Phase I Dose Finding in Clinical Trials---An Interface for Designs

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Abstract

Many dose finding methods have been published which can be categorized into two groups: nonparametric methods and parametric methods. We present brief review of these different designs to provide a general picture for those investigators or statisticians who will use these methods. The nonparametric traditional 3+3 design is most often used in Phase I clinical trial because it is simple and easy to use though advanced parametric methods outperform the traditional design. We developed an interface that would enable the investigators easily to use the advanced methods including continual reassessment methods (CRM), varieties of modified CRM methods such as escalation with overdose control (EWOC), two parameter logistic CRM together with option for 3+3 simulation, and other method such as modified toxicity probability interval (mPTI), to run simulation for a Phase I study design or to calculate the next dose for an ongoing Phase I study.

Keywords: parametric design, nonparametric design, interface, CRM, EWOC, mTPI, 3+3 design.

1.Introduction

Phase I clinical trial is a study when a new drug or treatment is first used in human subjects. Though first hand efficacy and toxicity profiles in animals are available from preclinical studies, the efficacy and toxicity on human beings are still uncertain. Thus, a careful design is required in Phase I clinical trials due to the differences between human and animals in physiology and other aspects. In addition, we have to treat people differently for ethic issue. In preclinical trials, it is very often that a randomized cohort with a large sample size was used to study a new drug without considering much of the ethic issue. But when we treat people with a new drug or a new treatment, we have to carefully balance the possible benefit and harm. For example, for cancer patients, it is not ethical to put patients on an over dose with higher toxicity or to put them on an under dose with no treatment effect for the reason that they join the clinical trial is to seek a possible cure. Therefore, in most of the phase I clinical trials, a small sample size cohort is used in adaptive manner using escalating dose levels. These adaptive approaches enable us to find a maximum tolerant dose (MTD) with acceptable dose limiting toxicity (DLT) rate predefined by investigators. These adaptive designs can be generally grouped into two categories: non-parametric designs and parametric designs. The widely used non-parametric design example is the traditional 3+3 design (Barry 1989) whereas the most referenced parameter design is continuous reassessment method (CRM) (O'Quigley et al. 1990). The advantage of many non-parametric designs is their simplicity. It is easy to understand and to implement with no need of special software. However, the drawback is that many of these designs do not use all available data in the decision rule and therefore converge slowly to the target dose or the doses near target. Parametric designs such as CRM over non-parametric designs have advantage, as all the available information is used to determine the dose for the next patient in these designs and hence they converge to the target dose or the doses near target. On the other hand, parameter designs usually are harder to understand and more difficult to use in comparison to non-parametric designs. Though the parametric designs perform better than the nonparametric designs, the nonparametric designs, such as 3+3

design, are most often used as most investigators feel that this approach is "safer". In fact, the traditional nonparametric design is no safer than CRM through simulation (Garrett-Mayer 2006). In the review of 53 published phase I trials by Iansonos and O'Quigley (Iasonos & O'Quigley 2014), CRM is shown to be safe as well. Therefore, if simple and easy to use software is developed, more investigators will be interested in using parametric designs in Phase I clinical trials. Interactive adaptive designs for Phase I clinical trials have been included in software such as EAST, but they are not free. In this paper, non-parametric designs and parametric designs will be reviewed first. Then, an easy to use interface to some parametric methods will be introduced and simulation results using our interface will be provided. Finally, some discussions will be presented.

2. Non-parametric designs

In non-parametric designs, no prior assumption of dose-toxicity curve is stipulated and no parameters are involved or estimated for dose escalation. Instead, dose allocation depends on the calculated statistics such as toxicity rate estimates according to a random walk rule or an up-and-down algorithm. The rule for dose allocation is as follows:

i. If $\hat{q}_j \leq \Gamma - \Delta$, then treat the next cohort at $d_{j+1.}$
ii. If $\hat{q}_j \geq \Gamma + \Delta$, then treat the next cohort at $d_{j-1.}$
iii. Otherwise, treat the next cohort at d_j.

