Contemporary Clinical Trials Communications 12 (2018) 145–153

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Interactive calculator for operating characteristics of phase I cancer clinical trials using standard 3 + 3 designs

Zhengjia Chen[a,b,*,1], Youyun Zheng[c,1], Zhibo Wang[b], Michael Kutner[a], Walter J. Curran[d], Jeanne Kowalski[a,b]

[a] Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, United States
[b] Biostatistics and Bioinformatics Shared Resource, Winship Cancer Institute, Emory University, Atlanta, GA, United States
[c] Department of Computer Science, Emory University, Atlanta, GA, United States
[d] Department of Radiation Oncology, Emory University, Atlanta, GA, United States

ARTICLE INFO

Keywords:
Standard 3 + 3 design
Statistical software
Operating characteristics
Cancer phase I clinical trials
Maximum tolerated dose
Dose limiting toxicity

ABSTRACT

Among various Phase I clinical trial designs, rule-based standard 3 + 3 designs are the most widely utilized for their simplicity and robustness. It is necessary to define crucial operating characteristics of a Phase I clinical trial before it starts. Based on the assumed probability of dose limiting toxicity (DLT) at each tested dose level, Lin and Shih elaborated formulas to calculate the five key operating characteristics of Phase I clinical trials using the two subtypes of standard 3 + 3 designs (with vs without dose de-escalation): probability of each dose level being chosen as the maximum tolerated dose (MTD); expected number of patients treated at each dose level; expected number of patients experiencing DLT at each dose level; target toxicity level (TTL) (expected probability of DLT at MTD); expected total number of patients experiencing DLT. Understanding these formulas requires advanced statistical knowledge and the formulas are too complicated to be used directly. To facilitate their application, we have developed stand-alone interactive software for convenient calculation of these key operating characteristics. The calculated results are presented in tables and plots that can be saved and easily edited for further use. Some examples of calculation using the software are presented and discussed.

1. Introduction

A Phase I clinical trial is the first test of a new investigational agent in humans after preclinical studies. The primary goal of a Phase I clinical trial is to estimate the maximum tolerated dose (MTD) as a recommended dosage for subsequent Phase II and III clinical trials [1]. For cytotoxic anti-cancer agents, it is generally assumed that both therapeutic and negative adverse effects will increase as the dose of agent increases, so that the MTD is the optimal dosage of the tested drug that maximizes its therapeutic effect within the limit of safe administration [1]. The primary endpoint used to assess the safety of administration is toxicity classified according to the Adverse Events Common Toxicity Criteria (CTCAE) established by the National Cancer Institute (NCI) [2]. In practice, the condition of each participating patient is monitored for the frequency, type, and severity of toxicity. Patients are classified as having dose limiting toxicity (DLT) if they have grade 3 or 4 non-hematology toxicity or grade 4 hematology toxicity [3,4]. The MTD can be viewed as the dose associated with a certain probability of a DLT [5]. Usually, patients participate in Phase I cancer clinical trials because they have responded poorly to traditional treatment regimens, and therefore volunteer to receive the Phase I investigational agent as a last resort for their disease. Consequently, even though Phase I cancer clinical trials are not designed to specifically for therapeutic benefit, this is often the expectation of the participants. Optimized designs, that accurately and rapidly determine the MTD, are crucial to minimize the number of patients receiving sub-therapeutic or overly-toxic doses for their treatment and to maximize the number of patients treated at dose levels in the vicinity of the MTD [6].

Many proposed Phase I designs can be classified into two groups based on the algorithm used: rule-based designs (such as standard 3 + 3 designs, accelerated titration designs, etc.) and model-based designs (such as the continual reassessment method (CRM), the escalation with overdose control (EWOC) method, etc.) [1,7–13]. Studies have shown that model-based designs (CRM and EWOC) are better at optimizing the MTD than standard 3 + 3 designs in terms of estimating dose accuracy and trial efficiency when the models employed are

* Corresponding author. Department of Biostatistics and Bioinformatics, Emory University, Atlanta, GA, United States.
E-mail address: zchen38@emory.edu (Z. Chen).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.conctc.2018.10.006
Received 16 July 2018; Received in revised form 2 October 2018; Accepted 28 October 2018
Available online 07 November 2018

reliable and the priors of parameters are informative [1,7,14–16]. But model-based designs require intensive computation and greater involvement of statisticians and are subject to more difficult interpretation [1]. More than 80% of Phase I clinical trials have used standard 3 + 3 design, which remain the most utilized designs due to simplicity of execution and robustness [17,18].

Despite the popularity of standard 3 + 3 designs, their operating characteristics were not fully investigated until Lin and Shin published the exact calculation formulas of the five key characteristics for the two subtypes of standard 3 + 3 designs (with vs without dose de-escalation) [19]. The formulas are based on the assumed true probability of the DLT at each tested dose level. The estimated five key characteristics of a Phase I clinical trial using standard 3 + 3 designs are: 1) the probability of each dose level being chosen as the MTD; 2) the expected number of patients treated at each dose level; 3) the expected number of patients experiencing a DLT at each dose level; 4) the target toxicity level (TTL) (expected probability of a DLT at the MTD); 5) the expected total number of patients experiencing a DLT [19].

In practice, before a Phase I clinical trial starts, it is necessary to identify its crucial operating characteristics in order to address ethical concerns and protect participants as well as maximize therapeutic effect for them [18]. Therefore, the operating characteristics of a Phase I clinical trial need to be estimated in the planning stage [19]. However, understanding the formulas published by Lin and Shih requires advanced statistical knowledge and the formulas are too complicated for general use. To bridge this gap and facilitate the application of these formulas, we have developed interactive stand-alone statistical software that enables clinicians without advanced statistics knowledge to easily estimate the necessary operating characteristics. The calculated results are presented in tables and plots, both of which can be saved and easily edited for further use. Using this software, statisticians, investigators, clinicians, etc. can optimize their Phase I clinical trials according to specific scientific purposes. The software is entitled "Calculator for Operating Characteristics of 3 + 3 Designs" and can be downloaded free from the website: https://scholarblogs.emory.edu/zhengjiachen/2017/10/23/chen-zheng-calculator-for-operating-characteristics-of-phase-i-clinical-trials/.

