Supporting information for "Approximate Bayesian Computation Design for Phase I Clinical Trials" by Huaqing Jin, Wenbin Du and Guosheng Yin

A Simulation Details

A.1 Detailed settings of compared methods

The detailed settings of the BOIN, CCD, CRM, keyboard, mTPI and UMPBI methods used in the simulation studies are listed as follows.

- **BOIN:** In the BOIN design, we choose $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$. Such setting follows Lin and Yin (2017) and Liu and Yuan (2015).

- **CCD:** Following Ivanova et al. (2007), we set the tolerance interval of the CCD method as $(0.2, 0.4)$ when $\phi = 0.3$ and $(\phi - 0.09, \phi + 0.09)$ when $\phi < 0.3$.

- **CRM:** we adopt the power model $p_j = \pi_j^{\exp(\alpha)}$ with the model skeleton selected by the method of Lee and Cheung (2009). We choose a halfwidth of the indifference interval of 0.05 and an initial guess of MTD at dose level $\lceil K/2 \rceil$. Note that such choices are popular in the literature (Lin and Yin, 2017, 2018).

- **Keyboard:** Following Yan et al. (2017), we set the proper dosing interval as $(\phi - 0.05, \phi + 0.05)$ for the keyboard design.

- **mTPI:** Following the discussion in Ji et al. (2010), we choose the equivalent interval as $(\phi - 0.05, \phi + 0.05)$.

- **UMPBI:** Following Lin and Yin (2018), the threshold parameter, i.e., the only tuning parameter, is selected as $\gamma(m_k) = \exp\left(c\sqrt{m_k}\right)$, with $c = \log(1.1)/3$.

For the real data application, we follow the original paper (Banerjee et al., 2017) and use the CRM design with a 2-parameter logistic model, i.e.,

$$\text{logit}(p_j) = \alpha + \exp(\beta)x_i,$$

where the model skeleton is still selected by the method of Lee and Cheung (2009) with a halfwidth of the indifference interval of 0.05 and an initial guess of MTD at dose level $\lceil K/2 \rceil$. The early stopping rule is set as terminating the trial if $\Pr(p_1 > \phi|\text{data}) > 0.95$.

A.2 Random Scenario Generation

We generate random scenarios to assess the performance of the phase I designs in Sections 3.1 and 3.2 with the method of Paoletti et al. (2004). Specifically, the procedure is detailed as follows.

1. Randomly select, with equal probabilities, one of the K dose levels as the MTD and denote that dose level as $\widetilde{k}$.

2. Let Φ be the cumulative density function (CDF) of the standard normal distribution. The probability of the MTD is $p_{\widetilde{k}} = \Phi(\epsilon_{\widetilde{k}})$ with $\epsilon_{\widetilde{k}} \sim N(\Phi^{-1}(\phi), \sigma_0^2)$, where ϕ is the target toxicity probability.

3. For $\{p_k\}_{k=1}^{\widetilde{k}-1}$, generate

$$p_{k-1} = \Phi\left[\Phi^{-1}(p_k) - \left\{\Phi^{-1}(p_k) - \Phi^{-1}(2\phi - p_k)\right\} I\left\{\Phi^{-1}(p_k) > \Phi^{-1}(\phi)\right\} - \epsilon_{k-1}^2\right],$$

   where $I(\cdot)$ is the indicator function and $\epsilon_{k-1} \sim N(\mu_1, \sigma_1^2)$.

4. For $\{p_k\}_{k=\widetilde{k}+1}^{K}$, generate

$$p_{k+1} = \Phi\left[\Phi^{-1}(p_k) + \left\{\Phi^{-1}(2\phi - p_k) - \Phi^{-1}(p_k)\right\} I\left\{\Phi^{-1}(p_k) < \Phi^{-1}(\phi)\right\} + \epsilon_{k+1}^2\right],$$

   where $\epsilon_{k+1} \sim N(\mu_2, \sigma_2^2)$.

Following Liu and Yuan (2015), we choose $\sigma_0 = 0.05$ and $\sigma_1 = \sigma_2 = 0.35$, and tune the parameters $\mu_1 = \mu_2$ to achieve desirable Δ, i.e., the average probability difference around the target.

B Toy example for the monotonically constrained sampling

For illustration of the monotonically constrained sampling problem, we show an example on how to sample three variables $\{X_i\}_{i=1}^3$ whose base distribution is Uniform$(0, 1)$ but with the constraint $0 < X_1 < X_2 < X_3 < 1$.