The principle of the rule is that the dose for the future cohort of patient(s) is decided based on the statistics of the observed data from the previous cohort of treated patient(s) following up and down algorithm. The first simple up and down algorithm with cohort of one patient (1+1 design) by Dixon and Mood (Dixon & Mood 1948) is used to find a dose with 50% dose limiting toxicity (DLT) which is higher than the most common accepted 33% threshold that tradition 3+3 design is expected to achieve. In similar principle, 5+5 is expected to find the dose with no more than 20% DLT. We call these designs A+B designs. Traditional 3+3 design (Barry 1989) is a special form of A+B designs and converges to a threshold less than 33%. The A+B design (Lin & Shih 2001), biased coin design (BCD) (Derman 1957) (Durham and Flournoy, 1994), group up-and-down design (Wetherill 1963), moving average up-and-down design (Ivanova et al. 2003), group up-and-down design (Gezmu & Flournoy 2006) are examples of non-parametric design for dose finding trials. Many non-parametric designs use isotonic regression to estimate dose toxicity curve. The only assumption is that the DLT rate is non-decreasing function of the dose. The isotonic estimated toxicity rate obtained using pool adjacent violator algorithm (PAVA) (Barlow, R E; Bartholomew, D J; Bremner 1972) rather than observed toxicity rate at current dose is used to decide whether the next cohort is treated at current dose or one dose above or below. These designs include isotonic design (Leung & Wang 2001), and the Cumulative Cohort Design (Ivanova et al. 2007). One other variation is statistic t design in which the t statistics instead of toxicity rate is used in the decision rule (Ivanova & Kim 2009). Some of these designs, such as BCD or group up-and-down designs are Markov processes, and therefore their limiting distributions are easy to compute.

3. Parametric designs for dose-finding trials

In parametric designs, a statistical model is stipulated with parameters being involved or estimated for dose escalation. Parameters are estimated using maximum likelihood or Bayesian methods. Parametric designs can be realized using maximum likelihood technique in frequentist form (O'Quigley & Shen 1996), however, most of them belong to a class of Bayesian designs using Bayesian theorem (O'Quigley et al. 1990). Decision of dose allocation is based on the posterior distribution of parameter(s)

according to Bayesian theorem. To be specific, the next patient is treated at the dose with the toxicity probability close to target *p* with parameter $\hat{\varphi}$ being calculated based on available data. The next patient will be treated at $d_{j+1} = \arg\min |F(d_k, \hat{\varphi}_j) - \hat{p}|$ (Cheung 2010).

The probability of DLT can be given by a multi-parameter model:

$$p_i = F\left(\frac{d_i - \alpha}{\beta}\right)$$

where α and β is unknown shift and scale parameters (Rosenberger & Haines 2002). The quantile of *F* is $\mu = \alpha + \beta F^{-1}(\Gamma)$ where Γ is a specified probability of toxicity and μ can be MTD. Two parameters are specified in the probability function and used in designs such as escalation with overdose control (EWOC) (Babb et al. 1998) which is a modification of continual reassessment method (CRM) (O'Quigley et al. 1990). The function *F* in EWOC is a logistical function. This two-parameter model and other varieties of CRMs are modifications of one parameter CRM first introduced by O'Quigley et al.(O'Quigley et al. 1990)

The one parameter working model is $P(d_j, a) = F(a)$ where d_j is the dose, and j=1,…, K (the dose level), and a is a parameter. In a Bayesian form of the CRM, the prior for a can be specified to be gamma distribution, log normal distribution or uniform distribution. The b_j is a model or a function which can be hyperbolic tangent, power or logistical function. The posterior mean of parameter a is calculated using all the outcomes, and the mean toxicity probability through plugging in mean of parameter a using exact integration. Besides, mean toxicity probability can also be derived through Monte Carlo simulation avoiding integration. Dose assignment is based on mean toxicity probability that is closest to the target toxicity rate**.** The CRMs can be used to reduce the number of patients to receive lower doses which may far below MTD as well and to achieve a more accurate estimation of MTD.

A typical Bayesian decision design has four features: (a) a data model, (b) a prior distribution for parameters, (c) loss function, and (d) a set of actions (Whitehead 2006). Some of the nonparametric Bayesian designs use a loss function in controlling over dose or making decision for dose allocation.