2. Materials and methods

There are two subtypes of rule-based standard 3 + 3 Phase I clinical trial designs: with dose de-escalation and without dose de-escalation. The subtype with dose de-escalation can re-evaluate previously tested dose levels that were tested with only 3 patients before determining the MTD. By contrast, the subtype without dose de-escalation cannot re-evaluate any previous dose levels tested with only 3 patients [18,19]. Therefore, the subtype with dose de-escalation is more conservative during MTD estimation than the subtype without dose de-escalation, leading to a larger total number of patients [18]. The MTD is defined as the highest dose level at which at most 1 of 6 patients experience a DLT during the observation window, and the immediately higher dose level has at least 2 patients who experience DLTs. In the case that all tested dose levels are over-dosed, no dose level is selected as the MTD. On the other hand, when all the dose levels are under-toxic, the highest dose level is selected as the MTD unless a higher dose level is added ad hoc and tested [18,19].

2.1. Schema for standard 3 + 3 phase I design

2.1.1. Standard 3 + 3 phase I design without dose de-escalation

To conduct a Phase I clinical trial using standard 3 + 3 design without dose de-escalation, the work-flow for each dose level is as shown in Fig. 1. Starting from dose level 1, a cohort of 3 patients is entered and treated at the recommended dose level. The next cohort of 3 patients will be held until the toxicity responses of the previous cohort of 3 patients have been obtained and the newly recommended dose level has been determined. Assuming that the newly recommended dose level to be tested is dose level i and the new cohort of 3 patients is treated at dose level *i*,

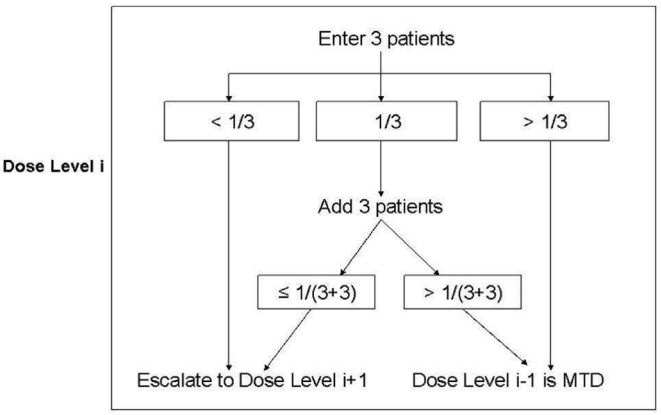


Fig. 1. Schema of a Phase I clinical trial with rule-based standard 3 + 3 design without dose de-escalation.

- If there is no DLT among the first cohort of 3 patients treated at dose level *i*, then dose escalation is recommended.
- If there is 1 DLT among the first cohort of 3 patients treated at dose level *i*, an additional cohort of 3 patients will be entered and treated at dose *i*.
  - o If there is no DLT among the second cohort of 3 patients treated at dose level *i*, dose escalation is recommended.
  - o If there is 1 or more DLT among the second cohort of 3 patients treated at dose level *i*, then dose *i*-1 will be determined as the MTD.
- If there are 2 or 3 DLTs among the first cohort of 3 patients treated at dose level *i*, then dose *i*-1 will be determined directly as the MTD.

2.1.2. Standard 3 + 3 phase I design with dose de-escalation

To execute a Phase I clinical trial using the rule-based standard 3 + 3 design with dose de-escalation, the work flow for each dose level is as shown in Fig. 2. Starting from dose level 1, a cohort of 3 patients is entered and treated at the recommended dose level. The next cohort of 3 patients will be held until the toxicity responses of the previous cohort of 3 patients have been obtained and the newly recommended dose level has been determined. Assuming that the newly recommended dose level to be tested is dose level *i* and the new cohort of 3 patients is treated at dose level *i*,

- If there is no DLT among the first cohort of 3 patients treated at dose level *i*, then dose escalation is recommended.
- If there is 1 DLT among the first cohort of 3 patients treated at dose level *i*, an additional cohort of 3 patients will be entered and treated at dose *i*.
  - o If there is no DLT among the second cohort of 3 patients treated at dose level *i*, dose escalation is recommended.
  - o If there is 1 or more DLT among the second cohort of 3 patients treated at dose level *i*, then dose de-escalation will occur and the dose *i*-1 will be tested further with a new cohort of 3 patients.
- If there are 2 or 3 DLTs among the first cohort of 3 patients treated at dose level *i*, then dose de-escalation will occur and the dose *i*-1 will be tested further with a new cohort of 3 patients.

When dose de-escalation is recommended:

- If 6 patients have already been treated at the dose *i*-1, and none or 1 out of the 6 patients in two cohorts experience DLT at dose *i*-1, dose *i*-1 will be determined as the MTD.

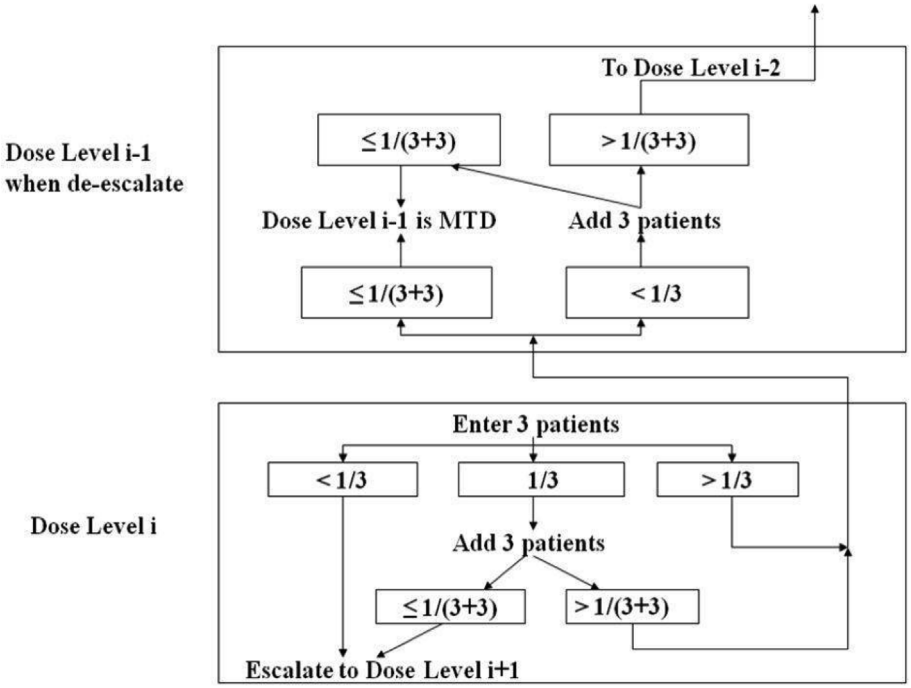


Fig. 2. Schema of a Phase I clinical trial with rule-based standard 3 + 3 design with dose de-escalation.

