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THE CHOICE OF PHASE I BAYESIAN ADAPTIVE DESIGNS IN CHINA

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Abstract- China is new to Bayesian adaptive designs. In Phase I, all designs are adaptive and Bayesian designs have been heavily researched and implemented in US. However, in China, especially inland areas, there ordinarily lacks logistical foundations and sufficient numbers of qualified biostatisticans to equip clinical trials with advanced designs. This paper focuses on the phase I oncology studies and explores the performance, practical issues, and potential usability of two Bayesian designs: the continual reassessment method (CRM) and the modified toxic probability interval (mTPI) design. We conclude that both designs provide desirable operating characteristics but the mTPI design is more suitable for China due to its transparency and simplicity. For example, mTPI does not require real-time online trial conduct tools that are otherwise needed to implement CRM. In addition, we propose a minor modification of the original mTPI that results in a sample size reduction compared to the original mTPI method.

Keywords- Phase-I design, Bayesian Adaptive design, China's clinical trial

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Introduction

Adaptive designs have been heavily researched in academia [1] and increasingly applied to real-life clinical trials by pharmaceutical companies globally. The goals of the adaptive design include higher statistical efficiency, improved patient outcomes and better ethical balance, especially with regard to the so-called patient-centered outcomes research (PCOR) today.

Adaptive approaches can lead to more effective treatments for participants in the trial itself, as well as better treatment of future patients having the disease or condition in question. Due to the need for lowering trial cost, the high concentration of over 1.3 billion population and enormous potential market, and fast patient recruitment, increasingly international pharmaceutical companies are transferring their corresponding clinical trial research, from early phases to late phases, to China. With the increasing awareness of civilians and some related toxic incidents of early phases in China and India, the Chinese State Food and Drug Administration (SFDA) has been considering to update their knowledge about the novel designs and are showing great interest in introducing more ethical and effective clinical trial design methods to local pharmaceuticals. Phase I clinical trial is the early and yet vital stage for a successful drug development and, due to its main goal is to locate the MTD (maximum tolerated dose), the SFDA has been showing great attention to this early phase.

In March 2011, a draft guideline about the phase I clinical trials design was proposed by the SFDA. This draft includes two files, one of which is about phase I clinical trial protocols and procedures, and the other about the laboratory's standard operating procedures and quality controls. Releasing this guideline is in preparation for the increasing activities of early phase trials in China by global pharmaceutical companies. The guideline paves ways to more formal regulation of trial conduct and patient safety protection later. For example, Phase I studies are typically first-in-man trials and dose-limiting toxicities are often resulted from the heavy dosage treated on cancer patients. The SFDA in China has the responsibility to safeguard patients from being exposed to toxic agents by poor trial design or trial conduct. Though not recommending any specific phase I statistical methods, the guideline manifests the determination of SFDA to regulate phase I clinical trials and advocate the investigators to pay attention to high-ethical and high-effective novel design methods.

Though in western countries, such as U.S., most of the pharmaceutical companies have realized the merits of adaptive designs, it is not the case for China. For example, in Xi Jing Hospital, a major medical center in western China, we conducted a small survey among the clinicians and asked them to provide lists of adaptive designs they are aware of or have used. In the case of Phase I oncology trials, all of the responders said that they were aware of

the 3+3 design, but not anything else. However, most of the clinicians expressed the willingness to learn and apply more efficient adaptive designs but are concerned about the complicated nature of the novel designs and the corresponding logistic requirements (such as IT support) for implementation.

This paper investigates the feasibility of Bayesian adaptive designs for phase I oncology trials in China, focusing on the two popular phase I Bayesian design methods: the continual reassessment method (CRM) [2] and the modified toxicity probability interval (mTPI) design [3]. There have been many discussions on the use of CRM for practical dose-finding trials [4,5]. More recently, mTPI has received much attention and has been successfully implemented for a published clinical trial [6-8]. There is a great opportunity to introduce this novel design to trials conducted in China, and we evaluate the feasibility of the application considering the current level of scientific and operational support. Through a thorough investigation we will show that the mTPI design can be directly applied while the CRM method will require more efforts for real-life applications. We also make a small modification to the mTPI design, and simulation results show that our modification of mTPI can save sample sizes in phase I studies without sacrificing original mTPI design's desirable performances.

