Comparison between Discrete and Continuous Doses for EWOC Designs

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Abstract

Although there is an extensive statistical literature showing the disadvantages of discretizing continuous variables starting with Cox [1], categorization is a common practice in clinical research which results in substantial loss of information. A large collection of methods in cancer phase I clinical trial design defines dose of a new agent as a discrete variable. A noteworthy exception is the Escalation With Overdose Control (EWOC) design [2] where doses can be defined either as continuous or as a grid of discrete doses. A Monte Carlo simulation study was performed to compare the operating characteristics of continuous and discrete dose EWOC designs. Four equally spaced grids with different interval lengths were considered. The loss of information was measured by several operating characteristics more interpretable for clinicians in addition to the usual statistical measures of bias and mean squared error.

Key Words: Escalation with overdose control, phase I, discrete dose, continuous dose

1. Introduction

Measurements of continuous variables are made in all fields of medicine. In medical research such continuous variables are often converted into categorical variables by grouping values into two or more categories.

Cox [1] derived an optimization criteria for discretizing a continuous covariable and showed that if a variable is normally distributed then categorizing it into six groups implies a minimum loss of 5.8% of information, 7.99% for five groups, 11.75% for four groups and 19.02% for three groups considering a quadratic loss function. Following the suggestion of Cox, Connor [3] found other criteria and reached similar conclusions based on the asymptotic relative efficiency of Cochran-Armitage trend test [4] when a continuous covariable, that is linearly related to a binary response variable, is discretized. In this way, several authors have pursued methodologies to provide optimal criteria of discretization for continuous covariables based on other test statistics. See [5], [6], [7], [8], [9].

On the another hand, an extensive statistical literature (see [10], [11], [12], [13], [14], [15] and [16]) have advised against categorization due the loss of power and precision of the estimated quantities. In particular, Lagakos [11] studied extensively the effects of mismeasuring covariables considering a likelihood test for a logistic model when a continuous covariable, which follows either a Normal or Exponential or Uniform distribution, is categorized and also evaluated the loss of information when the levels of an ordered categorical covariable is selected incorrectly considering the Cochran-Armitage trend test.

This debate is not different for cancer phase I clinical trials, although with its peculiarities. Phase I trials represent the first testing of an investigational agent in humans and act as a point of translation of years of laboratory research into the clinic. The major objective in phase I trials is to identify a maximum tolerable dose (MTD) for subsequent studies, whereas the primary end point in phase II and III trials is treatment efficacy. While phase I trials in other areas of medicine enroll healthy participants, phase I oncology trials typically enroll patients who have cancer and who have exhausted standard treatment options.

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Ideally, from a therapeutic perspective, clinical trials should be designed to maximize the number of patients receiving an optimal dose.

The fundamental conflict underlying the design of cancer phase I clinical trials is that increasing the dose slowly to avoid unacceptable toxic events must be balanced against treating many patients at suboptimal or nontherapeutic doses. [17]

Traditionally, dose finding has been conducted according to the 3 + 3 principle and its variants which require a pre-specified set of discrete doses. Although the use of rule-based designs is still prevailing, model-based designs such as the continual reassessment method (CRM) introduced by O'Quigley [18] and Escalation With Overdose Control (EWOC) by Babb et al. [2] gain popularity in clinical practice. [19]

In these model-based designs, a parametric model is considered to describe the relationship between the probability of a dose limiting-toxicity (DLT) and the dose level of the new agent which can be considered as a continuous or a discrete covariable. Among these designs, a large collection of methods usually defines dose of a new agent as a discrete variable. A noteworthy exception is the EWOC design where doses can be defined either as continuous or as a grid of discrete doses. For discrete doses, EWOC still will consider the same continuous dose algorithm, but a final rounding step is added to the algorithm.

