individuals. However, in clinical cancer care, combinations of complex factors such as the gap in knowledge of pathogenesis and the limited repertoire of approved agents resulted in many patients achieving only suboptimal responses to standard therapy. As a result, they often turn to experimental clinical trials as last resorts. Therefore, phase I cancer clinical trials also bear additional therapeutic purposes [2,3]. It is assumed that as the dose levels of cytotoxic agents increase, their therapeutic effects as well as toxic effects increase as well, which is why striking a balance between maximizing therapeutic effect in the majority of patient pools and minimizing the adverse effects to an acceptable portion of total patients is of utmost importance. Additional concern arises when considering the need for minimizing the number of patients subjected to biologically inactive dose levels as well. Thus,

accuracy of dose finding as well as rapidity of dose-escalation are two of the biggest goals and metrics when developing and examining clinical trial design performance [4,5].

This project focuses on the state of the art clinical trial design Escalation With Overdose Control (EWOC) combined with novel quasi-continuous toxicity metric system Normalized Equivalent Toxicity Score (NETS). Together, EWOC-NETS phase I cancer clinical trial design delivers high dose-finding accuracy and rapid dose-escalation all the while minimizing overdosing of study subjects as well as incorporating detailed toxicity information generated throughout clinical trials [6]. Despite its superior performance over rule-based designs, EWOC-NETS and other Bayesian adaptive clinical trial designs have not been widely utilized in clinical use due to its statistical complexity [7,8]. The difficulty of implementation has hindered its implementation because of the lack of statistician involvement and communication with clinicians in charge of clinical trials. Our project aims to make EWOC-NETS designs more accessible and applicable for all clinicians by creating a user-friendly and intuitive software that allows flexible parameter inputs and generates easily-interpreted results. In addition, physicians can also perform simulation using different toxicity scenarios to estimate the recommended MTD. Equipped with our robust and intuitive software, clinicians will be able to make their own Phase I Cancer Clinical Trials more efficient and accurate with minimum assistance from statisticians. It is our hope that the prevalent usage of EWOC-NETS resulting from the development of our software can facilitate and catalyze the efforts in cancer drug development worldwide.

Toxicity Information Categorization Methods

CTCAE

To achieve standardized treatment and AE reporting, a well-defined system for toxicity measurement was established and has been constantly evolving [9–11]. The Common Terminology Criteria for Adverse Events 5.0 (CTCAE v5.0) established in 2017 has been utilized as the latest golden standard for categorizing and reporting AE terminologies. This comprehensive grading system encompasses numerous physiological systems (i.e. cardiovascular, gastrointestinal, hepatobiliary systems and etc.) and various criteria for pediatrics, surgical, late toxicity and more. All AE terminologies are grouped according to the System Organ Classes (SOC), which are the physiological systems primarily affected by AEs. The SOCs are determined using Medical Dictionary for Regular Activities (MedDRA) hierarchy [12].

Ranging from Grade 1 to 5, each AE is also classified within for severity [13]. Grade 1 is defined as mild or asymptomatic symptoms that are clinically observed and warrants no intervention. Grade 2 is defined as moderate symptoms that require local or minimal intervention. Grade 3 is defined as severe but non-life-threatening symptoms that cause patients to have prolonged hospitalization. Grade 4 is defined as severe life-threatening symptoms that require immediate interventions. Grade 5 is defined as death related to the investigated treatment. In this multi-level grading system, various clinically measurable parameters were defined for classifying each grade within all AEs. For instance, hemoglobin ranges were defined for toxicities of different grades for patients experiencing anemia secondary to treatment. Threshold shift for audiogram in certain number of contiguous auditory tests were also determined to classify different grades of hearing impairment AEs.

Traditional Toxicity Information Categorization Methods

In most studies, patients experiencing toxicity/toxicities in a defined set of Grade 3 non-hematological, grade 4 hematological and grade 5 (death) toxicities would be deemed as experiencing Dose Limiting Toxicity (DLT). Examples of hematological toxicities include anemia leukopenia, neutropenia, lymphopenia and etc. On the other hand, non-hematological toxicities include a wider range of symptoms from nausea, vomiting, fatigue to cardiac arrhythmias, myocardial infarction, infections and so on. In other words, for instance, patients hospitalized for non-life-threatening hematological symptoms (grade 3 hematologic) are not deemed to be experiencing DLT, while patients experiencing life-threatening hematological symptoms (grade 4 hematologic) will be deemed as experiencing DLT. Take note that traditionally, toxicities in patients are indeed considered to be binary. This model of evaluation inevitably loses vast amount of detailed information on different toxicity grades because patients not only present with various numbers of non-DLT toxicities, but also, the DLTs one patient present with can vary in severity as well. Grade 0-2 non-DLTs may give indication for higher grade toxicity of that AE in higher doses. On the other hand, grade 3 and grade 4 DLTs are distinct in severity and should also be sufficiently differentiated.

Normalized Equivalent Toxicity Score (NETS) Quasi-continuous Categorization Methods

Aiming to minimize the critical loss of information, a novel toxicity categorization method was created [14]. This toxicity scoring system has been shown to provide robust representation of toxicity information and increase the accuracy of MTD estimation.

A range of different toxicity scoring system as well as weighted toxicity evaluation metrics incorporated into clinical trial designs have been implemented in the past and have

been shown to improve accuracy of MTD prediction as well as to decrease likelihood of over-dosing patients [15–17]. Even though these systems take into account various non-DLTs, some of them fail to represent multiple toxicities within one patient, while others require intensive oncologist input for weighting toxicities for statistical modeling.

NETS toxicity scoring system maps 4 traditional toxicity grades (excluding death/grade 5) to 6 adjusted toxicity grades and accounts for all toxicities so as to capture the comprehensive response profile for each patient. More specifically, mapping of toxicity is shown in Table 1.

To calculate NETS, Equivalent Toxicity Score (ETS) must first be calculated. For each patient i in the cohort, maximum toxicity incidence $T_{max,i}$ is identified. Using logistic functions, we can calculate ETS for each patient i with X toxicities by using the following equation:

$$\mathrm{ETS_i} = \mathrm{T_{max,i}} - 1 + \frac{1}{1 + e^{-\left(\alpha + \beta\left(\sum_{x=1}^{X} \frac{w_i T_{x,i}}{T_{max,i}} - 1\right)\right)}}$$

Since ETS calculation relies on logistic function model, α and β parameters must be determined by the Principle Investigator to stipulate how other toxicities lower than maximum adjusted grade toxicity affect ETSs. Parameter α determines the midpoint of the sigmoidal curve while parameter β determines the steepness of elevation. Since ETS increases as patients experience more toxicities, β must be positive. Parameter α represents the displacement of the sigmoidal curve midpoint which in turn alters the effect of other toxicities in raising ETS as well. Exceptions to this calculation are patients with no toxicity. In order to generate a range of ETS values bigger than or equal to 0, ETSs are arbitrarily designated 0 for those patients. In addition,

an approximate value of 0.1 is set for all patients with a single grade 1 toxicity. Thus, to ensure the consistency of the model by calculating the difference in ETSs between patients with single grade 1 toxicities ($ETS = \frac{1}{1+e^{-(\alpha)}} = 0.1$) and patients with no toxicities (ETS = 0), -2 is approximated as the general default value for α. All ETSs are then normalized by dividing them with the maximum adjusted toxicity grade possible (6 in clinical trials not considering death as toxicities, 7 in clinical trials considering death as toxicities)

Target Toxicity Level (TTL) vs. Target NETS (TNETS)

MTD in every Phase I Clinical Trial with binary toxicity designations are defined as the maximum dosage at which a predetermined percentage of patients experience DLTs. This percentage at MTD is known as TTL. Due to the small sizes of clinical trials, 3 patients are usually treated at each dosage. 33%, in other words 1 out of 3 patients, is usually set as the percentage of patients experiencing DLT at which MTD is declared. Declaration of MTD prediction marks the end of the clinical trial. Similarly, TNETS are calculated for the same purpose as TTL, given the NETS of every patient. Due to quasi-continuous nature of NETS, several conditions must be clarified by physicians before we could calculate TNETS: TTL for equivalent binary toxicity scenarios, ratio of possibilities of adjusted grade 5 and adjusted grade 6 toxicity incidences being the worst toxicity, ratio of possibilities of adjusted grade 1-4 toxicity incidences being the worst toxicity and minimum acceptable percentage of patients without toxicities. Assuming the following conditions: ratio of possibilities of adjusted grade 5 and adjusted grade 6 toxicity incidences being the worst toxicity is 1:1, ratio of possibilities of adjusted grade 1-4 toxicity incidences being the worst toxicity is 1:1:1:1, minimum acceptable

percentage of patients without toxicities is 7%, TTL in binary toxicity scenarios is 33%. Percentages of patients by adjusted toxicity grades are shown below in Table 2.