There have been many researches and publications on the designs for phase I dose-finding trials. In this paper, we focus on the CRM and mTPI designs, and investigate the safety, efficiency and logistical burden in practical applications in China. Though currently the 3+3 method is still the most popular design in phase I studies [1], we focus on adaptive designs to take the advantage of the fact that China is new to these designs, and are more open-minded and flexible to innovation.

The remainder of the paper is organized as follows. In Section 2, we briefly introduce the CRM and mTPI designs. We examine the performances of CRM and mTPI designs through simulations in Section 3. In Section 4, we extensively discuss the possibility of implementing both designs in China.

CRM and mTPI Designs

Bayesian methods are popular choices for phase I trial designs due to the requirement of small sample sizes and sequential decision making. Due to the characteristics of small sample sizes and requirements of sequentially monitoring safety in phase I stage, Bayesian methods have been implemented for phase I clinical trial designs, for instance, heavily in The University of Texas M. D. Anderson Cancer Center [9]. A long list of Bayesian adaptive phase I designs have been developed, with the majority of them focusing on the continual reassessment method (CRM) and its extension [2,10,11]. Recently, a new type of Bayesian adaptive design has been proposed using toxicity probability intervals for dose-finding decisions, i.e., the work in TPI [12], mTPI [3], a couple of more references.

The main difference between CRM-like and TPI-like designs is whether to assume a dose-response curve as the underlying model for dose toxicity. We will discuss the impact of curve-based and curve-free designs on logistic requirement for practical implementation, and perhaps sensitivity performance.

Phase I clinical trials are performed in many medical areas, but are particularly important in cancer, because of the severe side-effects of cytotoxic treatments. The goal is the identification of the maximum tolerated dose (MTD). The CRM design was proposed by O'Quigley, et al. [2], followed by many modifications and extensions. As the first model/curve-based design, CRM uses principled statistical inference. The mTPI design was proposed by Ji, et al. [3] as a modification to the toxicity probability interval (TPI) method [12]. The mTPI design uses a curve-free beta-binomial model to describe dose toxicity, and employs a Bayes rule for dose-finding decisions. Final MTD estimation under the mTPI is based on isotonic regression, a technique that allows ``borrowing information'' across doses which is the key idea in curve-based methods. Both CRM and mTPI methods demonstrate the convergence to the true MTD asymptotically [13].

The CRM Design

CRM employs dose-response curves as the key inference tool. The curves are represented by one or two unknown parameters and are estimated continuously based on the accumulative information collected in the trial. A classical CRM model is described as follows.

Let $(d_1,\ldots,d_J)$ denote a set of J prespecified doses for the drug under investigation, and let $(p_1,\ldots,p_J)$ be prespecified toxicity probabilities (skeleton) at those doses, $p_1<\ldots<p_J$. Let ϕ be the target toxicity rate specified by physicians. The first cohort of patients receives the lowest dose, d_1. For the comparison in this chapter, we use a power dose toxicity model which is the most popular CRM working model, where $\Pr(\text{toxicity at } dj)=\pi_j(\alpha)=p_j^{\exp(\alpha)}$ for $j= 1,\ldots,J$, where αis an unknown parameter and the p_j's can be viewed as "imputed" values for the toxicity probabilities, known as the "skeletons".

Suppose that among n_j patients treated at dose level j, y_j patients have experienced DLT. Let D denote the observed data, $D=(n_j, y_j)$, $j=1,\ldots,J$. Based on the binomial distribution for the toxicity outcome, the likelihood function is given by :

$$L(D|\alpha(=\prod_{j=1}^{J}\{p_j^{\exp(\alpha)}\}^{y_j}\{1-p_j^{\exp(\alpha)}\}^{n_j-y_j}$$

Posterior estimates, such as the posterior mean of $\pi_j(\alpha)$ can be used to estimate the toxicity probabilities. Using Bayes theorem, we can compute the posterior means of the dose toxicity probabilities given by D by :

$$\hat{\pi}_j=\int p_j^{\exp(\alpha)}\frac{L(D|\alpha)f(\alpha)}{L(D|\alpha)f(\alpha)da}da, j=1,\ldots J$$

where f(α) is a prior distribution for the parameter α. Commonly, one takes a normal prior distribution $N(0,\sigma^2)$ for α.