- If only one cohort of 3 patients has been treated at the dose *i*-1 and no DLTs were observed among the 3 patients, an additional cohort of 3 patients will be entered and treated at dose level *i*-1.
  - o If none or 1 out of the new cohort of 3 patients experiences a DLT, then dose level *i*-1 will be determined as the MTD.
  - o If 2 or 3 patients out of the new cohort of 3 patients experience a DLT, further dose de-escalation is required and a further lower dose level (such as dose level *i*-2) will be tested. The procedure of dose de-escalation will repeat until a MTD is determined or all dose levels have been determined to be over-toxic and no MTD is determined.

Calculations of operating characteristics have been reported by previous researchers [18,19]. Summarization of the equations can be found in the support information section.

2.2. Software programming

Based on the input values of true probabilities of a DLT, at each dose level, the probabilities of 0 and 1 patient out of every first cohort of 3 patients experiencing a DLT are calculated as $P^{dl}_{0/3}$ and $P^{dl}_{1/3}$ (*dl* stands for dose level), respectively. Using these probabilities, we are able to calculate, given $P^{dl}_{0/3}$ and $P^{dl}_{1/3}$, the probabilities of 0, 1, or more patients out of the two cohorts of 3 patients per cohort at each dose level as $P^{dl}_{\frac{0}{3}+\frac{1}{3}}$, $P^{dl}_{\frac{0}{3}+\leq\frac{1}{3}}$ and $P^{dl}_{\frac{0}{3}+\geq\frac{1}{3}}$, respectively. Probabilities $P^{dl}_{\frac{0}{3}+\frac{1}{3}}$ and $P^{dl}_{\frac{0}{3}+\geq\frac{1}{3}}$ can be easily interpreted as probabilities of dose escalation and de-escalation, respectively. In addition, $P^{dl}_{\frac{0}{3}+\leq\frac{1}{3}}$ only applies to the MTD dose level in scenarios with dose de-escalation and can be interpreted as the case in which dose escalation is indicated with 0 out of 3 DLTs in the first cohort at a particular dose level and upon dose de-escalation, none or only 1 patient at that particular dose level experiencing a DLT. The probability of dose de-escalation or stopping (for scenarios without de-escalation) $P^{dl}_{>1/3}$ is calculated by the formula $(1 - P^{dl}_{\frac{0}{3}} - P^{dl}_{\frac{0}{3}+\frac{1}{3}})$. These intermediate parameters enable us to calculate the final operating characteristics of each scenario. Having obtained the aforementioned intermediate parameters, we then can calculate the operating characteristics for scenarios with and without dose de-escalation.

For the scenario without dose de-escalation, the probability of each dose level x being chosen as the MTD is given by the product of summation of $P^{dl}_{0/3}$ and $P^{dl}_{\frac{0}{3}+\frac{1}{3}}$ of all dose levels lower than or equal to x multiplied by $P^{dl}_{>1/3}$ where $dl = x+1$. Special case considerations are given to situations where all doses are overly toxic and where all doses are under toxic. For all doses being overly toxic, the probability of dose level (0) being chosen as the MTD is given as $P^{1}_{>1/3}$. For all doses being under toxic, the probability of dose level (max dose) being chosen as the MTD is given by the product of summation of $P^{dl}_{0/3}$ and $P^{dl}_{1/3}$ of all dose levels.

The expected number of patients treated at each dose level k is obtained under all possibilities of each dose level chosen as the MTD. If the MTD dose level $x \geq$ k, then dose level k is expected to have either 3 patients among whom none experience a DLT or 6 patients among whom none or only 1 out of 6 experiences a DLT ($P^{k}_{0/3} + P^{k}_{\frac{0}{3}+\frac{1}{3}}$). If dose level x chosen as the MTD is equal to k-1, then the dose level is expected to have either 3 or 6 patients among whom more than or equal to 1 patient experiences a DLT ($1 - P^{k}_{0/3} - P^{k}_{\frac{0}{3}+\frac{1}{3}}$). If dose level x chosen as the MTD is smaller than k-1, then no patients are expected to be treated without dose de-escalation. And the trial will not escalate to that dose level. Each dose level has probabilities for each scenario associated with the MTDs at all possible dose levels. The expected number of patients treated at each dose level k is given by the summation of product of the probability of all dose levels x chosen as the MTD and the number of patients (3/6) with coefficient of probability for each scenario given each respective dose level x is chosen as the MTD.

For standard 3 + 3 design with dose de-escalation, the probability of each dose level x being chosen as the MTD is given by a product of combinations of probabilities. The combinations of probabilities for each dose level consist of the possibilities of dose de-escalation at all doses higher than dose x. Calculations are similar to that for the standard 3 + 3 design without dose de-escalation. The expected number of patients treated at each dose level for designs with dose de-escalation can also be calculated analogously. However, in addition to considering all possible possibilities for dose levels chosen as the MTD, all possible dose levels from which dose de-escalation starts are considered with respect to each and every dose level chosen as the MTD.

TTL is calculated by summation of the probabilities of each dose level chosen as the MTD multiplied by their respective true probabilities of a DLT, divided by summation of all probabilities of dose level being chosen as the MTD. The expected number of patients experiencing a DLT at each dose level is given by the product of true probabilities of a DLT and the expected number of patients treated at each dose level. Finally, the total number of patients expected to be treated is given by the summation of the expected number of patients treated at all dose levels.

For detailed calculation formulae, please refer to the support information section. Initial scripts were created for different scenarios of dose escalation scheme and number of dose levels. Calculations were validated using past simulation data. To enhance usability for users without programming background, a Shiny app was created with user-friendly interfaces for direct input and output. However, this still requires users to install R and RStudio in addition to the Shiny app. Therefore, a deploy package was created which includes Portable R for quick and convenient access to R and GoogleChromePortable to yield an accessible user interface.

Packages such as Shiny and ggplot2 were used to create the interactive statistical software. JavaScript was used to create dynamic input forms. HTML/CSS was used to create a user-friendly and aesthetically pleasing user interface.

3. Results and discussion

Estimating key operating characteristics under different scenarios of the true probability of a DLT prior to clinical trial planning facilitates the dose-finding process. Currently, there is no existing software to facilitate obtaining these important data, so clinicians without advanced statistical and programming knowledge must rely on statisticians to execute these calculations. Our statistical software fulfills this important need in the Phase I clinical trial planning process by offering an interactive and straightforward interface for users without statistical and programming knowledge. The five key operating characteristics are calculated and delivered in both tables and plots. Users can download our software in a zip file, and deploy by unzipping the zip file and clicking the “Run” file inside the folder. Since the program is Google Chrome portable and R-portable, no further installation of any supporting JVM or R is required.