Using percentage of patients as well as mid-range NETS for each adjusted toxicity grades, $TNETS = \sum_{i=1}^{6} P(patients_{adjusted\ grade\ i}) * mid - range\ NETS_{adjusted\ grade\ i}$, which in the above case is equal to 0.476.

Phase I Clinical Trial Designs

All clinical trials are designed to test dosages within pre-determined ranges of dosages X_{min} and X_{max}. One other important parameters that can be obtained from preclinical data is probability of DLT ρ_0 at starting dosage X_{min}. This parameter is very crucial in various models in calculating dose-toxicity relationships and determining starting dosages.

Rule-Based Clinical Trial Designs

The most traditional Phase I cancer clinical trial design is standard 3+3 design. Known for its simplicity, it has enjoyed great popularity ever since its conception. Rule-based clinical trial designs are divided into two types – with dose de-escalation and without dose de-escalation. Three patient cohorts are entered into every pre-determined dose level. If no patient experience DLT, then dosage is escalated to that of the next dose level and the trial continues. If 1 or more patient experience DLT, then either the trial is stopped and the MTD is declared (without dose de-escalation) or the trial de-escalate to the dosage of the previous dose level (with dose escalation).

Extensive studies have been done on its operating characteristics. For instance, formulae for calculating all characteristics has been listed in detail [18]. Simulation studies showed a monotonic decrease in toxicity level at Maximum Tolerated Dose (MTD) and recommended dose levels be maintained below 20 for desired therapeutic outcomes for participating patients [19]. Due to its rule-based nature, derivation of such designs such as standard 4+4 design or standard 5+5 design can also be easily implemented.

The biggest downfall is that rule-based clinical trials are not as accurate when used to predict MTD. As simulation has shown, when choosing different probabilities of DLT for different dose levels, TTL at MTD can change. Therefore, running multiple scenarios before start of trials can give only a rough estimation of MTD.

Another type of rule-based design is the Accelerated Titration Design [20]. Aimed at solving the one the biggest shortcomings of standard rule-based design which is its slow dose-escalation, the Accelerated Titration Design utilized high incremental dose steps as well as intra-patient dose escalation in an effort to increase the speed of completion of phase I cancer clinical trial and reduce under-dosed patients while not causing a significant increase in toxicities.

Despite their efforts to decrease the number of under-dosed patients, rule-based designs have long been criticized to subject too many patients to biologically ineffective dose levels. Many studies have shown that the common intuition that such designs would identify MTDs with approximately 30% DLT [19]. In order to come up with alternative ways to resolve that issue, many researchers have proposed a variety of Bayesian adaptive designs that have since

been implemented in clinical trials. Among them are designs such as Continual Reassessment Method (CRM), Baysian Optimal INterval (BOIN) design, Toxicity EQuivalance Range (TERQ) Design as well as Escalation With Overdose Control (EWOC). Even though these adaptive design are superior to rule-based designs in many aspects, they are limited in their usages in clinical settings due to its statistical and mathematical complexities [21].

Continual Reassessment Method (CRM)

CRM was one of the first adaptive clinical trial designs proposed and faced many concerns on its safety due to its potential for rapid dose escalation [22]. These concerns were later found to be unfounded, and CRM has been proven in many cases to be more accurate than rule-based designs. CRM features the usage of a *priori* logistic dose-toxicity curve. By treating patients at any given time at the MTD given by the dose toxicity curve, CRM minimizes the number of under-dosed patients [23]. In addition, by constantly utilizing patient responses to modify the slope (and midpoint depending on the number of parameters in the logistic model) to advise the next dose level, CRM can base dose-toxicity curve mostly on actual patient response data so that the resulting curve may look entirely different from the original curve.

Bayesian Optimal INterval (BOIN) Design

BOIN belongs to a special class of phase I clinical trial design named interval designs. This class of designs utilizes predetermined toxicity intervals for dosage decisions throughout the trial [24]. BOIN combines the Bayesian approach with toxicity intervals to minimize dosage decision error rates. Depending on the magnitude of the current toxicity rate with respect to a prespecified toxicity interval, dosages for the next patient is decided. For example, if the

current toxicity rate is bigger than the upper limit of the interval, dose de-escalation is indicated, and vice versa. Thus, selection of toxicity intervals becomes vital in accurately deciding dose transitions and minimizing errors in dose escalation and de-escalation.

The posterior probability of decision error of the toxicity range is calculated using the summation of prior distribution of dose assignment times likelihood function of decision error given each dose assignment according to the toxicity range: dose escalation, dose de-escalation, dose retention (at MTD). It was found that the upper and lower boundaries of the intervals minimize the decision error rate when posterior probability of dose escalation and de-escalation is higher than dose retention. This interpretation is intuitive given that maximizing the differences between boundaries can effectively decrease error rate due to the ease of differentiation between dose decisions. Prior distribution of dose assignment for each dose level can be provided by physicians. However, in the case of unavailability, uninformative prior which assumes equal likelihood of dose de-escalation, retention and escalation, can be used.

One of the biggest advantages of BOIN is its ease of implementation. Since the interval is prespecified prior to running the trial, principle investigators only need to calculate the observed toxicity rate to make decisions on dose assignments.

Toxicity EQuivalance Range (TEQR) Design

TEQR design represents a frequentist approach to interval designs [25]. Instead of calculating the posterior probability of decision error rates given ranges, empirical DLT rates are used in this model. Pre-established table of dose decision is made for increments of 3 patients treated at a given level. Dose assignment decision consist of escalation, de-escalation,

retention, de-escalate and do not return. The trial runs until MTD is located or a predetermined number of patients have been entered into the trial.

Similar to BOIN, TEQR is also easy to implement in a clinical setting because all the decision intervals are pre-determined. Clinicians only need to calculate observed toxicity ratio and make the dose assignment decision.

Escalation With Overdose Control (EWOC)

EWOC design is a Bayesian adaptive clinical trial design [26]. Using a logistic function to model dosage-toxicity response, EWOC reparametrizes MTD γ in terms of a set of known parameters such as X_{min} and θ as well as unknown parameters such as γ and ρ_0. Marginal posterior distribution of MTD is then calculated using informed prior and the reparametrized likelihood function. Using feasibility bound predetermined before the trial, the chosen MTD in the posterior distribution is chosen as the next dosage.

Compared to other designs mentioned above, EWOC is significantly more statistically complex and harder to implement in clinical settings. However, it has been shown to improve MTD γ prediction accuracy and reduce under-dosing of patients.

EWOC-NETS Design

EWOC-NETS is a phase I clinical trial design combining Bayesian adaptive model with a quasi-continuous toxicity scoring system. Coupling the improved performance of EWOC with the comprehensive incorporation of detailed toxicity information by NETS, EWOC-NETS is a significant step forward in facilitating drug discovery. Modifications for the changed toxicity

scoring system was made, namely the likelihood function. More details are presented in the following section.

With increased performance and accuracy comes higher statistical complexity. This significantly hinders the wide use of this clinical trial model.

Comparison between Dose Escalation Models

Comprehensive analysis on the operating characteristics of different phase I clinical trial design has been conducted [4]. Simulation trials were run on all trials mentioned above and metric were implemented to evaluate performances. It is found that in general, model-based designs both identify MTD more accurately, but also assign more patients to MTD. It is especially noted that the feasibility bound of the EWOC model effectively minimizes the over-dosing of patients. In addition, the accuracy of MTD selection remains as TTL increases for EWOC but not for other designs.

Methods

Model Computation

EWOC Model Computation

In the EWOC clinical trial design with binary toxicity definition, patient response y is equal to either 0 (no DLT) or 1 (DLT). Thus, probability of DLT at MTD γ is equal to the TTL θ:

$$P(y = 1, x = \gamma) = \theta$$

As for modeling the probability of DLT at lower doses x, a logistic function is utilized to represent the dose-toxicity relationship at each dose level.

$$P(y = 1, x) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}$$

Using this logistic function, we can use logistic transform of the equation to get the inverse logistic function of probability of DLT ρ_0 at starting dose X_{min}, and that of probability of DLT or TTL θ at MTD γ:

$$logit(\rho_0) = \beta_0 + \beta_1 X_{min}$$

$$logit(\theta) = \beta_0 + \beta_1 \gamma$$

Since β_0 and β_1 is crucial in the dose-toxicity predicting model as we calculate for MTD that corresponding to θ, it is important that we represent the two variables in a set of known parameters such as X_{min} and θ as well as unknown parameters such as γ and ρ_0. Arithmetic transformation yields the following equation:

$$\beta_1 = \frac{logit(\theta) - logit(\rho_0)}{\gamma - X_{min}}$$

$$\beta_0 = logit(\rho_0) - \frac{logit(\theta) - logit(\rho_0)}{\gamma - X_{min}} X_{min}$$

$$= \frac{logit(\rho_0)(\gamma - X_{min}) - X_{min} * logit(\theta) + X_{min} * logit(\rho_0)}{\gamma - X_{min}}$$

$$= \frac{\gamma * logit(\rho_0) - X_{min} * logit(\theta)}{\gamma - X_{min}}$$

γ and ρ_0 can be set *a priori* to beginning of clinical trial derived from preclinical data such as animal studies. Dose translation from animal to human studies using normalization of Body

Surface Area (BSA) has been suggested as one of the most appropriate ways of deciding a safe starting dose [27]. One tenth of the LD10 in mice is also one of the most used and safest derivation of starting dose used [5]. On the other hand, γ is set by estimation. Both parameters are updated as every new patient enters the cohort. As clinical trial progresses, γ can be updated with toxicity response information of previous patients for high accuracy of prediction by the end of the trials.