EWOC was the first dose-finding procedure to directly incorporate the ethical constraint of minimizing the chance of treating patients at unacceptably high doses. Its defining property is that the expected proportion of patients treated at dose s above the MTD is equal to a specified value α, the feasibility bound. [20]

The feasibility bound could varying along the trial as discussed by Tighouart and Rogatko [21]. The rationale behind this approach is that uncertainty about the MTD is high at the onset of the trial and a small value of α offers protection against the possibility of administering dose levels much greater than the MTD. As the trial progresses, uncertainty about the MTD declines and the likelihood of selecting a dose level significantly above the MTD become significantly smaller. Chu, Lin and Shih [22] compared the performance of different versions of CRM with EWOC both constant and varying α.

In this work, a Monte Carlo simulation study to compare the operating characteristics of continuous and discrete dose EWOC designs is presented. Four equally spaced grids with different interval lengths will be considered. The loss of information will be evaluated using the statistical measures bias and mean square error as well as specific measures to phase I clinical trials to quantify safety and efficacy of the trial. Several scenarios will be constructed based on four true values for the MTD such that the comparisons among continuous and discrete dose designs will be performed under three different sample sizes, five feasibility strategies, rounding choices and misspecified scenarios.

This article is organized as follows. In Section 2, the EWOC design is introduced. The simulation study is described in Section 3 and its results are presented in Section 4 with discussion in Section 5.

2. Escalation with Overdose Control

In this section, the EWOC design is described as Babb et al. [2]. Let X_{min} and X_{max} denote the minimum and maximum dose levels available for use in the trial. Note that the dose given to the first cohort of patients is not necessarily equal to X_{min} but there must be strong evidence that it is a safe dose. While the maximum dose is not a dose that one would ever use to treat a patient, it is a boundary that would never be exceeded.

In this way, the minimum and maximum doses are respectively the lower and upper bound of the support of the MTD γ which is defined by

$$P(DLT|dose = \gamma) = \theta, \tag{2.1}$$

such that θ is defined as the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity if the MTD γ is administered. The relationship between toxicity and dose level could be defined as

$$P(DLT|dose = x) = F(\beta_0 + \beta_1 x), \tag{2.2}$$

where F is a specified distribution function and β_0, β_1 are unknown parameters. Following (2.1) and (2.2), the MTD will be given by

$$\begin{aligned} \gamma &= \frac{F^{-1}(\theta) - \beta_0}{\beta_1} \\ &= X_{min} + \frac{F^{-1}(\theta) - \rho_0}{\beta_1}, \end{aligned}$$

where ρ_0 denotes the probability of a DLT at the initial dose often established as $x_1 = X_{min}$. Using the definition of the MTD and probability of toxicity at initial dose, one can show that

$$\begin{aligned} \beta_0 &= \frac{\gamma F^{-1}(\rho_0) - X_{min} F^{-1}(\theta)}{\gamma - X_{min}}, \\ \beta_1 &= \frac{F^{-1}(\theta) - F^{-1}(\rho_0)}{\gamma - X_{min}}. \end{aligned} \tag{2.3}$$

Denote by y_i the toxicity response (1 for DLT and 0 for no DLT) of the ith patient. The likelihood of the data $D_k = \{(x_i, y_i), u = 1, \ldots, k\}$ after observation of k patients is

$$L(\rho_0, \gamma | D_k) = \prod_{i=1}^{k} F(\beta_0 + \beta_1 x_i)^{y_i} [1 - F(\beta_0 + \beta_1 x_i)]^{1-y_i}. \tag{2.4}$$

for (β_0, β_1) defined as funtions of (ρ_0, γ) given in (2.3).

Prior information is incorporated for (ρ_0, γ) such that priors distributions could be chosen under the restrictions of $\gamma \in [X_{min}, X_{max}]$ and $\rho_0 \in (0, 1)$. The obvious choice is a $Beta(a_\rho, b_\rho)$ distribution for ρ_0 and a re-escaled $Beta(a_\gamma, b_\gamma)$ distribution for γ, but Tighouart et al. [23] examine a large class of prior distributions which could be considered.