3.1. User-friendly software

A step-by-step guide to using our statistical software follows:

Step 1. Users choose to calculate operating characteristics for standard 3 + 3 design with or without dose de-escalation (Fig. 3). Users should also keep in mind that, compared to the standard 3 + 3 design without dose de-escalation, the standard 3 + 3 design with dose de-escalation tends to be more conservative when estimating the MTD dose levels and requires a higher total number of patients since the de-escalation procedure re-evaluates previous dose levels tested with only 3 patients. The default option for the software is set to the standard 3 + 3 design without dose de-escalation.

Step 2. Users can select the number of dose levels according to their needs (Fig. 3). The input number will be used to generate the corresponding number of dose levels for inputting the true probability of a DLT and dosage (optional) for each dose level in the next step. After filling in the total number of dose levels, users will click ‘Next’.

Step 3. In this step, users can input the true probability of a DLT and dosage (optional) for each dose level (Fig. 4). These data usually come from the results of previous animal experiments. The dosage of the agent for each dose level is not needed for the calculation of various operating characteristics. Therefore, it is completely optional for the users (dose levels without dosage value input will appear as ‘NA’ in the final results). However, the probability of a DLT for each dose level is necessary since all calculations are based on the true probability of a DLT. A numeric value of $0 < n < 1$ is required for each dose level. Users will click ‘Calculate’ to obtain the operating characteristics.

Step 4. All operating characteristics are calculated and delivered in tables and plots according to the input true probability of a DLT of each dose level. Users obtain the results in both table and plot formats by clicking the “Save” buttons on the user interfaces. For plots, users can choose to download each file individually in the png format, or download all plots together in pdf format.

A User Manual can be found in the user interface detailing step-by-step instructions for the usage of our statistical software along with an introduction to the general characteristics of the standard 3 + 3 Phase I clinical trial design.

3.2. Interpreting calculation results

The calculated outputs are summarized in two forms: tables and plots. Users can toggle through Table Output and Plot Output pages to view calculation results (Figs. 4 and 5). All output files can be downloaded into users' local directories in csv and pdf format for further editing.

In the table output, the five key operating characteristics are listed clearly for each dose level: 1) Probability of each dose level chosen as the MTD, 2) Expected number of patients treated at each dose level, 3) Expected number of DLTs at each dose level, 4) Expected probability of a DLT at the MTD, 5) Expected total number of patients experiencing a DLT. Other operating characteristics are also listed, such as the overall rate of a DLT, probability of all dose levels being over toxic, and expected overall number of patients. One is unable to determine the MTD in the following situations: when dose escalation is not indicated at dose level 1 (MTD = dose 0), and dose level 0 (probability of all dose levels being over toxic) has the highest probability of being chosen as the MTD. But when dose escalation is indicated at the highest dose level, the highest dose level is chosen as the MTD if no additional higher dose level will be added and tested.

These characteristics are particularly important to clinicians because, with knowledge of the agent under investigation, clinicians can run scenarios to effectively predict the optimal dosages for treatment. As our simulation will show, under-toxic drugs have a lower overall rate of a DLT and will treat more patients overall while over-toxic drugs have a higher rate of a DLT and will treat fewer patients overall. If the tested drug is shown to be particularly toxic in animal testing, clinicians should pre-schedule conservative dosing to prevent irreversible toxicity in patients. The less aggressive scenarios (maximum true probability of DLT < 0.3) should be executed to reduce the overall rate of toxicity. On the other hand, if the tested agent is not expected to produce significant toxicity, clinicians should schedule aggressive dosing to achieve maximum therapeutic effect. The more aggressive scenarios (minimum true probability of DLT > 0.3) should be executed to quickly achieve the MTD while avoiding under-dosing too many patients. The dose level with the highest probability of being chosen as the MTD is usually the estimated MTD. Once scenarios are run according to previous estimations of the true probability of a DLT of the investigational agent, clinicians can begin the trial with a starting dose lower than the estimated MTD. After the trial is started, clinicians can observe patient DLTs with respect to dosages. Clinicians can further adjust the dose levels to be tested when running scenarios according to patient response. For example, if the toxicity of agent appears to be less severe and irreversible than expected from animal models, the clinician can run more overly aggressive scenarios to adjust the MTD estimation. On the other hand, if the toxicity of agent appears to be more severe and irreversible than expected from animal models, the clinician can exclude the more overly toxic dose levels from the study to avoid overdosing patients. Therefore, our statistical software is useful in both