After updating the posterior estimates of the toxicity probabilities at all of the doses, the recommended dose level for the next cohort of patients is the one that has a toxicity probability closest to the target ϕ. Thus a new cohort of patients is assigned to dose level j^*, which has the posterior mean closest to the target rate ϕ. The trial continues until the total sample size is exhausted or some other stopping rules are met. The dose with a posterior mean toxicity probability closest to ϕ is selected as the MTD.

Revisions have been proposed to improve the properties of CRM. For example, Faries [14] introduced several modifications of the CRM. Goodman, et al [15] developed practical improvements to the CRM. They changed the original design to assign more than one subject at a time to each dose level and limit each dose escalation by a single dose level. For a comprehensive introduction and information on the practical use of the CRM in phase I clinical trials, see the tutorial by Garrett-Mayer [16].

The mTPI Design

The dose-finding rules for the mTPI method consist of two major steps. In the first step, the physician provides an equivalence interval (EI), which leads to three toxicity probability intervals that partition the probability space (0,1). The EI sets up a small range in the form of (ϕ-ε_1, ϕ-ε_2); any doses with toxicity probability in the EI is considered an acceptable MTD. The other two induced intervals are (0, ϕ-ε_1) and (ϕ-ε_2, 1) that represent under dosing and over dosing, respectively. Building upon the EI, the mTPI method computes the unit probability mass (UPM) for the three toxicity probability intervals and sets up a decision-theoretic framework to guide dose escalation decision guided by the Bayes rule.

Let $p=(p_1,\ldots,p_J)'$ denote the toxicity probabilities for dose j =1,…,J, where J is the total number of candidate doses in the trial. The observed data include the n_j patients treated at dose j and the corresponding y_j experiencing toxicity. The likelihood function is a produce of binomial densities: $L(D|p_J)=\prod_{j=1}^{J}\{p_j\}^{y_j}\{1-p_j\}^{n_j-y_j}$

The mTPI design assumes independence among dose responses because few information is known about the toxicity of the candidate doses in phase I studies, the mTPI proposes to use models with vague priors for p_j so that the shape of the resulting posterior distributions will be decided mainly by the shape of the likelihood based on the observed data. In this design, priors of $p_j \sim Beta(1,1)$, with Beta density proportional to $x^{a-1}(1-x)^{b-1}$. Combined with the likelihood, the posterior of p_j follows independent $Beta\ (1+x_j, 1+n_j-x_j)$, for j=1,…,J. When strong prior information on the toxicity of the candidate doses are available, of course, informative beta priors can replace the vague priors.

Assume dose j is currently used to treat patients. To apply mTPI, one simply calculates three UPMs, defined as the probability of the interval divided by the length of the interval, for the EI, under-, and over-dosing intervals, given by for the over-dosing interval

$(\phi+\varepsilon_2,1), \qquad UPM_{Dj}=\dfrac{\Pr(p_j-\phi>\varepsilon_2\mid D)}{1-\phi-\varepsilon_2};$

for the EI $(\phi-\varepsilon_1,\phi+\varepsilon_2), \quad UPM_{Sj}=\dfrac{\Pr(-\varepsilon_1\le p_j-\phi>\varepsilon_2\mid D)}{\varepsilon_2-\varepsilon_1};$

for the under-dosing interval $(0,\phi-\varepsilon_1), \qquad UPM_{Ej}=\dfrac{\Pr(p_j-\phi<-\varepsilon_2\mid D)}{\phi-\varepsilon_1};$ for over dosing.

A dose-assignment rule B_j based on these three UPMs chooses the decision with the largest UPM, that is, $B_j=\arg\max_{m\in(D,S,E)} UPM(m_j)$.