NETS Model Computation

As stated above, NETS toxicity scoring system comprehensively and quantitatively summarizes toxicity information from every patient and leverages detailed toxicity incidences to create a quasi-continuous range of toxicity scores. First, CTCAE toxicity grades are mapped to NETS adjusted toxicity grades for every patient i (Table 1). Second, maximum adjusted toxicity grade for every patient i $T_{max,i}$ is determined. Third, logistic function is utilized to account for the effect of other toxicities on ETS. ETS is finally normalized by the maximum adjusted toxicity grade G_{max} (6-8 depending on the scenario and mapping of CTCAE toxicity grades).

$$NETS_i = \frac{T_{max,i} - 1 + \frac{1}{1 + e^{-\left(\alpha + \beta\left(\sum_{x=1}^{X} \frac{w_i T_{x,i}}{T_{max,i}} - 1\right)\right)}}}{G_{max}}$$

EWOC-NETS Model Computation

Due to the difference between the quasi-continuous nature of NETS and the discrete binary nature of traditional toxicity categorization, TNETS are calculated instead of TTL for the definition of MTD. As such, MTD is defined by the dosage at which patients' NETSs equal TNETS.

Just as how we model binary toxicity response in a logistic function of dosage, we model NETS for patient i in a logistic function of dosage as follows:

$$NETS_i = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x)}}$$

$$logit(NETS_i) = \beta_0 + \beta_1 x$$

Concordant with the assumption of the positive correlation between dose and toxic effect, β_1 is set to be a positive number. Again, applying the same logic of reparameterization to represent β_0 and β_1 with a combination of known and set a priori parameters, we obtain the following relationship:

$$\beta_1 = \frac{logit(TNETS) - logit(\rho_0)}{\gamma - X_{min}}$$

$$\beta_0 = \frac{\gamma * \ logit(\rho_0) - X_{min} * logit(TNETS)}{\gamma - X_{min}}$$

We can thus model NETS of patient i at dose x using the above reparameterization as:

$$logit(NETS_i) = \frac{logit(TNETS)(x_i - X_{min}) + logit(\rho_0) * (\gamma - x_i)}{\gamma - X_{min}}$$

Since NETS consist of a family of probability distribution generated with a logistic function of toxicities other than maximum toxicity according to its calculation shown above, a quasi-Bernoulli likelihood approach can successfully incorporate NETS into parametric models. Maximizing the quasi-Bernoulli likelihood function of parameters γ and ρ_0 given data can yield consistent results because the Bernoulli distributions resulting from the logistic function of

other toxicities shown above belong to the binomial family. Likelihood function given total of k patients:

$$L(\rho_0, \gamma \,|\text{data}) = \prod_{i}^{i=k} \frac{e^{\frac{logit(TNETS)(x_i - X_{min}) + logi\ (\rho_0)*(\gamma - x_i)}{\gamma - X_{min}} * NETS_i}}{1 + e^{\frac{logit(TNETS)(x_i - X_{min}) + logit(\rho_0)*(\gamma - x_i)}{\gamma - X_{min}}}}$$

In order to obtain the posterior distribution of γ and ρ_0, Markov Chain Monte Carlo (MCMC) is utilized to update the posterior distribution $\pi\ (Data|\gamma, \rho 0)$. Let $h(\rho_0, \gamma\ )$ be the prior distribution. MCMC sampler uses the above likelihood function to update the marginal posterior distribution for γ and ρ_0 [26]. The updated posterior distribution is used as prior distribution for the next iteration when a new patient is treated at a new dosage. A total of 30000 simulations are run every time for calculation and the last 5000 iterations are chosen to represent the marginal posterior distribution of γ and ρ_0.

$$\pi\ (Data|\gamma, \rho_0) = \frac{L(\rho_0, \gamma \,|\text{data}) * h(\rho_0, \gamma\ )}{\iint_{[0, TNETS] \times [X_{min}, X_{min}]} L(\rho_0, \gamma \,|\text{data}) * h(\rho_0, \gamma\ ) \text{d}\rho_0 \text{d}\gamma}$$

Feasibility bound α is defined so that the dosages picked for the next dose level is the dosage at which the likelihood of being MTD is equal to α. The same process is repeated until either: 1) pre-determined total number of patients are enrolled in the trial or 2) the same dosage has been recommended for a certain number of times. The median of the marginal posterior distribution of γ is chosen as the recommended MTD as a result of the trial.

EWOC-NETS Simulation

Simulation were run using real clinical trial data from study A09712. The trial consisted of 9 doses in total with the minimum dosage of 20 mg and maximum dosage of 350 mg

administered over 6 weeks. Using standard 3+3 design, the trial recommended dose level 6 as the MTD, which later turned out not be true in phase II clinical trials. The true MTD was tested to be dose level 8. 5000 simulations were conducted on different values for variable β when calculating NETS. During each respective dose level, using preprocessed information for all patient toxicity information by specific toxicity grades at that dose level, we sample 3 patients with replacement to represent the cohort. We then calculate the dose assignment using feasibility bound of marginal posterior distribution of MTD gamma. The dose level with the dosage closest to the calculated MTD gamma by feasibility bound is chosen for the next cohort of patients. Feasibility bound was set at 25% initially at start of each simulation conservatively and increment by 5% after each dose assignment until it reaches the medium at 50%. If a dose level is recommended 4 times in a row, then that dose level will be deemed as the MTD. Percentage of time each dose level is recommended as MTD was calculated and compared to real trial result in an effort to see which phase I clinical trial design is the most accurate.

Programming

Programming language

R language was used in creating this software. Html and CSS was used in positioning and styling elements of the UI in a intuitive fashion. Command line was utilized for calling Google Chrome Portable for interface, R Portable for running scripts and 'runShinyApp.R' file for running front-end and back-end scripts, including CSS files, R scripts and etc.

R packages

Various packages were utilized for different purposes in creating this software.

Shiny package was utilized for its function of creating user interfaces and connecting input data with user-defined back-end algorithms. Input parameters includes: α and β values and equivalent TTL for calculating NETS on page 1, X_{min}, X_{max}, γ and ρ_0 for the calculation for EWOC.

Shinyjs package was used for calculations and various features to be reactive to button clicks. For example, new patient information is updated to the total toxicity information table from which calculation of posterior distribution is executed. Importing data from previous patients is also enabled to ensure working efficiency and ease of use.

DT and ggplot packages were used for storing data and plotting various calculation results for direct visualization.

Deploying procedures

Back-end and front-end script as well as CSS and image files are stored in separate folder. VB script is created so as to call R script that contains command line calls which establish an interface window, connect the interface window with back-end and front-end R script in separate folder. This deployment method does not require user to have any additional software installed on the computer. In order to use the software, simply download the file and click on the executable VB script.

Results

EWOC-NETS Calculator

Input Parameters

The interface of the software is as shown below (Figure 1-3). Input parameters consist of 3 pages. X_{min}, X_{max}, γ, ρ_0 and equivalent TTL for the calculation for EWOC on page 1, α, β values for calculating NETS on page 2 as well as new patient toxicity input on page 3. In addition, batches of data from previously enrolled patients can be imported from existing data, therefore allowing for more efficient workflow.