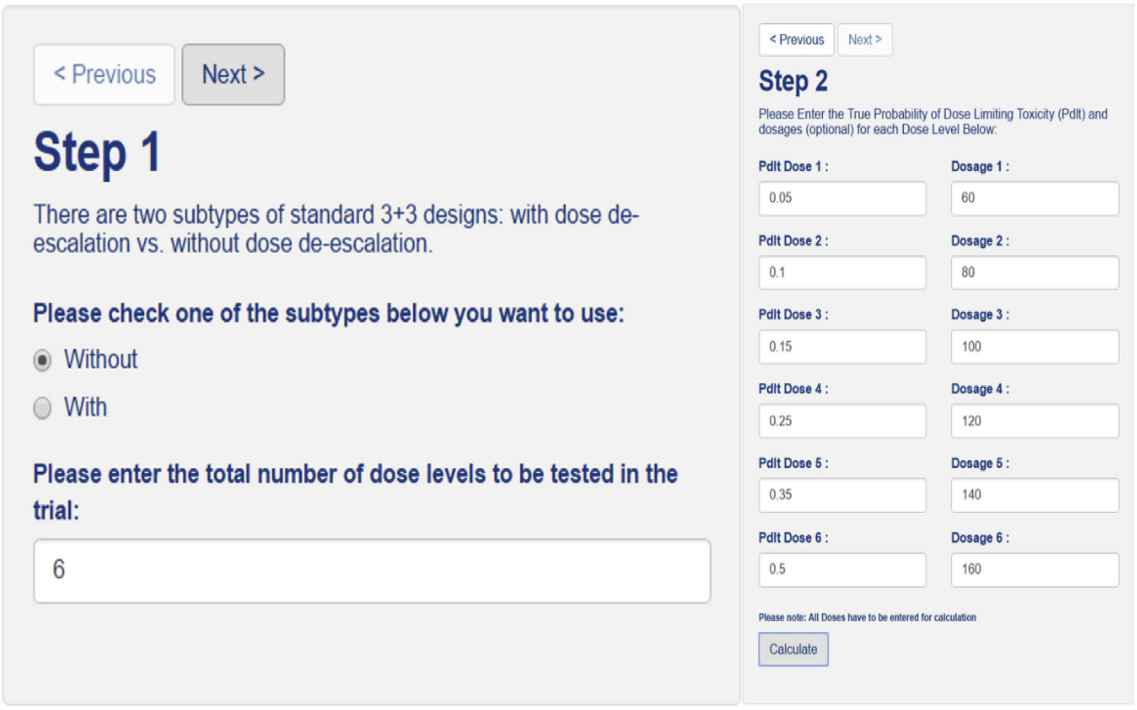
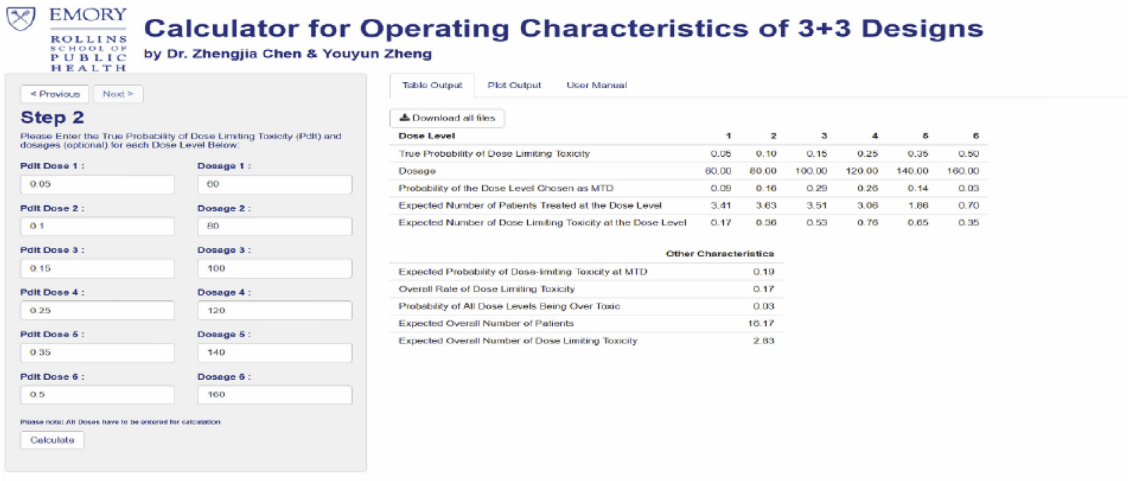


Fig. 3. Software package "Calculator for Operating Characteristics of 3 + 3 Designs": Step 1 for selecting clinical trial design and the total number of dose levels; Step 2 for inputting the True Probability of Dose Limiting Toxicity (required) and dosage (optional) for each dose level.



Tips on Interpretation and Recommendation:

1. Under-toxic drugs have a lower overall rate of a DLT and will treat more patients overall while over-toxic drugs have a higher rate of a DLT and will treat fewer patients overall. If the tested drug is shown to be particularly toxic in animal testing, clinicians should pre-schedule conservative dosing to prevent irreversible toxicity in patients. The less aggressive scenarios (maximum true probability of DLT <0.3) should be executed to reduce the overall rate of toxicity.
2. On the other hand, if the tested agent is not expected to produce significant toxicity, clinicians should schedule aggressive dosing to achieve maximum therapeutic effect. The more aggressive scenarios (minimum true probability of DLT >0.3) should be executed to quickly achieve the MTD while avoiding under-dosing too many patients.
3. The dose level with the highest probability of being chosen as the MTD is usually the estimated MTD. Once scenarios are run according to previous estimations of the true probability of a DLT of the investigational agent, clinicians can begin the trial with a starting dose lower than the estimated MTD.
4. After the trial is started, clinicians can observe patient DLTs with respect to dosages. Clinicians can further adjust the dose levels to be tested when running scenarios according to patient response. For example, if the toxicity of agent appears to be less severe and irreversible than expected from animal models, the clinician can run more overly aggressive scenarios to adjust the MTD estimation. On the other hand, if the toxicity of agent appears to be more severe and irreversible than expected from animal models, the clinician can exclude the more overly toxic dose levels from the study to avoid over-dosing patients.

Fig. 4. Tables showing the data summary of calculation results for each dose level from the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