EWOC is a modified CRM in essence with safety measure to restrict a pre-specified proportion of patients to expose to a dose far above MTD. EWOC assigns doses based on the posterior probability that is overdosing. The loss function used in EWOC design is

$$l_a(x, \gamma) = \begin{cases} \alpha(\gamma - x) & \text{if } x \le \gamma \text{ (undose)} \\ (1-\alpha)(x - \gamma) & \text{if } x > \gamma \text{ (over dose)} \end{cases}$$

where γ is the parameter and $\gamma \in [X_{min}, X_{max}]$.

Neuenschwander et al. (Neuenschwander et al. 2008) proposed a Bayesian method which can be used to solve an overdose issue too, and defined a rule to assign dose based on maximum posterior probability within an interval. The loss function in the approach is

$$L(\theta, d) = \begin{cases} l_1 = 1 & \text{if } \pi_\theta(d) \in (0, 0.2] \quad \text{(under-dosing)} \\ l_2 = 0 & \text{if } \pi_\theta(d) \in (0.2, 0.35] \quad \text{(Targeted toxicity)} \\ l_3 = 1 & \text{if } \pi_\theta(d) \in (0.35, 0.6] \quad \text{(Excessive toxicity)} \\ l_4 = 2 & \text{if } \pi_\theta(d) \in (0.6, 1] \quad \text{(Unacceptable toxicity)} \end{cases}$$

Ji et al. (Ji et al. 2007) (Ji et al. 2010) described a rule to assign doses based on the maximum posterior probability within an interval. A set of loss functions (Ji et al. 2010) were defined as following,

$$L(D,p_i)=\begin{cases} N_D, & \text{if } p_i-p_T<-\varepsilon_1 \\ K_D, & \text{if } -\varepsilon_1\le p_i-p_T<\varepsilon_2 \\ 0, & \text{if } p_i-p_T>\varepsilon_2 \end{cases}$$

$$L(S,p_i)=\begin{cases} N_S, & \text{if } p_i-p_T<-\varepsilon_1 \\ 0, & \text{if } -\varepsilon_1\le p_i-p_T<\varepsilon_2 \\ M_S, & \text{if } p_i-p_T>\varepsilon_2 \end{cases}$$

$$L(E,p_i)=\begin{cases} 0, & \text{if } p_i-p_T<-\varepsilon_1 \\ K_E, & \text{if } -\varepsilon_1\le p_i-p_T<\varepsilon_2 \\ M_E, & \text{if } p_i-p_T>\varepsilon_2 \end{cases}$$

where $L(D,p_i)$ is the loss function for de-escalating, $L(S,p_i)$ is for staying, and $L(E,p_i)$ is for escalating.

These designs together with other designs such as cumulative cohort design and t-statistic design etc. can also be grouped into one new class of design called interval design because the interval is pre-specified. The decision making is based on the information at the current dose. These methods are easy to implement like the standard '3+3' but use cumulated data at current dose and therefore more efficient. In these designs, the interval for these designs is fixed regards of the sample size and target toxicity rate. Suyu Liu and Ying Yuan (Liu, S; Yuan 2015) proposed a Bayesian optimal interval design in which the interval is optimal for the sample size and target toxicity rate, which has favorable operating characteristic in having low risk to assign patients to sub-therapeutic and overly toxic doses. Oran et al (Oron et al. 2011) showed that interval designs are converged similar to CRM.

4. Interfaces to implement parametric designs

4.1 Interfaces

Using R version 3.2.0, we developed an interface to implement two kinds of parametric designs, CRM with different modifications and mTPI using the published package or open codes. The interface can naturally integrate with package bcrm by Sweeting et al (Sweeting et al. 2013). After the bcrm package is installed, users can use our user friendly and simple to use interface to run it. We also directly included Ji's code (Ji et al. 2010) and extended the mTPI method to produce the same output format as package bcrm. In addition, 3+3 simulation is coming with bcrm package, so 3+3 simulation results can also be generated using our interface.