Finally, the calculation of the posterior distribution for (ρ_0, γ) is available [24] and implemented using numerical integration and Markov chain Monte Carlo sampler

$$\pi(\rho_0, \gamma | D_k) = c(D_k) L(\rho_0, \gamma | D_k) \pi(\rho_0, \gamma), \tag{2.5}$$

where $c(D_k)$ is a normalizing constant.

Hence, the $k + 1$ patient receives the dose given by the α-quantile of the γ posterior distribution

$$x_k = \Pi^{-1}(\alpha | D_k), \tag{2.6}$$

for α being the probability that the dose selected by EWOC is higher than the MTD.

For a discrete dose design, EWOC could either round down x_k to the closest dose prioritizing safety or just round to the nearest dose preferring ability to explore the available grid of doses.

3. Simulation study

Escalation with Overdose Control was applied for continuous dose and discrete dose which were denoted by dose designs. The minimum and maximum dose were established as $X_{min} = 0$ and $X_{max} = 1$. Considering the discrete dose design, four equally spaced grids with different interval lengths between two doses given by 0.05, 0.10, 0.2 and 0.25 such that each grid will be indicated by its interval length. In this way, the grid 0.05 has 21 doses, the grid 0.10 has 11 doses, the grid 0.20 has 6 doses and the grid 0.25 has 5 doses.

The DLT proportion threshold is established equal to 0.33 such that four true values of MTD $= \{0.2, 0.4, 0.6, 0.8\}$ were considered. In this way, the dose design 0.25 does not contain any true MTD as an element of its grid making this dose design the worst possible situation while the dose design 0.20 contains the smallest number of doses such that all elements are possible true MTD making the most desirable situation. Three different sample sizes $n = 20, 40, 60$ and five strategies were considered for the feasibility bound and the rounding down and nearest choices are applied.

For the feasibility strategy F(0.25), α was fixed equal to 0.25; in strategy I(0.25), α started equal to 0.25 and increased by 0.05 for each new patient up to 0.5; in strategy C(0.25), α started equal to 0.25 and increased by 0.05 for each new patient up to 0.5 only if the previous patients has no DLT; in strategy I(0.05), α started equal to 0.05 and increased by 0.05 for each new patient up to 0.5; in strategy C(0.05), α started equal to 0.05 and increased by 0.05 for each new patient up to 0.5 only if the previous patients has no DLT.

A Monte Carlo study is performed considering 1000 replicates for each study design. The classical statistical measures of bias and mean square error (mse) were evaluated as well as operating characteristics more interpretable for clinicians: average DLT rate, percentage of trials which DLT rate is greater than $\theta + 0.10$, percentage of trials which DLT proportion is outside the interval $\theta \pm 0.10$ (refereed as target rate interval), the percentage of trials with estimated MTD within the optimal interval defined as True MTD $\pm$ 0.15 $\times$ True MTD (refereed as optimal interval), and the percentage of patients receiving optimal doses.

It is important to highlight that, from the perspective of a patient participating in a dose finding trial, the best design is the one with the highest proportion of patients receiving optimal doses. All the simulations were performed using the R-package EWOC in development available at GitHub.

4. Results

In this section, the true model and the working model are both the Logistic model. There are 20 (4 true MTD $\times$ 5 feasibility strategies) simulations for each sample size and dose design which can be interpreted concomitantly analyzing the median and the quartiles of the operating characteristics.

Figures 1 and 2 show results of the bias and the mean square error (MSE) of the five EWOC designs considering different sample sizes. The bias decreases as the sample size increases as can be seen by the inter-quartile distance such that the median bias of the continuous dose design is always slightly positive while is negative for the discrete dose designs.

The bias is a decreasing function of the number of pre-selected doses among the discrete dose designs. The MSE follows the same pattern.