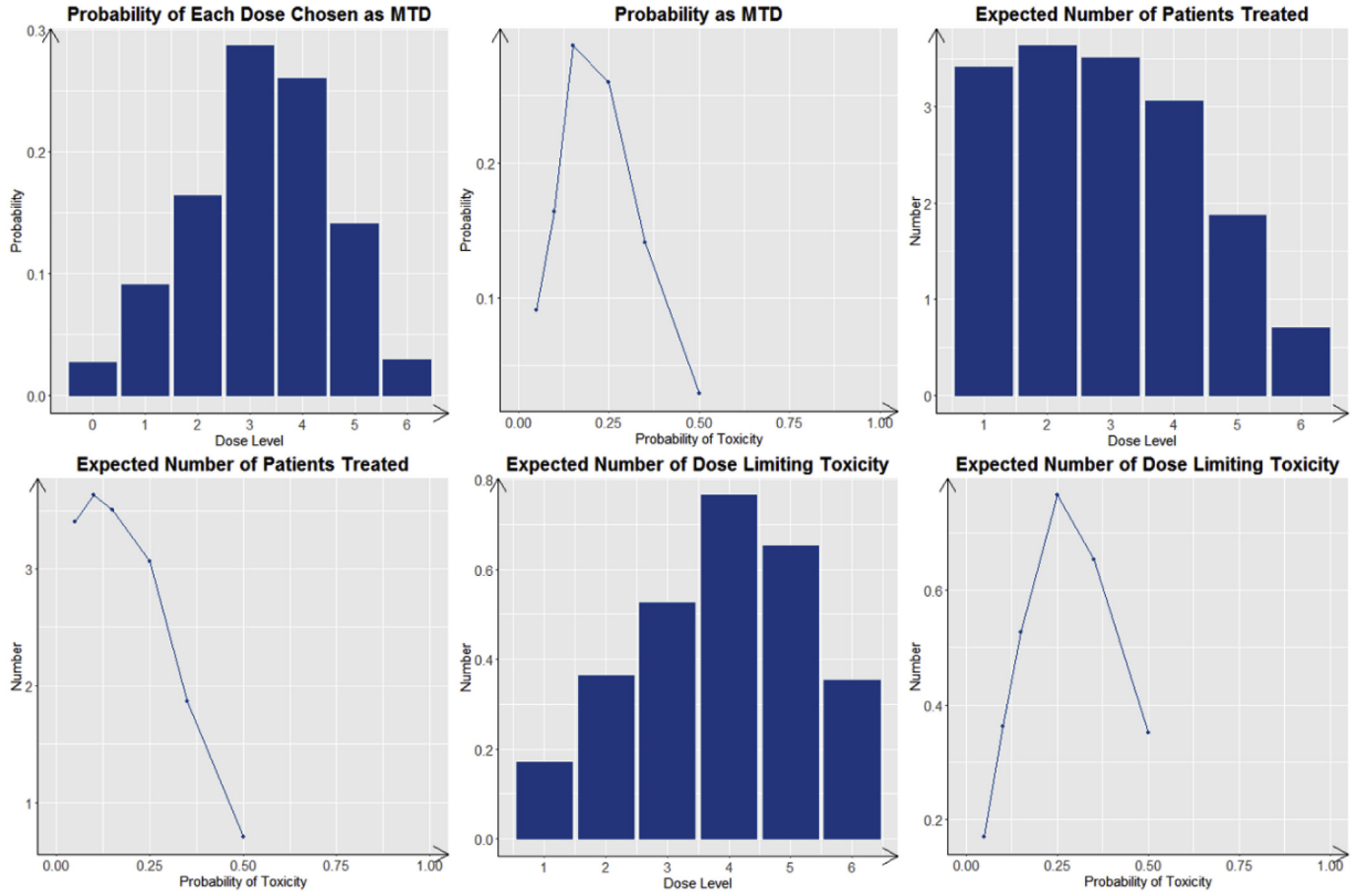


Fig. 5. Bar plots and scatter plots representing key operating characteristics generated by the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Table 1
Operating characteristics of standard 3 + 3 clinical trial designs without dose de-escalation in under/moderate/over-toxic conditions with 3 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic			Moderately-toxic			Over-toxic		
	1	2	3	1	2	3	1	2	3
True probability of DLT	0.05	0.1	0.2	0.15	0.3	0.5	0.3	0.5	0.8
Dosage	10	20	30	10	20	30	10	20	30
Probability of the dose level chosen as MTD	0.091	0.257	0.625	0.412	0.333	0.069	0.409	0.084	0.001
Expected number of patients treated at the dose level	3.406	3.63	3.662	3.975	3.518	1.659	4.323	2.039	0.279
Expected number of DLT at the dose level	0.17	0.363	0.732	0.596	1.055	0.83	1.297	1.019	0.223
Other Characteristics									
Expected probability of DLT at MTD	0.087			0.217			0.334		
Overall rate of DLT	0.118			0.271			0.382		
Probability of all dose levels being over toxic	0.027			0.186			0.506		
Expected overall number of patients	10.698			9.153			6.641		
Expected overall number of DLT	1.266			2.481			2.54		

simulation and maintenance purposes. In addition, for investigators applying for grants to support Phase I clinical trials, operating characteristics are often required as necessary information by the review committees. With our statistical software, those operating characteristics are easily obtainable.

There are limited resources available to clinicians for calculating key operating characteristics of rule-based standard 3 + 3 clinical trial designs [20,21]. Several applications such as EWOC V2.0 facilitate the usage of advanced statistical designs, but have no user-friendly interface, making these difficult for clinicians to utilize [21]. To maximize work efficiency of users, our statistical software can be used on any Windows computer without installing R).

3.3. Multiple scenario simulations

Multiple simulations were run for standard 3 + 3 designs with and without dose de-escalation in scenarios with different dose levels and distributions of true probability of a DLT for the agent. Operating characteristics of under-toxic, moderate-toxic, and over-toxic scenarios with 3, 6 and 10 dose levels were calculated and compared (Tables

Table 2
Operating characteristics of standard 3 + 3 clinical trial designs with dose de-escalation in under/moderate/over-toxic conditions with 3 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic			Moderately-toxic			Over-toxic		
	1	2	3	1	2	3	1	2	3
True probability of DLT	0.05	0.1	0.2	0.15	0.3	0.5	0.3	0.5	0.8
Dosage	10	20	30	10	20	30	10	20	30
Probability of the dose level chosen as MTD	0.097	0.251	0.625	0.44	0.283	0.069	0.374	0.054	0.001
Expected number of patients treated at the dose level	3.663	4.25	3.662	5.02	4.211	1.659	5.239	2.223	0.279
Expected number of DLT at the dose level	0.183	0.425	0.732	0.753	1.263	0.83	1.572	1.111	0.223
Other Characteristics									
Expected probability of DLT at MTD	0.086			0.209			0.325		
Overall rate of DLT	0.116			0.261			0.375		
Probability of all dose levels being over toxic	0.027			0.207			0.572		
Expected overall number of patients	11.576			10.891			7.741		
Expected overall number of DLT	1.341			2.846			2.906		

Table 3
Operating characteristics of standard 3 + 3 clinical trial designs without dose de-escalation in under/moderate/over-toxic conditions with 6 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic						Moderately-toxic						Over-toxic					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
True probability of DLT	0.01	0.03	0.05	0.1	0.15	0.25	0.05	0.1	0.15	0.25	0.35	0.5	0.3	0.35	0.4	0.5	0.7	0.9
Dosage	10	20	30	40	50	60	10	20	30	40	50	60	10	20	30	40	50	60
Probability of the dose level chosen as MTD	0.01	0.03	0.09	0.16	0.28	0.43	0.09	0.16	0.29	0.26	0.14	0.03	0.3	0.14	0.05	0.01	0	0
Expected number of patients treated at the dose level	3.09	3.25	3.37	3.59	3.47	3.03	3.41	3.63	3.51	3.06	1.87	0.7	4.32	2.14	0.84	0.25	0.04	0
Expected number of DLT at the dose level	0.03	0.1	0.17	0.36	0.52	0.76	0.17	0.36	0.53	0.77	0.65	0.35	1.3	0.75	0.34	0.13	0.03	0
Other Characteristics																		
Expected probability of DLT at MTD	0.112						0.189						0.328					
Overall rate of DLT	0.098						0.175						0.334					
Probability of all dose levels being over toxic	0.001						0.027						0.506					
Expected overall number of patients	19.791						16.174						7.594					
Expected overall number of DLT	1.933						2.83						2.535					