The interface package is available at https://apps2.ctsicn.org/~ywang/interface.php, and is in a calculator form including four buttons as shown in Fig 1. These four buttons are for one parameter CRMs, two parameter logistic CRM, mTPI, and help. After click on any one of the first three buttons, a secondary interface will pop up. In the second interface, there is a button for the calculating the next dose when a study is in the proceeding. Clicking it after you input different parameters, the observed values, and the parameters, you will see the calculation of next dose displayed on the R screen.

To run a simulation, some parameters needed to be defined first such as the maximum number of dosages, the target toxicity probability, dosages or estimated toxicity rate at each dose just as the calculation of next dose too. Since there are many different modifications for CRMs, other parameters can be defined in the option menu bars with appropriate default values. Different models can also be chosen such as power, tangent or logistic, and as well as different types of prior distributions, namely, gamma distribution, uniform, log normal distribution or bivariate log normal distribution. Users can also choose

the overdose control (EWOC) method. After clicking on 'run simulation' bar in the run menu, the outcome will be shown on R screen when the simulation has been finished.

To demonstrate how to use the interface, we provide an example step by step in detail below. Before running our r interface, users need install our r package interface and other r package: bcrm, Brugs, R2WinBUGS, rjags by clicking the button 'install packages from local zip files' or 'install package' under 'Package' menu of R software (version 3.2.0). First, load our interface through clicking loading package button under the "Packages" menu in R software and then choose 'interface' from the pop or directly type require(interface) in the command line of R software. Second, type 'interface()' in the command line of R software and a calculator form interface will pop up as shown on the top of Figure 1. Third, with a click of 'One Parameter CRMs' button, another interface will show up as at the bottom of Fig 1. Users need to fill in the corresponding parameters. For example, if a prior distribution of Gamma is chosen, the user needs to fill the two prior distribution parameters: a and b with 1s where Gamma (a = 1, b = 1) is an exponential distribution. Prespecify the number of doses: 6, and actually dosage used required for the two parameters CRM or use the default (optional) otherwise. Then specify the target probability (accepted toxicity rate:0.2) and sample size: 27. Fill in the prior toxicity rate and the true toxicity rates for each dose (.05 ~ 0.7). To calculate dose for next patients, click 'Calculate Next Dose' button after filling number of toxicities (0) and number of patients (3), the results will be shown in the R screen. Fourth, to run simulation, users can choose to click the 'Options' menu, it will list other options such as a model (tangent, power, or one parameter logistic model), a method (exact, rjags, Brugs, R2WinBUGS), number of iterations (10, 50, 100, 500, 1000, 5000, 10000), cohort size (1 ~ 6), and compare with 3+3 (Yes/NO). All these options have their own default values. After you click the 'Run simulation' button under the 'Run' menu, the results will show up in the R screen as in Figure 1.

4.2 Simulation using interfaces

We use the interface to compare the performance of CRM and mTPI using the scenarios described in Ivanova and Kim (Ivanova & Kim 2009) for there are no direct comparison of these methods in these scenarios reported yet. CRM using tangent model with exponential prior (Gamma(a = 1, b = 1)), namely exponential prior, and mTPI are used in the simulation. We ran the simulation 5000 times with a sample size of 27. As can be seen in table 1, column 2 ~ column 7 show the percent recommendation of a dose as MTD, and column 8 ~ column 12 show percentage of DLT fallen in each categories [0.0, 0.2], [.2, 0.4], etc. As regarding to make correct recommendation, CRM is better than mTPI in the first 3 scenarios with less than 0.09, 0.5 of difference in scenario 1, 2 and with only 0.02 of difference in scenario 3 in percent of recommendation, but mTPI performs much better than CRM in scenario 4. As regarding to DLT, mTPI and CRM is comparable in scenario 1 and 3, but CRM is better than mTPI in scenario 2 and 4 since more patients are allocated in the interval of [0.0, 0.2]. In scenario 4, the true toxicity rate in bold is bigger than the target, therefore, a great proportion of DLT is located in [0.2, 0.4]. Overall, the results show that CRM is comparable to mTPI.