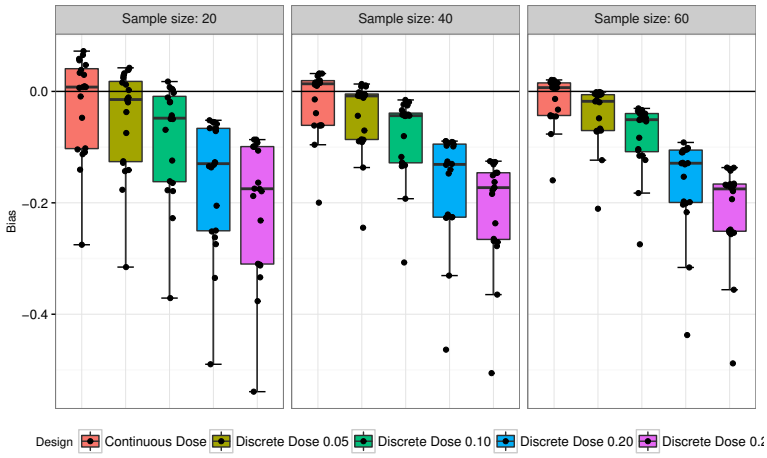

Figure 1: Bias as a function of sample size and dose design

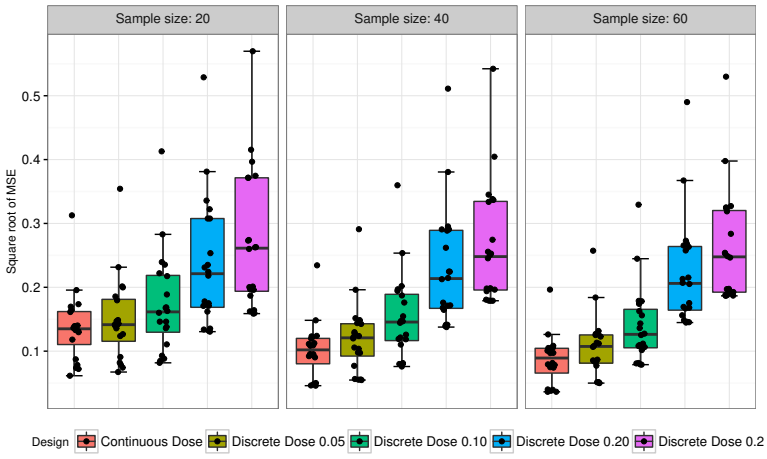

Figure 2: MSE as a function of sample size and dose design

Figures 3 and 4 present results of the DLT proportion average and the percentage of trials such that DLT proportion is greater than $\theta + 0.1$. The continuous dose design and the discrete dose designs 0.05 and 0.10 present simulations exceeding the DLT threshold, although the medians as well as the quartiles become closer to θ as the sample size increases.