The mTPI design imposes an extra safety rule which prohibits escalation to toxic doses that have been previously used. Introducing a random variable $\tau_j = I\{P((p_j>\phi|data)>\xi)\}$, where I{} is the indicator function and $\xi \in (0,1)$ is a cutoff value (e.g., ξ=0.95), mTPI incorporates τ_{j+1} into the proposed dose-assignment rule B_j.

Let $UPM(\tilde{E},j)=UPM(E,j)(1-\tau_{j+1})$ and define a new dose-assignment rule with this toxicity exclusion to be $B_j=\arg\max_{m\in(D,S,\tilde{E})} UPM(m,j)$

When τ_{j+1} =1, dose j+1 is considered highly toxic and the UPM associated with escalation equals 0. Therefore, escalation will never be chosen for dose finding. Readers are encouraged to consult Ji et al. [3].

Performances Evaluation

Though comparison of mTPI and CRM has been carried out with computer generated trails [3], in this section, mTPI and CRM provide comparable operating characteristics with mTPI slightly holding an edge on maintaining safety. Here we include six additional scenarios in [Table-1].

Table 1- Simulation results comparing the mTPI method, the CRM, and the 3+3 design. The true probabilities of toxicity rate are presented as percentages for each scenario (first row of each scenario). The selection percentages for the true MTDs are in bold face.

	Recommendation percentage at dose level ϕ=0.25									Toxicity %	Avg. No of patients
	Dose	1	2	3	4	5	6	7	8		
Sc 1		5	25	50	60	70	80	90	95	none		
mTPI	%MTD	14	**78**	8	0	0	0	0	0	0	24	30
	# Pts	7.1	18.3	4.4	0.2	0	0	0	0			
CRM	%MTD	6	**83**	11	0	0	0	0	0	0	27	30
	# Pts	5.7	18.6	4.9	1	0	0	0	0			
3+3	%MTD	24	**58**	16	2	0	0	0	0	0	25	12
	# Pts	4	5	2.6	0.4	0	0	0	0			
Sc 2		1	2	3	4	5	25	50	60	none		
mTPI	%MTD	0	0	0	2	16	**71**	10	1	0	16	30
	# Pts	3.2	3.5	3.5	4	5.2	8.1	2.3	0.1			
CRM	%MTD	0	0	1	1	20	**61**	16	2	0	16	30
	# Pts	3.1	3.4	3.3	3.7	4.7	7	3.8	0.9			
3+3	%MTD	0	0	1	2	25	**56**	11	0	0	13	24
	# Pts	3.1	3.2	3.2	3.3	3.9	4.8	2.3	0.3			
Sc 3		1	5	50	60	70	80	90	95	none		
mTPI	%MTD	0	**82**	17	0	0	0	0	0	0	21	30
	# Pts	3.2	15.9	10.3	0.6	0	0	0	0			
CRM	%MTD	0	**49**	51	0	0	0	0	0	0	26	30
	# Pts	3.1	13	12	1.8	0	0	0	0			
3+3	%MTD	0	**70**	28	2	0	0	0	0	0	22	13
	# Pts	3.1	5.2	4.4	0.7	0.1	0	0	0			
Sc 4		40	50	60	70	80	90	95	99	none		
mTPI	%MTD	31	2	0	0	0	0	0	0	**67**	41	19
	# Pts	16.8	2	0.2	0	0	0	0	0			
CRM	%MTD	47	2	0	0	0	0	0	0	**51**	42	23
	# Pts	20.2	2.5	0.2	0	0	0	0	0			
3+3	%MTD	9	1	0	0	0	0	0	0	**52**	43	6
	# Pts	4.7	0.5	0.6	0.7	0	0	0	0			
Sc 5		15	25	35	45	55	65	75	85	none		
mTPI	%MTD	29	**45**	20	4	0	0	0	0	0	24	30
	# Pts	12.4	10.9	5	1.1	0.1	0	0	0			
CRM	%MTD	36	**47**	14	2	0	0	0	0	0	24	30
	# Pts	13.8	11.4	3.6	0.9	0.2	0	0	0			
3+3	%MTD	29	**37**	20	7	1	0	0	0	0	26	12
	# Pts	4.4	3.9	2.4	0.9	0.2	0	0	0			
Sc 6		5	15	25	35	45	55	65	75	none		
mTPI	%MTD	2	28	**42**	23	4	0	0	0	0	20	30
	# Pts	4.9	10.2	9.3	4.5	0.9	0.1	0	0			
CRM	%MTD	4	37	**45**	12	2	0	0	0	0	20	30
	# Pts	5.5	11.5	8.9	3.4	0.7	0.1	0	0			
3+3	%MTD	9	28	**34**	22	5	0	0	0	0	21	15
	# Pts	3.6	4.3	3.8	2.3	0.8	0.2	0	0			