To start, users will decide on parameters such as X_{min}, X_{max}, γ, ρ_0 and TNETS which were set with arbitrary values and should be changed based on each individual clinical trial (Figure 1). Namely, X_{min}, X_{max} represents the predetermined minimum therapeutic dosage to maximum dosage, whereas γ and ρ_0 come from estimation of preclinical trial animal study data. Since the goal of the trial is to find MTD within [$X_{min,}$ X_{max}], γ must be within the range of those two values. ρ_0 represents the estimation of probability of DLT at X_{min}, and thus must be [0,TNETS]. Equivalent TTL defaults as 0.33, a routine value given the small size of phase I clinical trials, and also given the historic use of 3+3 rule-based designs. This feature was implemented specifically for easy interpretation of MTD under binary toxicity categorization. Equivalent TTL is then converted to a singular value in a more detailed and comprehensive scoring system given several assumptions: ratio of adjusted grade 5 and adjusted grade 6 toxicity incidences is 1:1, ratio of adjusted grade 1-4 toxicity incidences are 1:1:1:1, minimum acceptable percentage of patients without toxicities is 7%. The corresponding TNETS value is shown below the input to inform user of the equivalent TNETS to the given TTL value. Importing data is enabled so that user can download their existing data for further analysis after the next round of patients are treated. The imported files must conform to the nx12 matrix (n being number of patients)

format with columns representing features in the following sequence from left to right: patient identifier (optional, can leave blank), dose level, dosage, adjusted toxicity grade 1-6 incidences, maximum adjusted toxicity grade incidence, ETS, NETS. Users can delete rows of patient information by clicking the specific row and then clicking 'delete' button. Table 3 shows a sample input for the application with 6 patients at 2 dose levels.

On the second page, users must decide on the coefficients for NETS calculation (Figure 2). As stated above in section on NETS calculation, -2 is the most appropriate value for α that ensures the consistence due to the arbitrary designation of NETS as 0.1 for patients having a single adjusted grade 1 toxicity incidence. Therefore, -2 was set as the default value for α. On the other hand, β determines the effect of other toxicities on NETS compared with the highest adjusted toxicity grade incidence. Default value for β was set as 0.25, a common value for this parameter.

The third page of the input includes patient identifier, dose level, dosage, incidences of toxicities by adjusted grade (Figure 3). This allows for new patient information to be added into the model for posterior distribution update calculation. Dosage should not be smaller than X_{min} and X_{max} as defined by the clinical trial. Clicking 'Calculate' button begins the MCMC calculation for marginal posterior distribution of γ and ρ_0.

Obtaining and Interpreting Results.

Sample table and figure output generated using data from Table 3 is shown. Both posterior distribution of γ and ρ_0 in data table by quantile and in graphs in the forms of

histograms, density plots as well as trace plots were generated for different aspects of the results (Figure 5-11).

First, marginal posterior distribution calculated by MCMC was represented in data table by 5% quantile (Table 4). This was shown because feasibility bound is usually set as 0.25 and increment in 5% until it reaches 50%. Representing 5% quantile of the marginal posterior distribution of MTD gamma allows users to easily see the recommended dosage for the next dosage assignment.

Second, density plots of the distribution of γ and ρ_0 was represented (Figure 6-7). Feasibility bound α can be approximated on the density plot to indicate the MTD γ according to the proposed posterior distribution, which can be used as the dosage for the patient. In addition, density plot of marginal posterior distribution of ρ_0 was also shown. Dosage plot with respect to number of patient enrolled in the trial gave an overall representation of the trial progress (Figure 5).

In addition, marginal posterior distribution was further represented in 5% quantile in histograms (Figure 8,10). Users can use these histograms to choose values of MTD gamma closest to the feasibility bound, which will be the dosage for the next patient. Trace plots were generated to validate the results of MCMC sampler. Stabilized chains were observed, which meant that the results were good representations of true distribution given data (Figure 9,11).

EWOC-NETS Simulator

Input Parameters

The interface of the simulator functionality includes two pages of input in order for the simulations to be run (Figure 12-13). All the parameters that must be defined in the EWOC-NETS calculator must be defined for the EWOC-NETS simulator on page 1, with the exception of coefficients for NETS calculation α and β. Due to the purpose of the simulator, it can be assumed that no real data is present, and that the simulation is based on estimation of NETS at each dose level. Simulation-related parameters must be defined for each individual's need. Iteration count of higher than 5000 and a minimum of 1000 iteration is recommended for burn-in. Starting feasibility bound can be changed, but a conservative starting feasibility bound is usually recommended. In addition, an additional parameter for maximum dose level is added.

The second page of the simulator enables users to input the Average NETS (ANETS) expected at each dose level as well as the dosage for the corresponding dose level (Figure 13). These pairs of input are dynamically generated according to the number of possible dose levels. For each dose level, three NETS were generated randomly according to a normal distribution with a standard deviation of 0.1 around the ANETS of that dose level. Using those NETS, the marginal posterior distribution of MTD gamma is then updated. Feasibility bound was used to determine the dose level for the next dose assignment. Once a dose level is recommended two times in a row, then that dose level is deemed the MTD.

A dedicated panel was utilized to present a table of the mid-range NETS with respect to their most severe toxicity. This is to help clinicians in estimating the ANETS for each dose level by considering the most severe toxicities for each dose level.

<u>Obtaining and Interpreting Results</u>

A sample output table is presented following simulation of 10 times using ANETS and dosages as shown (Figure 15). Other parameters were ran as shown in Figure 12-13. Percentage recommended as MTD, number of patients treated at each dose level per simulation and average sample NETS for each dose level are calculated to provide users with a better overview of the simulations and detailed information on each dose level. As expected, the recommended dose level was chosen as dose level as the ANETS is closest to TNETS.

Downloading Software

Software is available for download online. After downloading the compressed folder, extract all files from the folder. Click on 'run' and open application.

Discussion

The real trial which utilizes 3+3 clinical trial design recommended dose level 6 as the MTD for phase II clinical trial, two dose levels lower than what is used in later stages of testing. On the other hand, 92-94% of the 5000 simulations recommended dose level 8 as the MTD, which shows EWOC-NETS a highly accurate clinical trial design at predicting the correct MTD (table 5). In addition, it is shown that values 0.1-0.5 affect the accuracy of MTD prediction of EWOC-NETS to a negligible extent, and that it will be appropriate for users to use any value within that range. On average, the trial admitted 21.7 patients, about half of the total cohort tested in the real trial, which means that EWOC-NETS dose-escalated in a quicker and more accurate manner than 3+3 clinical trial designs.

We present here the first implementation of EWOC-NETS through an openly-available stand-alone software for clinical uses. Combining the state-of-the-art Bayesian adaptive clinical trial design EWOC and novel quasi-continuous toxicity scoring system NETS, EWOC-NETS model is a highly efficient and accurate model compared to traditional rule-based and other adaptive designs. Our software was developed with the goal of solving the bottleneck issue in the implementation of advanced phase I clinical trial design in patient care that is the lack of statistician expertise and guidance. We provide a readily usable solution by bring a software that allows users to input easily interpretable parameters and generate straightforward representation of simulation results from statistically complex dose-toxicity model, all of which can be stored and re-imported for further analysis as the clinical trials progress. It has been shown that Bayesian adaptive models such as EWOC-NETS are able to treat 55% patients in the therapeutic window, compared with 35% for rule-based designs [21]. Despite its superior performance, prevalence of use of such clinical trial designs has not been observed. It is our hope that with the release of our software, more clinicians and Principle Investigators will decide to adopt EWOC-NETS as their design of choice for their own cancer phase I clinical trials. Consequently, more patients can be treated effectively, and more lives can be saved. The added benefit of increased MTD prediction accuracy will no doubt facilitate the drug development process as well, saving even more lives. Lastly, this is the first version of our software, and we will strive to keep maintaining it for issues and bug fixes. Any suggestions for additional functions and features will be appreciated.

List of Tables

CTCAE Defined Toxicity Grades	NETS Toxicity Scoring System Adjusted Grades
Grade 1	Adjusted grade 1
Grade 2	Adjusted grade 2
Grade 3 hematologic/non-DLT	Adjusted grade 3
Grade 4 non-hematologic/non-DLT	Adjusted grade 4
Grade 3 non-hematologic/DLT	Adjusted grade 5
Grade 4 hematologic/non-DLT	Adjusted grade 6
Grade 5	Adjusted grade 7

Table 1. Mapping of CTCAE defined toxicity grades to NETS toxicity scoring system adjusted grades. Grade 5 (equivalent of NETS = 1) is not usually considered in the model because death incidence usually causes the trial to be suspended.

NETS Toxicity Scoring System Adjusted Grades	Percentage in cohort
Adjusted grade 1	15
Adjusted grade 2	15
Adjusted grade 3	15
Adjusted grade 4	15
Adjusted grade 5	16.5
Adjusted grade 6	16.5
Adjusted grade 0	7

Table 2. Percentage of patients in cohort given: ratio of adjusted grade 5 and adjusted grade 6 toxicity incidences is 1:1, ratio of adjusted grade 1-4 toxicity incidences are 1:1:1:1, minimum acceptable percentage of patients without toxicities is 7%, TTL in binary toxicity scenarios is 33%.