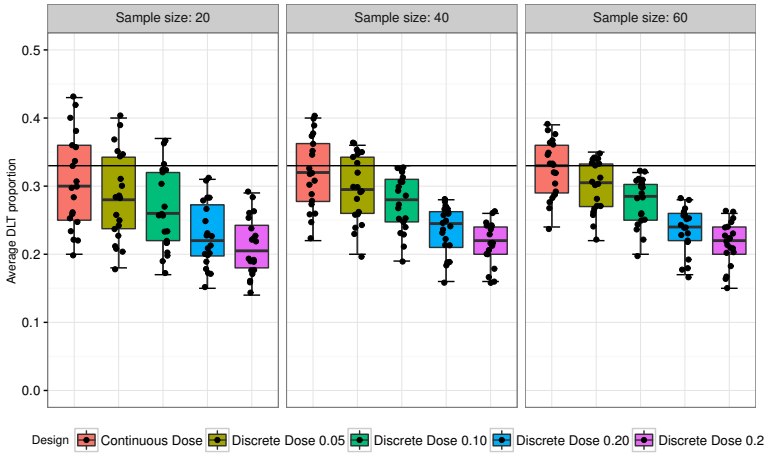

Figure 3: DLT Average as a function of sample size and dose design

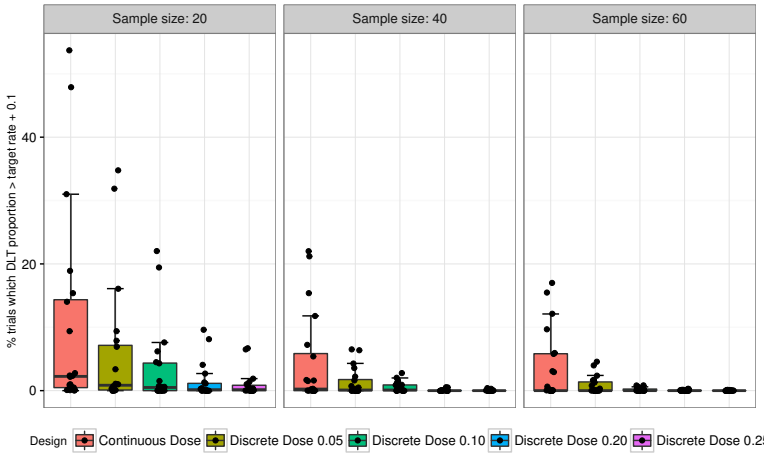

Figure 4: Percentage of trials such that DLT proportion is greater than $\theta + 0.1$ as a function of sample size and dose design

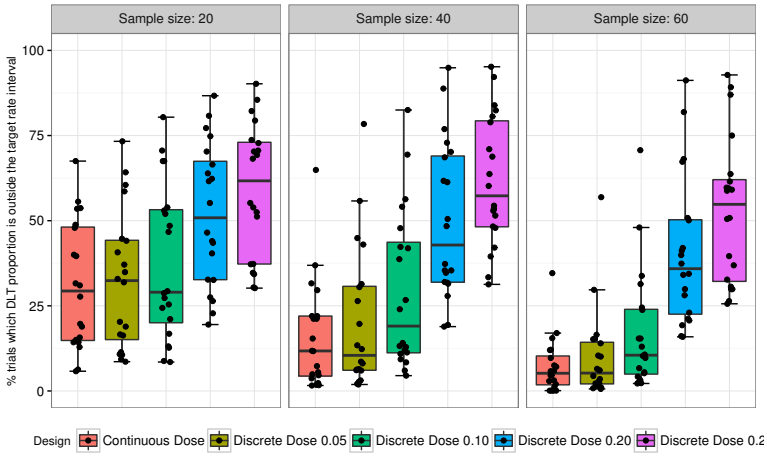

Figure 5: Percentage of trials such that the observed DLT proportion is outside the interval $[\theta - 0.1; \theta + 0.1]$ as a function of feasibility strategy and design

Figure 5 quantifies the percentage of trials such that the observed DLT proportion is outside the interval $[\theta - 0.1; \theta + 0.1]$ which is a trade-off between safety and ability to explore the range of doses adequately. The continuous dose design presents the lowest percentages closely followed by the discrete dose design 0.05 and 0.10 while the dose designs 0.20 and 0.25 are significantly far.

Although the discrete dose design 0.20 and 0.25 are equally the safest designs, they also have high percentages of trials outside the DLT proportion interval which represents missed opportunities to explore the range of doses to estimate accurately the MTD as showed in Figure 1. This pattern is strongly related to the rounding choice as will be seen in next sections.

Figures 6 and 7 present the percentage of trials such the MTD estimate is inside the optimal interval and average percentage of doses inside the optimal interval. The continuous dose design is somewhat better than the all discrete dose designs such that the difference are emphasized when the sample size increases.

Nonetheless, the differences are not so significant for the average percentage of dose inside the optimal interval, except for the discrete dose design 0.25.