Table 4
Operating characteristics of standard 3 + 3 clinical trial designs with dose de-escalation in under/moderate/over-toxic conditions with 6 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic						Moderately-toxic						Over-toxic					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
True probability of DLT	0	0	0.1	0.1	0.2	0.3	0.1	0.1	0.2	0.3	0.4	0.5	0.3	0.4	0.4	0.5	0.7	0.9
Dosage	10	20	30	40	50	60	10	20	30	40	50	60	10	20	30	40	50	60
Probability of the dose level chosen as MTD	0	0	0.1	0.2	0.3	0.4	0.1	0.2	0.3	0.2	0.1	0	0.3	0.1	0	0	0	0
Expected number of patients treated at the dose level	3.1	3.3	3.6	4	4.1	3	3.7	4.1	4.2	3.7	2.2	0.7	5	2.4	1	0.3	0	0
Expected number of DLT at the dose level	0	0.1	0.2	0.4	0.6	0.8	0.2	0.4	0.6	0.9	0.8	0.4	1.5	0.9	0.4	0.1	0	0
Other Characteristics																		
Expected probability of DLT at MTD	0.111						0.182						0.325					
Overall rate of DLT	0.098						0.176						0.333					
Probability of all dose levels being over toxic	0.001						0.027						0.555					
Expected overall number of patients	21.21						18.48						8.72					
Expected overall number of DLT	2.087						3.248						2.904					

1–6). For each different dose level, progressing from under-toxic to over-toxic scenarios, we consistently observed decreases in the dose level with the highest probability of being chosen as the MTD and the expected total number of patients and an increase in the overall rate of toxicity. In addition, as the true probability of a DLT increases, fewer patients are expected to be treated, which mitigates the toxicity effect on patients. In all over-toxic scenarios, the probabilities of all dose levels being over-toxic (probability of dose level 0 being chosen as the MTD) were all above 50% and were highest among all, suggesting that our software could indeed detect situations in which drugs are over-toxic and recommend a less toxic MTD. The targeted toxicity level (TTL, expected probability of a DLT at the MTD) increased as the distribution of the true probability of a DLT of a drug shifted to the right and as dose levels increased, ranging from below 15% in under-toxic scenarios with 3 dose levels to a maximum of no more than 33.3% in over-toxic scenarios with 10 dose levels.

Table 5
Operating characteristics of standard 3 + 3 clinical trial designs without dose de-escalation in under/moderate/over-toxic conditions with 10 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic										Moderately-toxic										Over-toxic									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
True probability of DLT	0	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0	0.1	0.1	0.2	0.3	0.4	0.5	0.6	0.8	0.9	0.3	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.8	0.9
Dosage	10	20	30	40	50	60	70	80	90	100	10	20	30	40	50	60	70	80	90	100	10	20	30	40	50	60	70	80	90	100
Probability of the dose level chosen as MTD	0	0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0	0.1	0.2	0.3	0.3	0.1	0	0	0	0	0.3	0.1	0.1	0	0	0	0	0	0	0
Expected number of patients treated at the dose level	3.3	3.4	3.4	3.4	3.2	2.9	2.4	1.9	1.3	0.7	3.3	3.4	3.6	3.5	3	1.8	0.7	0.2	0	0	4.3	2.1	0.9	0.3	0.1	0	0	0	0	0
Expected number of DLT at the dose level	0.1	0.2	0.2	0.3	0.4	0.4	0.4	0.4	0.3	0.2	0.1	0.2	0.4	0.5	0.8	0.6	0.3	0.1	0	0	1.3	0.7	0.3	0.1	0	0	0	0	0	0
Other Characteristics																														
Expected probability of DLT at MTD	0.148										0.194										0.321									
Overall rate of DLT	0.118										0.153										0.322									
Probability of all dose levels being over toxic	0.01										0.01										0.506									
Expected overall number of patients	25.779										19.447										7.878									
Expected overall number of DLT	3.051										2.972										2.54									

Table 6
Operating characteristics of standard 3 + 3 clinical trial designs with dose de-escalation in under/moderate/over-toxic conditions with 10 dose levels, calculated using the software package "Calculator for Operating Characteristics of 3 + 3 Designs".

Dose level	Under-toxic										Moderately-toxic										Over-toxic									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
True probability of DLT	0.03	0.05	0.07	0.1	0.12	0.15	0.18	0.22	0.26	0.3	0.03	0.05	0.1	0.15	0.25	0.35	0.45	0.6	0.75	0.9	0.3	0.33	0.36	0.4	0.45	0.5	0.55	0.65	0.75	0.9
Dosage	10	20	30	40	50	60	70	80	90	100	10	20	30	40	50	60	70	80	90	100	10	20	30	40	50	60	70	80	90	100
Probability of the dose level chosen as MTD	0.03	0.05	0.09	0.11	0.14	0.15	0.15	0.12	0.08	0.08	0.03	0.09	0.17	0.3	0.25	0.11	0.03	0	0	0	0.26	0.12	0.05	0.02	0	0	0	0	0	0
Expected number of patients treated at the dose level	3.33	3.5	3.64	3.68	3.52	3.23	2.76	2.15	1.44	0.74	3.33	3.62	4.02	4.19	3.63	2.14	0.8	0.16	0.01	0	4.96	2.45	1.06	0.39	0.12	0.03	0	0	0	0
Expected number of DLT at the dose level	0.1	0.18	0.26	0.37	0.42	0.48	0.5	0.47	0.38	0.22	0.1	0.18	0.4	0.63	0.91	0.75	0.36	0.1	0.01	0	1.49	0.81	0.38	0.16	0.05	0.01	0	0	0	0
Other Characteristics																														
Expected probability of DLT at MTD	0.146										0.185										0.319									
Overall rate of DLT	0.12										0.157										0.322									
Probability of all dose levels being over toxic	0.01										0.01										0.552									
Expected overall number of patients	27.981										21.895										9.001									
Expected overall number of DLT	3.369										3.43										2.9									

Comparing standard 3 + 3 designs with and without dose de-escalation, we observed that without dose de-escalation, the TTL was higher while the probability of all doses being over-toxic, the expected overall number of DLTs, and the expected overall number of patients were always lower, though the differences decreased as the number of dose levels increased. These observations corroborate that standard 3 + 3 clinical trial designs with dose de-escalation are more conservative in recommending the MTD while involving more patients, since additional steps are involved in dose de-escalation.