Proposition 1. *The probability density function (pdf) of the joint uniform distribution of* (X_1, X_2, X_3) *under the constraint* $0 < X_1 < X_2 < X_3 < 1$ *is*

$$f(x_1, x_2, x_3) = f_1(x_1|x_2)f_2(x_2)f_3(x_3|x_2), \tag{B.1}$$

where

$$f_2(x_2) \sim \text{Beta}(2, 2),\ \ f_1(x_1|x_2) \sim \text{Uniform}(0, x_2),\ \ f_3(x_3|x_2) \sim \text{Uniform}(x_2, 1).$$

Proof: By definition, the pdf of (X_1, X_2, X_3) can be written as

$$f(x_1, x_2, x_3) = CI_{\{0<x_1<x_2<x_3<1\}},$$

where C is a constant and I is an indicator function. Noting that the joint pdf can be rewritten as

$$f(x_1, x_2, x_3) = CI_{\{0<x_1<1\}}I_{\{0<x_2<1\}}I_{\{0<x_3<1\}}I_{\{x_1<x_2\}}I_{\{x_2<x_3\}},$$

the marginal distribution of X_2 is obtained by

$$\begin{aligned} f_2(x_2) &= \int\int f(x_1, x_2, x_3)\,\mathrm{d}x_1\,\mathrm{d}x_3 \\ &= \int CI_{\{0\le x_3\le 1\}}I_{\{0\le x_2\le 1\}}I_{\{x_2<x_3\}}\int I_{\{x_1<x_2\}}I_{\{0\le x_1\le 1\}}\,\mathrm{d}x_1\,\mathrm{d}x_3 \\ &= \int Cx_2I_{\{0\le x_3\le 1\}}I_{\{0\le x_2\le 1\}}I_{\{x_2<x_3\}}\,\mathrm{d}x_3 \\ &= C(1-x_2)x_2I_{\{0\le x_2\le 1\}} \\ &= 6(1-x_2)x_2I_{\{0\le x_2\le 1\}}, \end{aligned}$$

which corresponds to the pdf of Beta$(2, 2)$. The conditional density of (X_1, X_3) given X_2 is

$$f(x_1, x_3|x_2) = \frac{f(x_1, x_2, x_3)}{f_2(x_2)} = \frac{I_{\{0\le x_1\le x_2\}}I_{\{x_2\le x_3\le 1\}}}{(1-x_2)x_2} = f_1(x_1|x_2)f_3(x_3|x_2),$$

because given X_2, X_1 and X_3 are independent, and thus each follows a uniform distribution. □

We explore four ways to sample (X_1, X_2, X_3) under the monotonicity constraint.

- **Method 1:** sample (X_1, X_2, X_3) following the distributions in (B.1).
- **Method 2:** sample three variates from Uniform$(0, 1)$ independently, and then sort them in an ascending order and label the sorted samples as X_1, X_2, X_3.
- **Method 3:** sample $X_1, X_2, X_3 \sim$ Uniform$(0, 1)$ independently and only keep the samples satisfying $X_1 < X_2 < X_3$.
- **Method 4:** sample (X_1, X_2, X_3) as follows,

$$\begin{aligned} X_2 &\sim \text{Uniform}(0, 1), \\ X_1|X_2 &\sim \text{Uniform}(0, X_2), \\ X_3|X_2 &\sim \text{Uniform}(X_2, 1). \end{aligned}$$

The estimated densities of (X_1, X_2, X_3) under the four sampling methods are shown in Figure A.1. Clearly, the first three sampling methods lead to equivalent distributions while

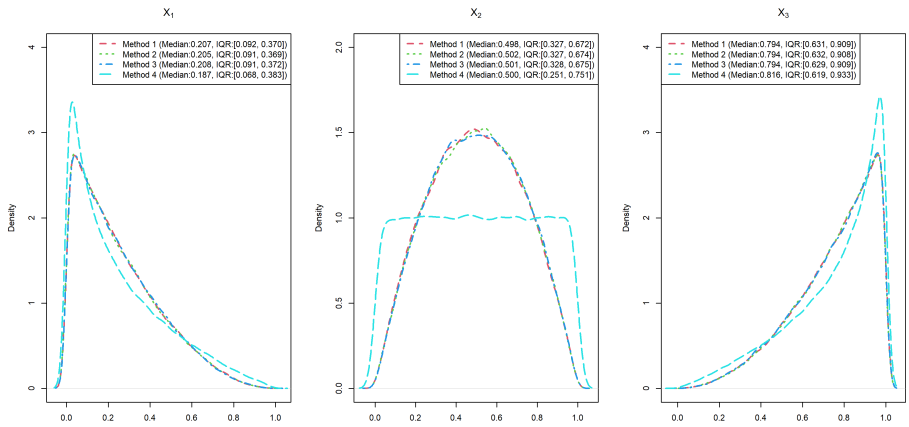

Figure A.1: The densities of X_1 (left), X_2 (middle) and X_3 (right) under the four different sampling methods.

the last one yields a different one. Method 1 requires tedious derivations which would be more complicated if more random variables are involved. Method 2 is natural and simple to incorporate the monotonicity constraint, and Method 3 is less efficient.