Each simulated trial has eight doses with a maximum sample size of 30 patients. The target toxicity is set as p_T=0.25. The starting dose is the lowest dose and the cohort size is three. We simulated 1,000 trials on computer to compare the mTPI to the CRM and the 3+3 with respect to the patient assignments, toxicity responses, and final doses selected as the MTD for all the trials. For the CRM, we assume that α follows a normal prior distribution with mean 0 and standard deviation σ^2 in $p_j^{\exp(\alpha)}$. For the equivalence interval in mTPI, $\varepsilon_1=\varepsilon_2$=0.05 is used, which seems arbitrary, however, sensitivity analysis has been demonstrated the robustness to the choices of $\varepsilon'S$ [3].

Specifically, our scenarios 1-4 are the cases in which the neighboring doses around the MTD are very close to each other, which are "hard" scenarios for designs to make accurate estimation based on small sample sizes. It should be manifested that these scenarios are naturally apt to the CRM approach since CRM uses smooth curves to borrow information across doses. Scenario 6 in [Table-1] is a case in which all toxicity rates are equal and safe. In the simulations, CRM chooses true toxic rates as skeletons in all cases.

[Table-1] shows that the mTPI method exhibits comparable operating characteristics overall to the CRM method. we can see that in all scenarios, except scenario 5, the toxicity percentages of mTPI are smaller than those of CRM, an observation made previously in the literature. The average sample size of CRM approach is larger than that of mTPI approach in scenario 5. With respect to the selection percentage for the true MTD, in scenarios 1 and 3, the mTPI is better than the CRM, while in scenarios 2 and 4, the CRM is better than the mTPI. Though the CRM generally performing well for most cases, the surprising scene is in scenario 6, in which all doses are safe (uniformly 5% toxicity rate)CRM and dose should be escalated to higher level along the trial process according to the dose escalation rule of CRM method, that the dose movement is stagnant and reluctant to move to higher dose level. We also can see that the mTPI method almost always yields the lowest overall toxicity percentage compared to the CRM. By considering the simplicity of mTPI method, the above results are encouraging.

The software used here for CRM design is CRM Simulator, which is from M.D. Anderson's biostatistical department.

From the above simulation study, combined with other similar comparisons in literatures, we find that the CRM and mTPI perform similarly although the mTPI method is comparatively safer than the CRM method.

Practical Consideration Related to China

User-Friendly Software

Both CRM and mTPI methods provide easy-to-access software. The download websites for CRM design software include The University of Texas MD.Anderson Cancer Center's Biostatistics department's software download web page, Cheung's dfcrm R package, Mo's CRM R package and recent Sweeting's bcrm R package. The sites for mTPI design software currently are at The University of Texas MD.Anderson Cancer Center's Biostatistics department's software download web page and Dr.Yuan Ji's personal website. Therefore, from the point of view of the availability of software, both of methods can be freely and conveniently acquired and the software's' qualities are acceptable.

Biostatisticians and Clinical Researchers in China

As far as we know, most biostatisticans in China are not familiar with Bayesian methods, and do not have sufficient experiences in implementing Bayesian tools on their own. Consequently, very few clinical trials in China are design by Bayesian methods. Correct understanding and grasping Bayesian design methods to put into real practice is a major challenge to local biostatisticans, and even more difficult for local physicians and clinical researchers.