	Patient ID	Dose Level	Dosage	Adjusted Grade							ETS	NETS
				1	2	3	4	5	6	max		
Patient 1	1	1	30	2	3	4	1	0	0	4	3.320821	0.55347
Patient 2	2	1	30	3	2	1	0	0	0	3	2.195185	0.365864
Patient 3	3	1	30	2	3	1	1	0	0	4	3.212069	0.535345
Patient 4	4	2	40	2	2	2	3	1	0	5	4.310026	0.718338
Patient 5	5	2	40	2	2	2	3	0	1	6	5.268941	0.878157
Patient 6	6	2	40	3	1	1	2	2	1	6	5.285638	0.88094

Table 3. A sample input data table imported into the software.

Quantile	rho0	gamma
0.05	0.024	4.8334
0.1	0.0481	9.8876
0.15	0.0714	15.1704
0.2	0.0954	19.6327
0.25	0.1175	24.3642
0.3	0.1412	29.2157
0.35	0.165	34.1331
0.4	0.1871	38.9164
0.45	0.2101	44.0679
0.5	0.2337	48.9156
0.55	0.2568	54.1359
0.6	0.2834	59.4836
0.65	0.308	64.7436
0.7	0.332	69.9123
0.75	0.3547	74.6245
0.8	0.3783	79.6865
0.85	0.4026	84.8752
0.9	0.4288	89.3919
0.95	0.455	94.4303
1	0.4762	99.9959

Table 4. Marginal posterior distribution of γ and ρ_0 by every 5% quantile.

Dose Level	Beta		
	0.1	0.25	0.5
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0.02%	0	0.06%
7	5.62%	7.72%	7.88%
8	94.36%	92.28%	92.06%
9	0	0	0

Table 5. Simulation results from 5000 simulation using different β values.

List of Figures

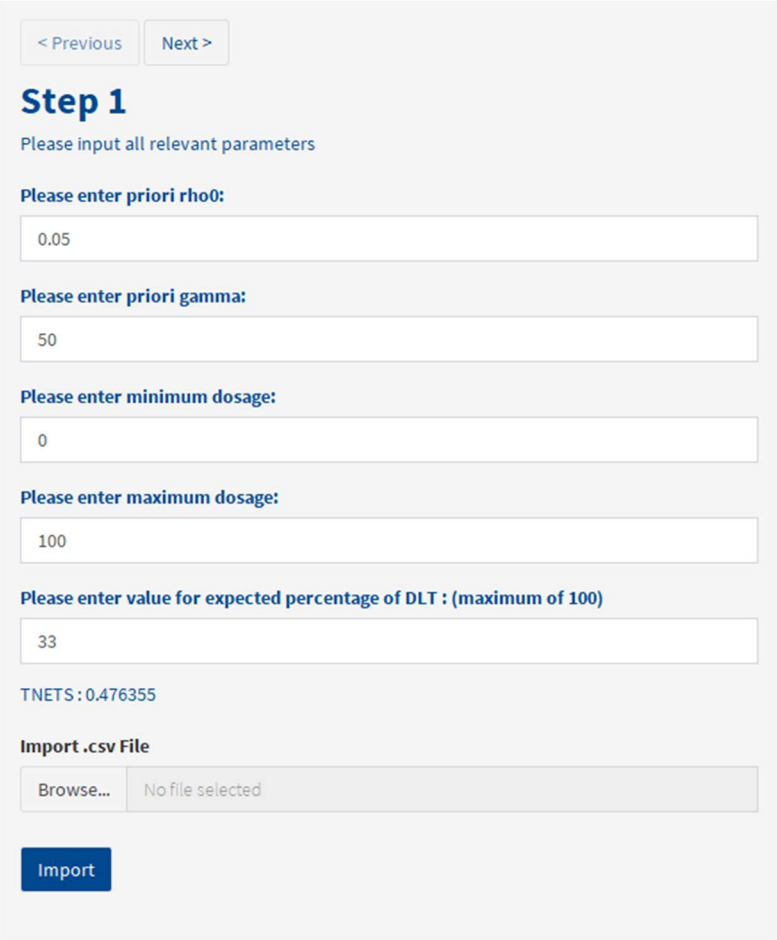


Figure 1. Page 1 input of the user interface of the EWOC-NETS calculator. Page 1 input of the user interface include include X_{min}, X_{max}, γ and ρ_0 and equivalent TTL for calculating TNETS. Users can also import data conforming to n*12 dimension defined standards.

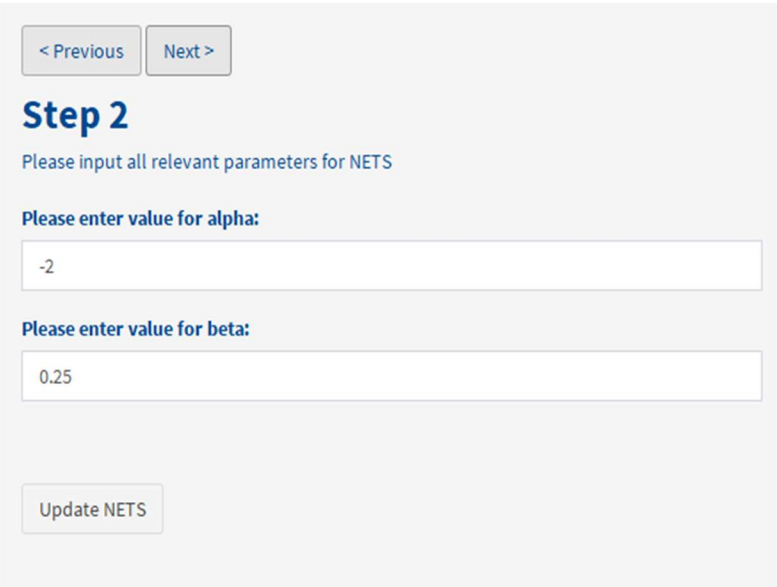


Figure 2. Page 2 input of the user interface of the EWOC-NETS calculator. Page 2 input of the user interface include α, β values for calculating NETS.

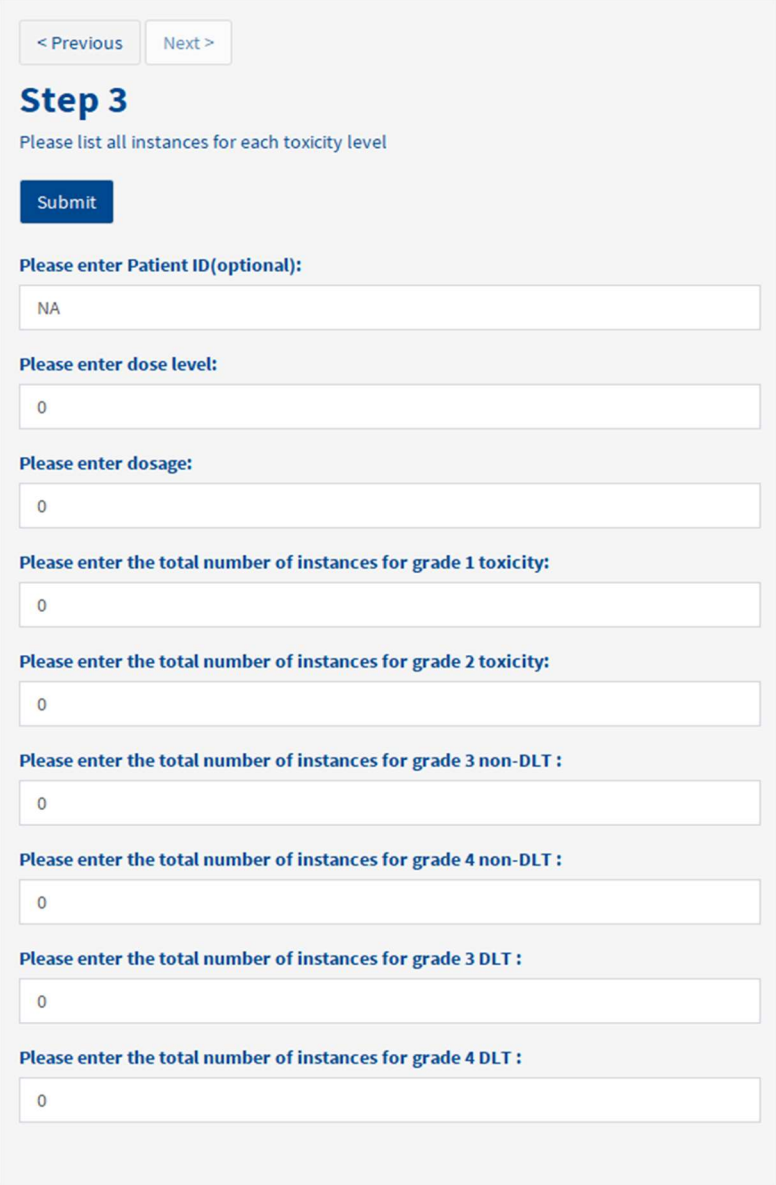
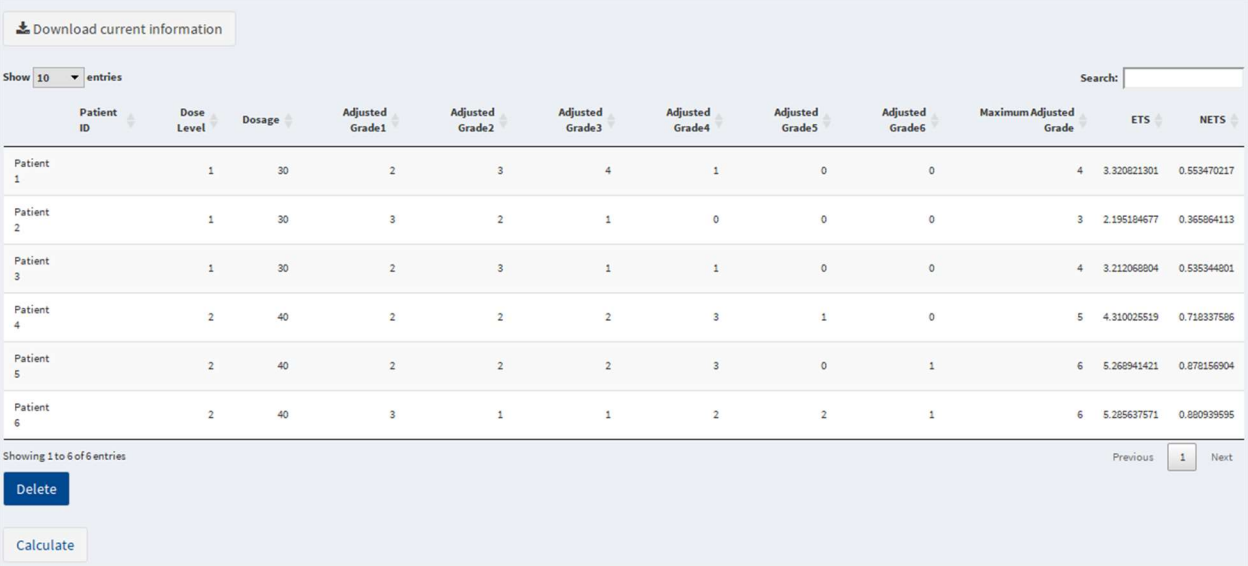