4. Conclusions

We describe the development of stand-alone interactive software for the convenient calculation of the five key operating characteristics of rule-based standard 3 + 3 Phase I clinical trial designs under different scenarios and parameters. Our statistical software, entitled “Calculator for Operating Characteristics of 3 + 3 Designs”, is a valuable tool for clinical trial practitioners and is convenient to use during the planning stages of a Phase I clinical trial. Users can freely and easily download our stand-alone software and use without any programming or statistical knowledge, following the step-by-step instructions provided. The calculation results generated are summarized in tables and displayed in graphs, all of which can be downloaded and saved by the user for further use. Standard 3 + 3 designs continue to be the most widely used design for Phase I clinical trials, thus our software will facilitate the conduct of Phase I clinical trials and contribute to improving healthcare [22]. This is the first version of the statistical software and we will continue to improve its functionality. Any feedback regarding our software is greatly appreciated and will be valuable in creating future versions.

Competing interests

The authors have declared that no competing interests exist.

Financial disclosure

Supported in part by NIH/NCI Grants No. P30CA138292 (Z.C. J.K., and M.K.), and Phase I Program of Winship Cancer Institute of Emory University (Z.C.).

CRediT authorship contribution statement

Zhengjia Chen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Youyun Zheng:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Zhibo Wang:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Michael Kutner:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Walter J. Curran:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Jeanne Kowalski:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Acknowledgements

Supported in part by NIH/NCI Grants No. P30CA138292 (Z.C. J.K., and M.K.), and Phase I Program of Winship Cancer Institute of Emory University (Z.C.). We thank Dr. Anthea Hammond for editing. Research reported in this publication was also supported in part by the Phase I program and the Biostatistics and Bioinformatics Shared resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2018.10.006.

References

[1] D.M. Potter, Phase I studies of chemotherapeutic agents in cancer patients: a review of the designs, J. Biopharm. Stat. 16 (2006) 579–604.
[2] A. Trotti, A.D. Colevas, A. Setser, V. Rusch, D. Jaques, et al., CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment, Semin. Radiat. Oncol. 13 (2003) 176–181.
[3] R.D. Pentz, M. White, R.D. Harvey, Z.L. Farmer, Y. Liu, et al., Therapeutic misconception, misestimation, and optimism in participants enrolled in phase 1 trials, Cancer 118 (2012) 4571–4578.
[4] N.J. Meropol, K.P. Weinfurt, C.B. Burnett, A. Balshem, A.B. Benson 3rdet al., Perceptions of patients and physicians regarding phase I cancer clinical trials: implications for physician-patient communication, J. Clin. Oncol. 21 (2003) 2589–2596.
[5] W.F. Rosenberger, L.M. Haines, Competing designs for phase I clinical trials: a review, Stat. Med. 21 (2002) 2757–2770.
[6] K.M. Wong, A. Capasso, S.G. Eckhardt, The changing landscape of phase I trials in oncology, Nat. Rev. Clin. Oncol. 13 (2016) 106–117.
[7] Z. Chen, Y. Zhao, Y. Cui, J. Kowalski, Methodology and application of adaptive and sequential approaches in contemporary clinical trials, J. Probab. Stat. (2012), https://doi.org/10.1155/2012/527351.
[8] Z. Chen, M.D. Krailo, S.P. Azen, M. Tighiouart, A novel toxicity scoring system treating toxicity response as a quasi-continuous variable in Phase I clinical trials, Contemp. Clin. Trials 31 (2010) 473–482.
[9] R. Simon, B. Freidlin, L. Rubinstein, S.G. Arbuck, J. Collins, et al., Accelerated titration designs for phase I clinical trials in oncology, J. Natl. Cancer Inst. 89 (1997) 1138–1147.
[10] D.H.-Y. Leung, Y.-G. Wang, Isotonic designs for phase I trials, Contr. Clin. Trials 22 (2001) 126–138.
[11] Z. Chen, Y. Yuan, Z. Li, M. Kutner, T. Owonikoko, et al., Dose escalation with overdose and under-dose controls in Phase I/II clinical trials, Contemp. Clin. Trials 43 (2015) 133–141.
[12] Z. Chen, Y. Cui, T.K. Owonikoko, Z. Wang, Z. Li, et al., Escalation with overdose control using all toxicities and time to event toxicity data in cancer Phase I clinical trials, Contemp. Clin. Trials 37 (2014) 322–332.
[13] Z. Chen, Z. Li, R. Zhuang, Y. Yuan, M. Kutner, et al., Adaptive estimation of personalized maximum tolerated dose in cancer phase I clinical trials based on all toxicities and individual genomic profile, PLoS One 12 (2017) e0170187.
[14] J. O'Quigley, M. Pepe, L. Fisher, Continual reassessment method: a practical design for phase 1 clinical trials in cancer, Biometrics 46 (1990) 33–48.
[15] J. Babb, A. Rogatko, S. Zacks, Cancer phase I clinical trials: efficient dose escalation with overdose control, Stat. Med. 17 (1998) 1103–1120.
[16] Z. Chen, M. Tighiouart, J. Kowalski, Dose escalation with overdose control using a quasi-continuous toxicity score in cancer Phase I clinical trials, Contemp. Clin. Trials 33 (2012) 949–958.
[17] A. Rogatko, D. Schoeneck, W. Jonas, M. Tighiouart, F.R. Khuri, et al., Translation of innovative designs into phase I trials, J. Clin. Oncol. 25 (2007) 4982–4986.
[18] Z. Chen, M.D. Krailo, J. Sun, S.P. Azen, Range and trend of expected toxicity level (ETL) in standard A + B designs: a report from the Children's Oncology Group, Contemp. Clin. Trials 30 (2009) 123–128.
[19] Y. Lin, W. Shih, Statistical properties of the treatment alorrighm-based designs for Phase I cancer clinical trials, Biostatistcs 2 (2001) 203–215.
[20] Z. Chen, Z. Wang, H. Wang, T.K. Owonikoko, J. Kowalski, et al., Interactive software "isotonic design using normalized equivalent toxicity score (ID-NETS(c)TM)" for cancer phase I clinical trials, Open Med. Inf. J. 7 (2013) 8–17.
[21] Z. Xu, M. Tighiouart, A. Rogatko, EWOC 2.0: interactive software for dose escalation in cancer phase I clinical trials, Drug Inf. J. 41 (2007) 221–228.
[22] A.R. Hansen, D.M. Graham, G.R. Pond, L.L. Siu, Phase 1 trial design: is 3 + 3 the best? Canc. Contr. 21 (2014) 200–208.