Our comparison of CRM and mTPI has prompted the following observations, which are critical to the choice of their method by Chinese statisticians. The CRM method requires appropriate specification of skeletons, which is not an easy task even for expert statistician (e.g., Yuan and Yin, [17]). Specifically, the CRM method needs careful calibration of parameters before the start of a trial, as stated in the Preface of Cheung's book [18], "These patterns, characterized collectively as a trial-and-error approach...,worked will in the sense that they gave reasonable operating characteristics to a design. However, it was time-consuming (*weeks of simulation*) and would require an intimate understanding of the CRM...". In contrast, the mTPI design is almost a calibration-free method, and the questions for physicians to answer merely include a MTD target value, a MTD equivalent interval and a maximum sample size of phase I trial. The simplicity of the mTPI is extremely suitable for China's unique situation where lacking of biostatistics expertise in clinical trials.

We conducted a small survey to inquire physicians' preferences after introducing the 3+3, CRM and mTPI methods to a group of clinical researchers and physicians in the Xijing hospital, a major hospital in western China. All participants responded positively towards the mTPI and clarified they could understand the mechanism of the design easily. In contrast, they expressed concerns of failing to fully understand the mathematical details involving the CRM method, as well as its complex operational requirements. The physicians were all attracted by the decision spread-sheet tables generated by the mTPI (see [Fig-1] to find out how to input the information that mTPI requires generating the spread-sheet interim decision table). And the most important point is that the physicians realized that the traditional 3+3 design can not offer enough flexibility to make use of updating knowledge that is accumulated with the trial progresses. They admitted that this short introduction gave them a deep understanding upon the inadequacies of the 3+3 method and some of them said that they'd like to adopt the mTPI approach in the future if possible.

Oversight of an ongoing complex adaptive bayesian design is necessary to ensure that the algorithm is functioning properly and that the trial is being conducted as planned. Because such oversight requires unblinding to treatment assignment, a body independent from the sponsor and free from substantial conflicts of interest should be charged with this oversight. The oversight body must be familiar with complex adaptive trial designs and may require special expertise or education.

Operational Difficulties in Conducting Clinical Trials using Bayesian Adaptive Designs in China

Implementation of an adaptive trial, like CRM, involves integration of data capture, drug supply management, data analysis, and an interactive communication system among all stakeholders [19]. The logistical considerations include budget administration, information technology, protocol issues, drug supply, etc. Fast and reliable data capture is the basis for an adaptive trial that is dependent on real-time updating. To implement the adaptations, the data monitoring committee needs to meet regularly and quickly. Adaptive trials will

also make drug supply during the trial harder. Procedures need to be in place to capture and archive the database used for each adaptation. During the trial, data are continually collected, queried, and cleaned and the database evolves over time. Archiving the database at the time of each adaptation allows for validation of the results by outside parties should that be warranted.

All of the above-listed components are mandatory for implementing the CRM method. As far as we know, currently in China, data systems are still a work in progress. Many of the China's hospitals are encountering this challenge, even like the Xijing Hospital, which is at the A-plus level, which is the highest grade of qualification of hospitals in China, still has no reliable networks and can not enable real-time data capture, validation, and analysis of trial-emergent data. Lacking of infrastructure and high-quality data will discourage the CRM method to be efficiently adopted in real clinical trial studies. On the contrary, the mTPI almost provides a decision table [Fig -1] to clinicians a priori, which easily avoids this problem and meanwhile attracts local physicians in the situation of insufficient number of qualified adaptive clinical trial biostatisticans.