Figure 3. Page 3 of the user interface of the EWOC-NETS calculator. Page 3 of the user interface include data necessary for inputting a new patient in cohort.



Download current information

Show 10 entries

Search:

	Patient ID	Dose Level	Dosage	Adjusted Grade1	Adjusted Grade2	Adjusted Grade3	Adjusted Grade4	Adjusted Grade5	Adjusted Grade6	Maximum Adjusted Grade	ETS	NETS
Patient 1		1	30	2	3	4	1	0	0	4	3.320821301	0.553470217
Patient 2		1	30	3	2	1	0	0	0	3	2.195184677	0.365864113
Patient 3		1	30	2	3	1	1	0	0	4	3.212068804	0.535344801
Patient 4		2	40	2	2	2	3	1	0	5	4.310025519	0.718337586
Patient 5		2	40	2	2	2	3	0	1	6	5.268941421	0.878156904
Patient 6		2	40	3	1	1	2	2	1	6	5.285637571	0.880939595

Showing 1 to 6 of 6 entries

Previous 1 Next

Delete

Calculate

Figure 4. Presentation of patient toxicity information. Patient toxicity information from either importing or input one-by-one for each patient or a combination of the two is shown in the main panel of the application for direct presentation. Delete button allow users to delete wrong information and reinput the correct version. Calculate signals the back-end algorithm to calculate marginal posterior distribution via MCMC. Furthermore, users can download the current version of the patient toxicity information for future use.

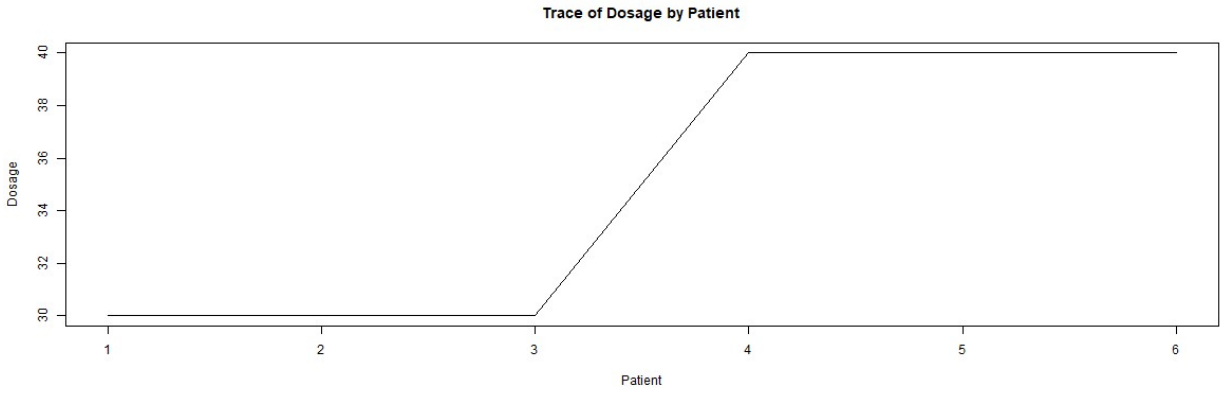


Figure 5. Dosage trace plot representing the overall progress of the clinical trial. Dosage trace plot was arranged on the top of the graphs for tracking of trial progress.

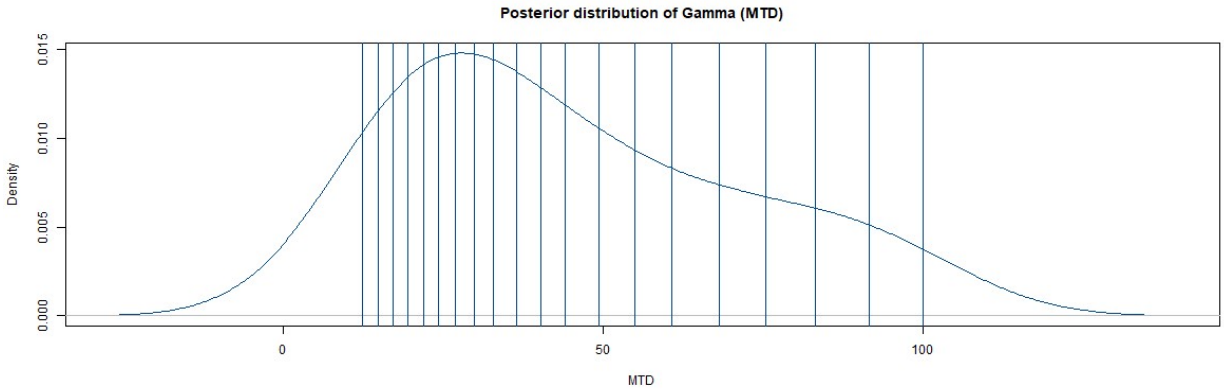


Figure 6. Density plot of marginal posterior distribution of MTD γ. Density plot of marginal posterior distribution was shown for presentation of the distribution of simulation results. Vertical lines of each 5% quantile was shown for more intuitive interpretation.

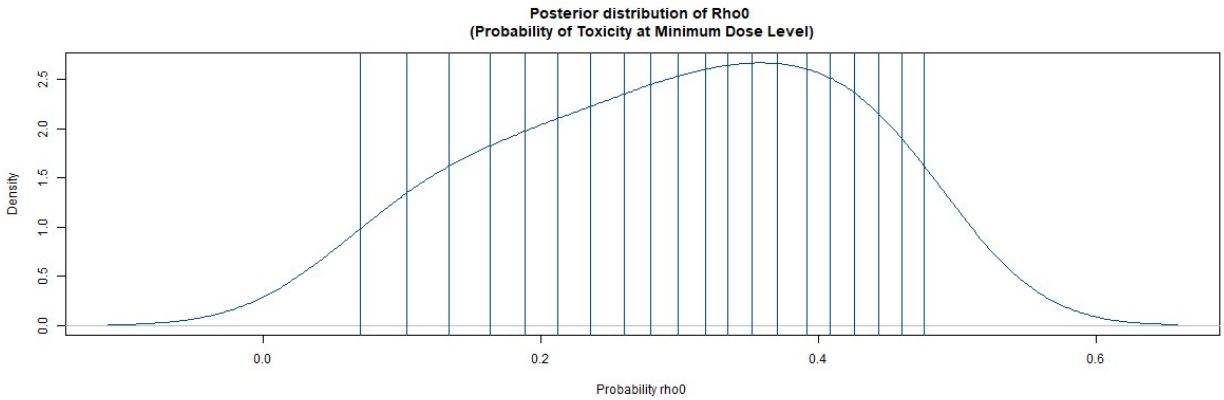


Figure 7. Density of marginal posterior distribution of probability of DLT at X_{min}, ρ_0. Density plot of marginal posterior distribution was shown for presentation of the distribution of simulation results. Vertical lines of each 5% quantile was shown for more intuitive interpretation.