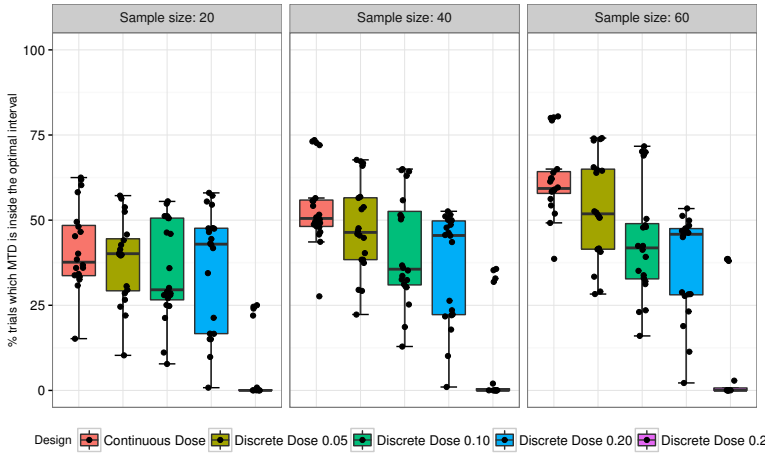

Figure 6: Percentage of trials such the MTD estimate is inside the MTD optimal interval as a function of sample size and dose design

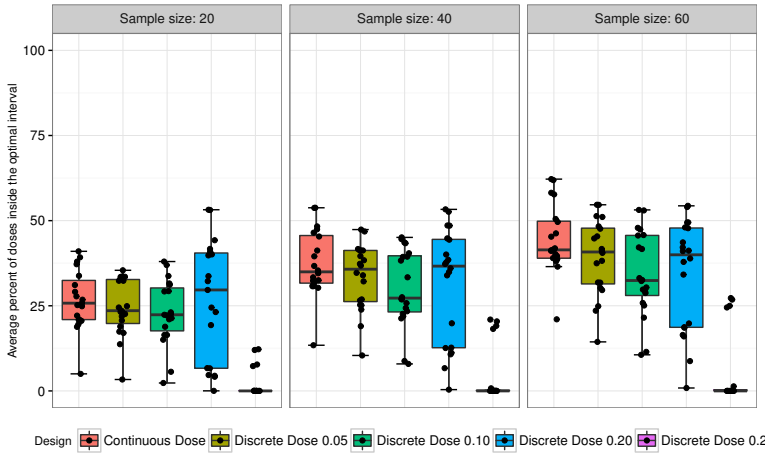

Figure 7: Average percentage of doses inside the optimal interval as a function of sample size and dose design

5. Discussion

Dose designs could be defined as the essential part of a clinical trial in which the researchers have to define the set of possible doses to be evaluated such that one dose will be established as the MTD. The two possible dose designs are continuous dose and discrete dose. The former defines a infinite dose set defined by the minimum and the maximum doses while the latter defines a pre-specified finite set of doses.

Discrete dose designs are much more often applied than continuous dose for several reasons which are commonly presented: use of 3 + 3 principle and its variants, small sample sizes allow only a few doses to be evaluated, anticancer drugs are only available as an oral formulation and discrete dose designs are robust against misspecification.

The up-and-down approach was first described by Dixon and Mood [25] with the greatest advantage of simplicity and ease of implementation. Moreover, such designs are easily understood by clinicians although its several drawbacks have been discussed.

Rogatko et al. [26] discussed the knowledge transfer from more effective statistical designs to clinical practice. Discrete dose design is a feature incorporated into model based designs from rule based designs by historic reasons trying to increase the acceptability of more sophisticated designs which contrasts to the last estimated percent of available oral anticancer drugs of 10% in 2010. [27]

Furthermore, the definition of a pre-selected set of doses usually corresponds to an arbitrary decision. If the rounding down choice is applied, the continuous dose design presents better statistical and efficiency measures, although the discrete dose designs are safer than the continuous dose. Notice that the assumption that the true MTD is a element of the pre-selected set of doses is essential for the efficiency measures which is hard to evaluate in practical trials. In addition, the good operating characteristics are directed related to the number of pre-selected doses for the discrete dose designs.

The next steps is the comparison between discrete and continuous dose designs under different feasibility strategies, rounding systems and misspecification models.

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