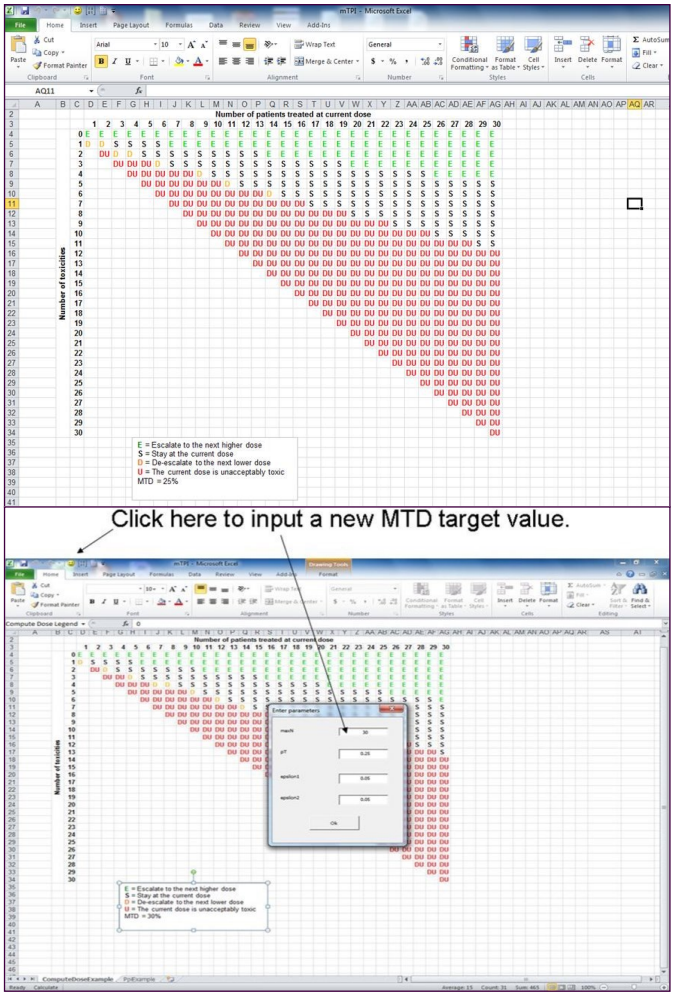

Fig. 1- mTPI Excel Macro software

An Extra Rule for mTPI Design

Although the mTPI has demonstrated good statistical performances in its original version, we found that mTPI can be modified to further save sample sizes while still keeping the ideal performances if we add an extra early stopping rule for the trial. Since saving sample sizes is very important especially in phase I clinical trial studies, therefore, the small modification has its merit clinically. To be specifically, smaller sample sizes means :(1) more patients could avoid potential hazards, (2) the drug development is expedited, and (3) financial resources can be saved.

We compute the dose's posterior probabilities of falling into the EI (equivalent interval of MTD) during the whole dose escalation processes and set an extra rule: the trial will stop if the posterior probability of the EI greater than a cutoff value. The rationale of this early stopping rule is that the trial should have sufficient information to stop if the EI has enough posterior probability compared with those of the other two sub-intervals. Through extensive simulations, we found the cutoff value of 0.35 is appropriate. This cutoff is less than 0.5, which wonders us initially. But we finally realized that the value is relatively small is still reasonable because the EI interval is much narrower compared with the other two intervals. Detailed simulation information refers to [Table-2]. From [Table-2], we can see that this minor modification of mTPI can reduce the total sample size as well as keep the good operating characteristics of the original mTPI method. For instance, in Scenario 5, the total sample size is decreasing from 30 of the original mTPI to 24.8 of the modification of mTPI, which is about 17% percentages reduction. Meanwhile the toxicity selection percentage is the same. Other scenarios indicate the similar results.

Table 2- Simulation results comparing the proposed modification of mTPI method(mTPI) and the original mTPI method. The selection percentages for the true MTDs are in bold face.*