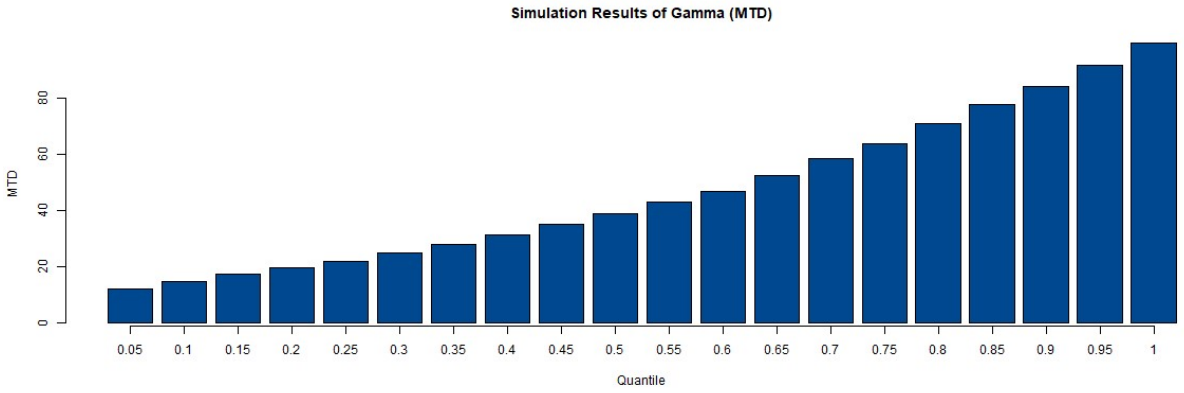


Figure 8. Histogram representing the quantile of the marginal posterior distribution of MTD γ. Values of the quantile-corresponding values according the resulting distribution were shown in histogram for direct interpretation. Given feasibility bound, users can estimate the predicted MTD γ for use at the next dosage.

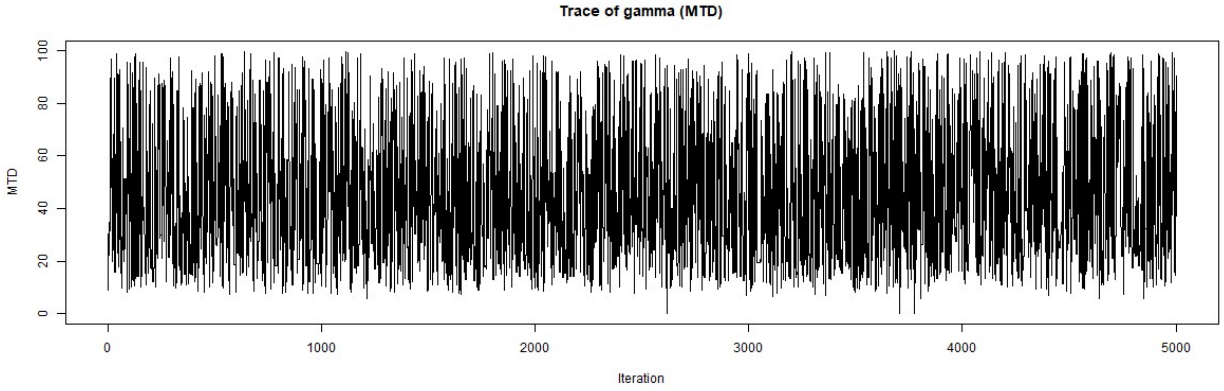


Figure 9. Trace plot representing the trace of the last 5000 iteration of a total of 30000 iteration calculating the likelihood of MTD γ. Stabilized chain as shown in the graph signifies that the burn-in period has finished and that the results are good representation of the true posterior distribution.

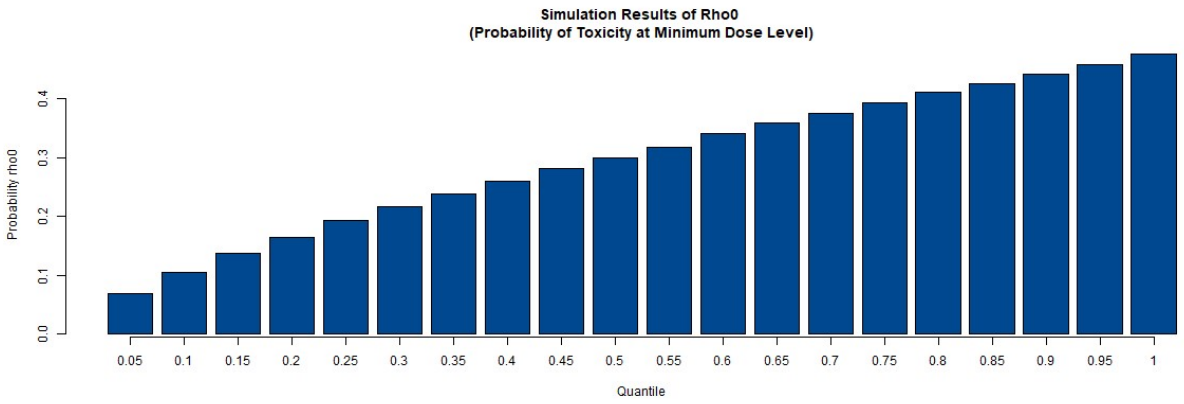


Figure 10. Figure 8. Histogram representing the quantile of the marginal posterior distribution of probability of DLT at X_{min}, ρ_0. Values of the quantile-corresponding values according the resulting distribution were shown in histogram for direct interpretation.

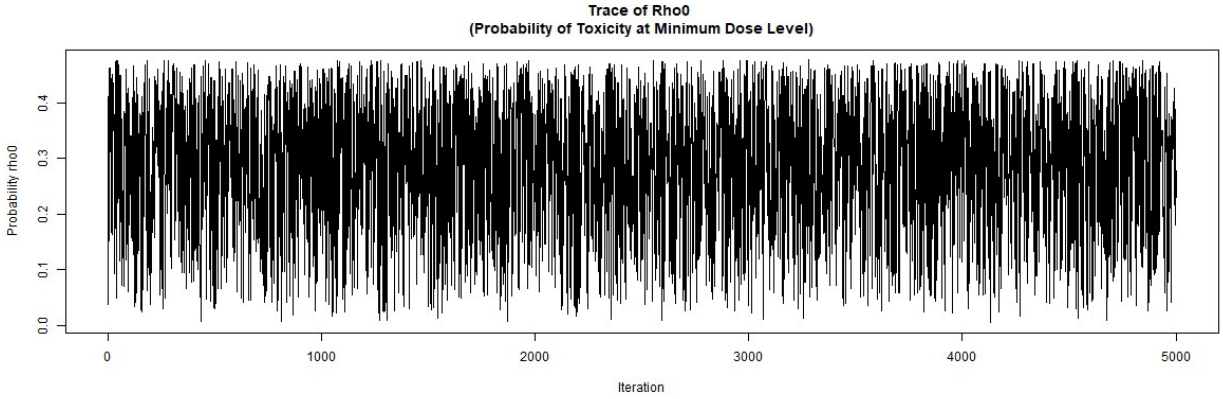


Figure 11. Trace plot representing the trace of the last 5000 iteration of a total of 30000 iteration calculating the likelihood of probability of DLT at X_{min} ρ_0. Stabilized chain as shown in the graph signifies that the burn-in period has finished and that the results are good representation of the true posterior distribution.