5. Discussion

Using R, we developed a user friendly interface which can integrate CRM and mTPI open source package or R codes directly or indirectly to make these parametric Phase I clinical trial designs more easily to use. Through simply modifying our R code, we can integrate other open source package or R code to implement other parametric designs because our primary interface is in calculator form. This interface will enable us to implement mTPI as well as different kinds of CRM including one parameter CRM, or two-parameter CRM in which EWOC is included. Additional 3+3 simulation can be chosen to implement for comparison. In addition, more buttons can be added in this calculator. Other modified CRMs such as time to event CRM (TITE-CRM) by introducing weight into the likelihood function for delayed outcome or other designs such as isotonic design, t statistics designs, Bayesian optimal interval

design could also be included in the future. Second, using scenarios described in Anastasia and Kim (Ivanova & Kim 2009), we compared mTPI and CRM. The overall performance of CRM is comparable to mTPI. Though Bayesian scheme is used in mTPI with parameters being stipulated, mTPI is different from CRMs. In CRMs, all the data are used to calculate the toxicity probability using Bayesian scheme. In mTPI, only current cohort data are used to calculate loss or gain function to decide the next dose assignment. Therefore, mTPI shown to be better than tradition 3+3 design (Ji & Wang 2013) is more like nonparametric methods such as 3+3 design in using partial data, as may explain why mTPI is comparable to (Ji & Wang 2013) or not better than CRMs using the first three scenarios. Nevertheless, mTPI is comparable to CRM using randomly selected scenarios to avoid cherry-picking scenarios, and mTPI is simpler than CRM for the parameters in mTPI are fixed (Liu, S; Yuan 2015). Whereas we do not need standardized doses in mTPI, we need to specify prior toxicity rates in CRM to calculate standardized doses through plugging in the prior toxicity rates in the probability function. Different choice of prior distributions would affect the results of CRM though the form of the prior distribution was not shown to affect the results considerably (Chevret 1993). Third, although CRM seems complicated, using our interface, it only requires the following few steps to run simulation or calculate next dose: 1) standardize doses through providing prior toxicity probability; 2) specify target toxicity probability and maximum number of doses; 3) specify other parameters with default values included; 4) specify observed toxicity data required only for next dose calculation. Fourth, in Phase I clinical trials, the cohort size or the cohort size at startup is usually 2~5 patients though cohort size of 1 is used to find the first toxicity in the first stage of two-stage CRM. It is important to avoid escalation that is too rapid or too slow (Cheung 2005). With that goal in mind, the group size or cohort size s in the start-up should be chosen according to the target toxicity level Γ. Ivanova et al (Ivanova et al. 2003) suggested choosing group size according to the following formula $s = \lfloor \log(0.5) / \log(1-\Gamma) \rfloor$. For example, if $\Gamma = 0.5$, the start-up with $s = 1$ is used; if $\Gamma = 0.3$, the start-up with $s = 2$ is used; if $\Gamma = 0.2$, the start-up with $s = 3$ is used. Finally, in Phase I clinical trials, skipping any untried dose is not allowed in nonparametric designs or mTPI, in contrast, skipping dose is allowed in CRMs. As there are concerns that this will cause an over dose problem, restriction of skipping any untried dose or skipping no more than a certain number of untried doses has been proposed and used in CRM (Moller 1995). Hence, in this interface, we do not allow to skip dose in CRM.

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Figure 1, Interface for Phase I dose designs