		Recommendation percentage at dose level ϕ=0.25								Toxicity %	Avg. No of patients
	Dose	1	2	3	4	5	6	7	8		
Sc 1		5	25	50	60	70	80	90	95	none	
mTPI	%MTD	14	**78**	8	0	0	0	0	0		
	# Pts	7.1	18.3	4.4	0.2	0	0	0	0	0	24	30
mTPI*	%MTD	14	**76**	9.2	0.8	0	0	0	0		
	# Pts	6.8	15.1	4.7	0.4	0	0	0	0	0	24.7	26.9
Sc 2		1	2	3	4	5	25	50	60	none		
mTPI	%MTD	0	0	0	2	16	**71**	10	1			
	# Pts	3.2	3.5	3.5	4	5.2	8.1	2.3	0.1	0	16	30
mTPI*	%MTD	0	0	0	1.4	14	**73**	9.9	0		
	# Pts	3.1	3.4	3.7	3.9	4.9	8.3	2.2	2.2	0	14	29.8
Sc 3		1	5	50	60	70	80	90	95	none		
mTPI	%MTD	0	**82**	17	0	0	0	0	0			
	# Pts	3.2	15.9	10.3	0.6	0	0	0	0			
mTPI*	%MTD	0	**82**	18	0	0	0	0	0			
	# Pts	3.2	15.6	10.1	0.7	0	0	0	0	0	21	30
Sc 4		40	50	60	70	80	90	95	99	none		
mTPI	%MTD	31	2	0	0	0	0	0	0			
	# Pts	16.8	2	0.2	0	0	0	0	0			
mTPI*	%MTD	34	2.5	0	0	0	0	0	0			
	# Pts	15.2	1.9	0.2	0	0	0	0	0	**67**	41	19
Sc 5		15	25	35	45	55	65	75	85			
mTPI	%MTD	29	**45**	20	4	0	0	0	0	**67**	41	17.2
	# Pts	12.4	10.9	5	1.1	0.1	0	0	0	0	24	30
mTPI*	%MTD	33	**41**	21	3.2	0	0	0	0			
	# Pts	9.7	4.7	4.7	1.1	0.1	0	0	0	0	24	30
Sc 6		5	15	25	35	45	55	65	75			
mTPI	%MTD	2	28	**42**	23	4	0	0	0	0	24	24.8
	# Pts	4.9	10.2	9.3	4.5	0.9	0.1	0	0			
mTPI*	%MTD	3.3	30	**42**	21	3	0	0	0	0	20	30
	# Pts	4.7	8.7	8.6	4.1	1.6	0.8	0	0	0	20	37

**Overall % toxicity out of all the simulated trials.*

We must admit that, though this kind of improvement by setting an arbitrary cutoff 0.5 is theoretically unproved here; our exploration here aims to indicate that the mTPI may be improved further. We will delve this topic furthermore in the future work.

Discussion

Even though the CRM method and related extensions possess sound theoretical frames and could be modified to accommodate complex scenarios, like combination therapy and non-monotonic biological agents, we think it is more feasible for clinicians to equip with the mTPI as the first bayesian tool for phase I studies in China.

From the statistical performances' point of view, the two approaches show the similar results and both of them demonstrate the desirable theoretical properties, however, we should bear in mind that the good simulation results of CRM design are based upon the assumption of the usage of true skeletons for CRM method. And the truth is, in most real-world cases, the attainment of true skeletons for prospective doses is never achieved. From practical feasibility point of view, the mTPI method is easier to understand for local physician, though the survey sample is small, it can disclose the relevant information. More importantly, it is almost a calibration-free approach, and the only job for clinician is to be asked for defining an equivalent interval of MTD value, which is fairly easy job. Implementation of the CRM method requires magnitudely more efforts even for statisticians with relevant expertise. From the logistical point of view, there never exists a short and quick way to set up complete database systems for implementing the CRM approach in China, while the mTPI method can provide a decision table immediately and sequentially as the new data enters in by an Excel macro add-on without sacrificing any efforts. As we show the example trial demo to our physicians in Xijing hospital, all physicians were impressed by this handy Excel generating decision table and agreed with us that the trial could progress smoothly.

Based on our experiences and understanding of China's current clinical trial's situation, we envision the mTPI method would be a reliable, an ethical and easy-to-apply design to introduce to China's clinical trials. At this moment, we are also considering to write report to China's SFDA (State Food and Drug Adminstration) to pay attention to the mTPI method and consider to make thoroughly discussions with them about the various existed competing phase I designs.

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Conflicts of Interests: Authors declare there is no conflict of interest

Ethical Statements

In this manuscript, ethics approval from ethics committee was deemed unnecessary because the results of ours are merely based on the computational simulations.

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