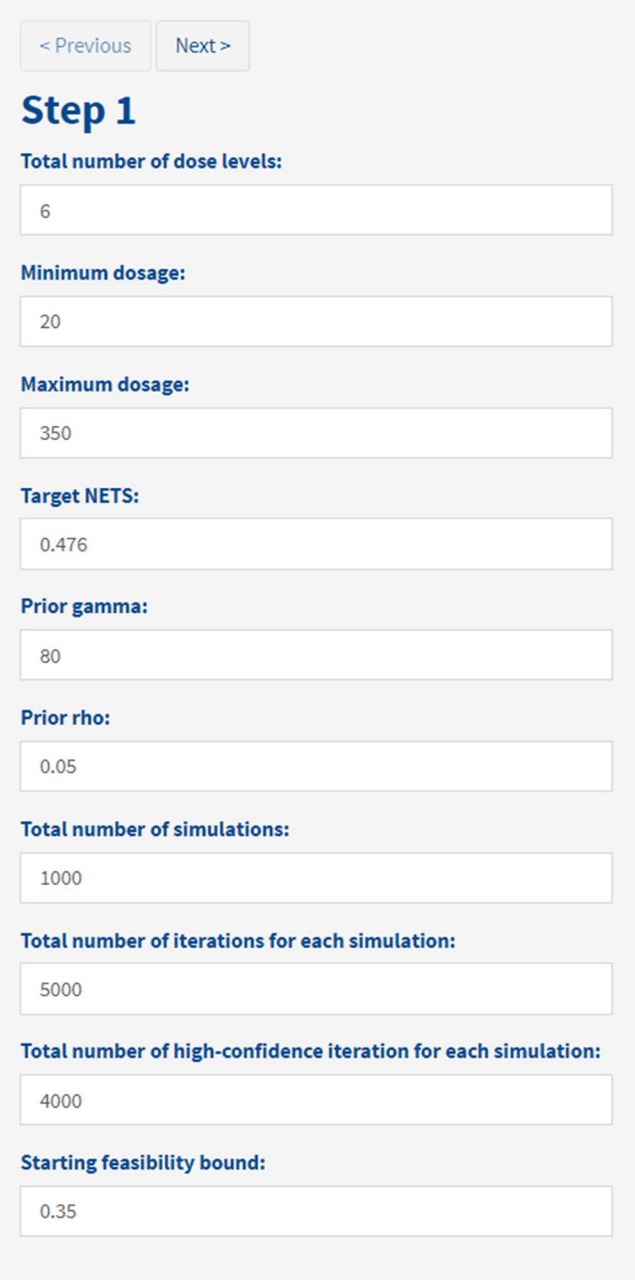


Figure 12. Page 1 input of the user interface for the EWOC-NETS simulator. Page 1 input of the user interface for the EWOC-NETS simulator includes total number of dose levels, minimum dosage, maximum dosage, TNETS, prior gamma, prior rho0, total number of simulations to be run, total number of iterations to be run in each simulation, total number of iterations picked considering burn-in, starting feasibility bound.

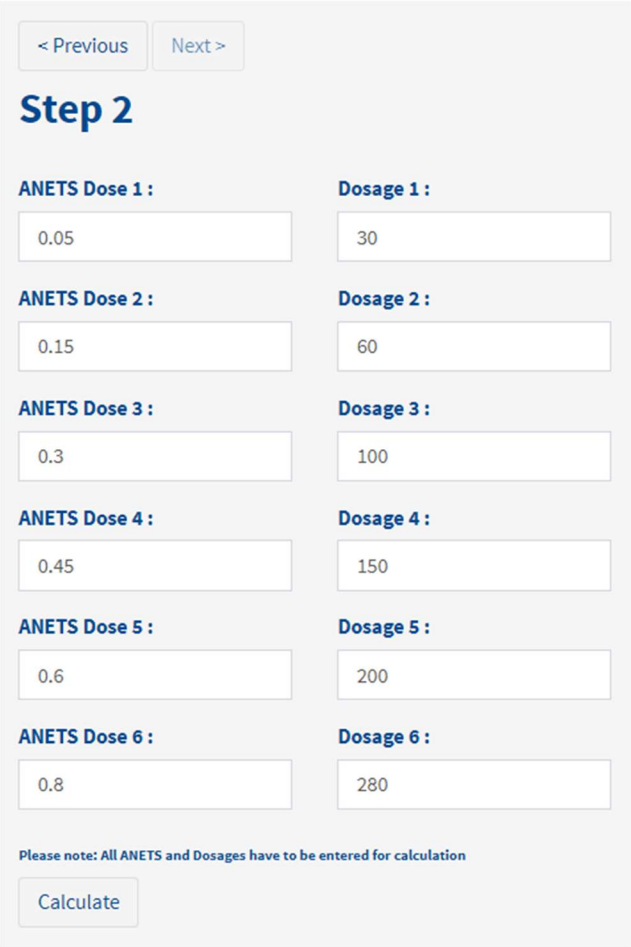


Figure 13. Page 2 input of the user interface for the EWOC-NETS simulator. Page 2 input of the user interface for the EWOC-NETS simulator includes the corresponding inputs of ANETS and dosage value for each dose level, which are essential for the simulations.

Most.Severe.Toxicity	Maximum.Adjusted.Grade	Range.of.NETS	Mid.range.NETS
Grade 0	0	0	0.00
Grade 1	1	[1/60 - 1/6)	0.09
Grade 2	2	[1/6 - 1/3)	0.25
Grade 3 non-DLT	3	[1/3 - 1/2)	0.42
Grade 4 non-DLT	4	[1/2 - 2/3)	0.58
Grade 3 DLT	5	[2/3 - 5/6)	0.75
Grade 4 DLT	6	[5/6,1)	0.92

Figure 14. Table presented in the mid-range NETS tab on the user interface of the EWOC-NETS simulator. Table of mid-range NETS are provided for clinicians to estimate ANETS for each dose level given their estimation of the most severe toxicity at each dose level.

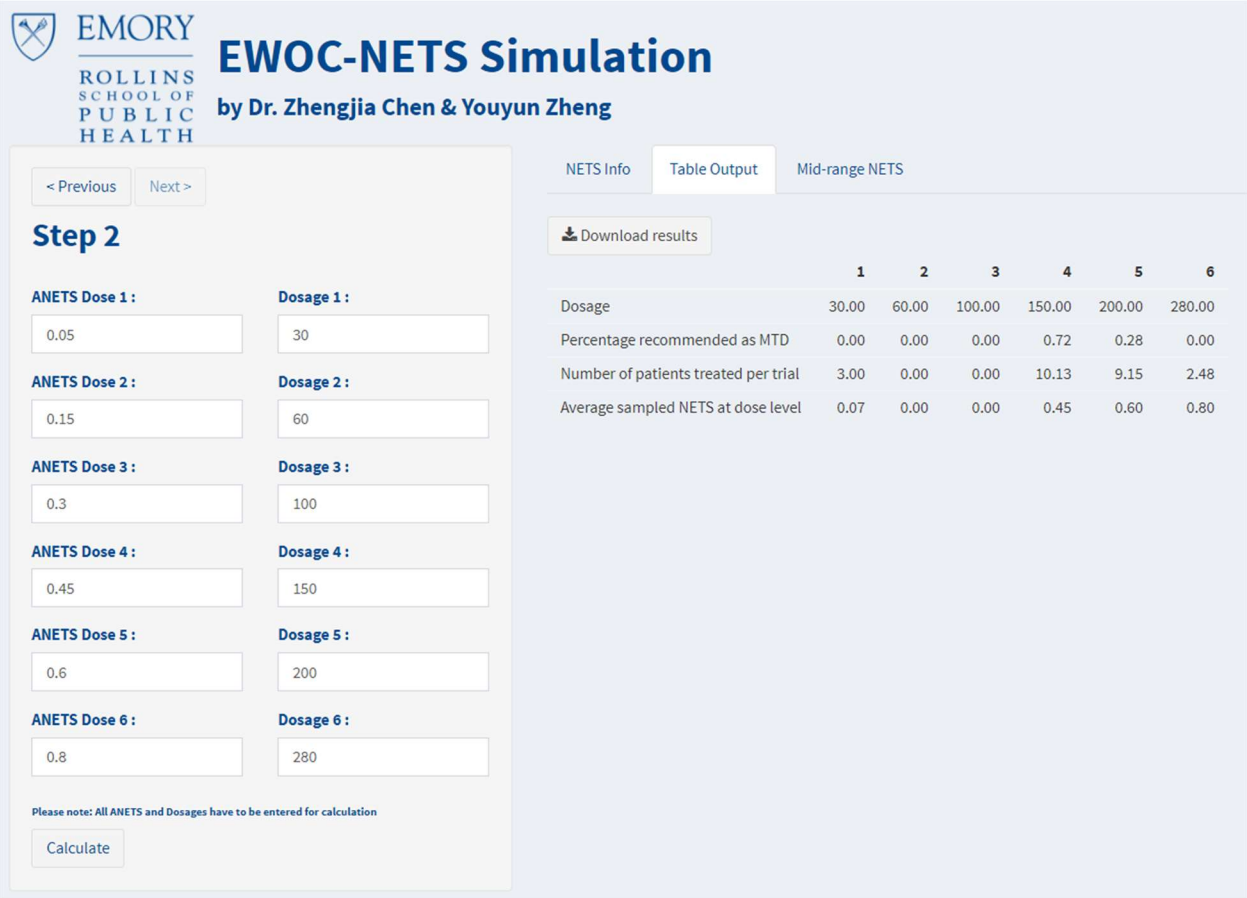


Figure 15. The simulation results table shown on the table output panel on the user interface of the EWOC-NETS simulator. Output includes percentage of dose level being recommended as MTD, average number of patients treated at dose level per simulation, average sampled NETS at dose level.

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