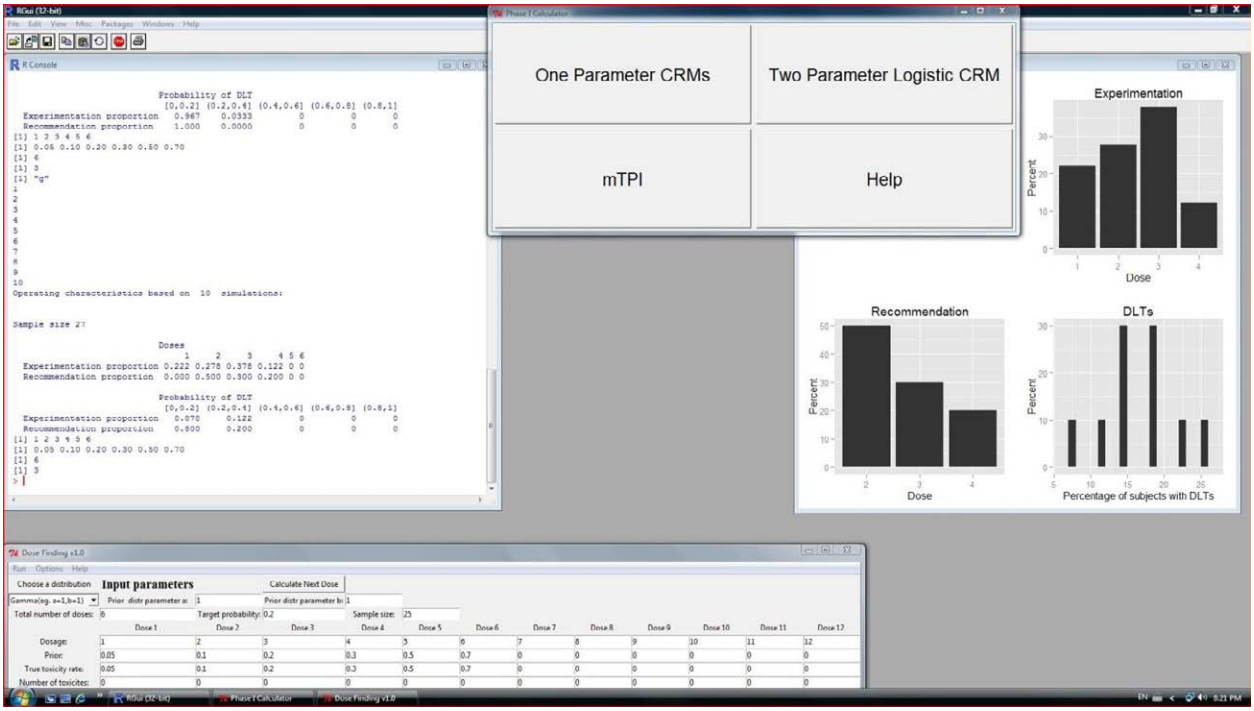

Table 1. Proportion of trials each dose was recommended as the MTD and allocation for mTPI and CRM. The target DLT rate is 0.20 and the total sample size is $n = 27$. Numbers at the MTD are in bold.

	Percent recommendation						Allocation				
	d1	*d2*	*d3*	*d4*	*d5*	*d6*	*[0.0, 0.2]*	*[0.2, 0.4]*	*[0.4, 0.6]*	*[0.6, 0.8]*	*[0.8, 1.0]*
Scenario 1	0.05	0.10	**0.20**	0.30	0.50	0.70					
mTPI	0.07	0.25	**0.40**	0.25	0.03	0.00	0.72	0.25	0.03	0.00	0.00
CRM	0.02	0.22	**0.49**	0.26	0.02	0.00	0.72	0.26	0.02	0.00	0.00
Scenario 2	0.05	0.06	0.08	0.11	**0.19**	0.34					
mTPI	0.03	0.05	0.10	0.27	**0.36**	0.18	0.82	0.18	0.00	0.00	0.00
CRM	0.01	0.04	0.13	0.37	**0.41**	0.05	0.95	0.05	0.00	0.00	0.00
Scenario 3	0.06	0.08	0.12	**0.18**	0.40	0.71					
mTPI	0.06	0.11	0.21	**0.48**	0.15	0.00	0.85	0.15	0.00	0.00	0.00
CRM	0.01	0.09	0.27	**0.50**	0.12	0.00	0.88	0.12	0.00	0.00	0.00
Scenario 4	0.00	0.00	0.03	0.05	0.11	**0.22**					
mTPI	0.00	0.00	0.02	0.09	0.31	**0.58**	0.42	0.58	0.00	0.00	0.00
CRM	0.00	0.00	0.00	0.09	0.64	**0.28**	0.73	0.28	0.00	0.00	0.00