C The selection of $S(\cdot, \cdot)$

In Section *Optimal Dose Selection*, after we obtain the weighted samples, we need to select a suitable function $S(\cdot, \cdot)$ to yield reasonable estimators of $\hat{p}_{n,k}$'s . The common choices are among weighted mean, weighted median and weighted mode functions.

In Figure A.2, we present the typical density function of the posterior weighted samples. It is clear that the density function is not uni-modal, and therefore the weighted mode function is not suitable in this case.

We also compared the performance of the three choices when the target DLT rate is $\phi = 0.2$ and the number of dose levels is 5 under 5000 randomly generated scenarios. The results are presented in Table A.1.

The results indicate that the weighted mode function is not a satisfactory choice for our ABC design. Both the weighted median and weighted mean function yield decent perfor-

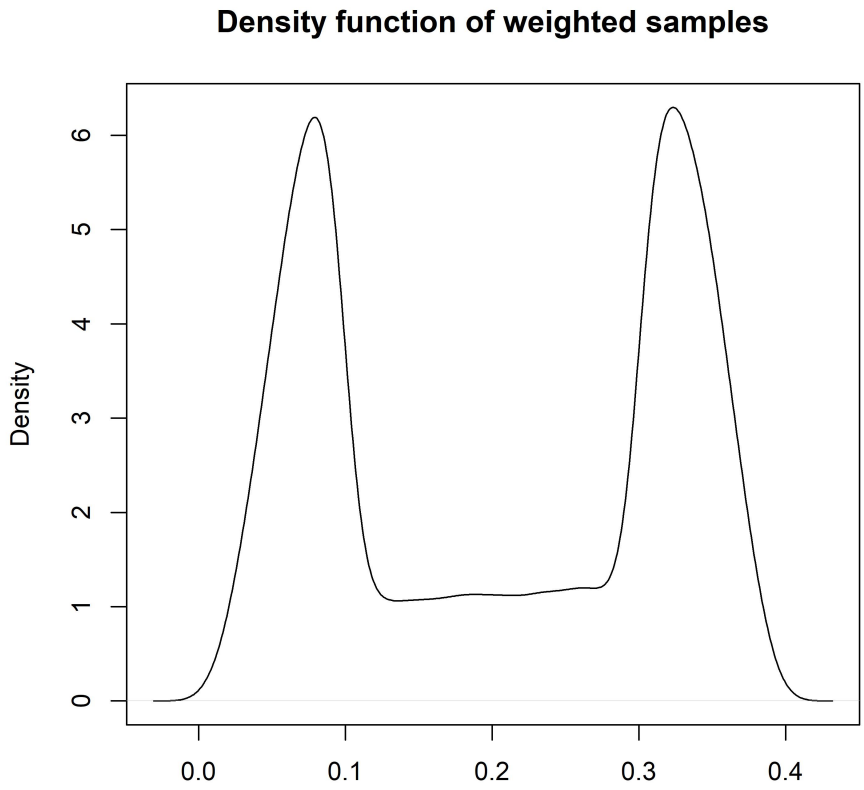

Figure A.2: The kernel density estimate of the posterior weighted samples from the ABC design.

Table A.1: Simulation results with sample size 30 based on 5000 randomly generated dose–toxicity scenarios under the average probability difference of $\Delta = 0.1$ around the target toxicity probability $\phi = 0.2$ with 5 dose levels.

	MTD sel. (%)	MTD allo. (%)	Overdose sel. (%)	Overdose allo. (%)
ABC-mean	54.58	41.24	14.32	17.02
ABC-median	56.56	42.21	16.68	18.29
ABC-mode	50.30	38.90	19.00	17.81

mance. The ABC design with weighted median function is more efficient while the ABC design with weighted mean function is safer. In our paper, we adopt the weighted median over the weighted mean because the median is more robust compared with the mean.

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