Statistical Review and Evaluation
Fit-for-Purpose Initiative

Application	Bayesian Optimal Interval (BOIN) Design as an Efficient Statistical Methodology for Phase I Dose Finding Clinical Trials
Applicant	Ying Yuan, Ph.D., and J. Jack Lee, Ph.D. The University of Texas MD Anderson Cancer Center
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1 Executive Summary

A submission was received from Dr. Ying Yuan and Dr. J. Jack Lee, The University of Texas MD Anderson Cancer Center, under the fit-for-purpose (FFP) initiative, intended to support the use of the Bayesian Optimal Interval (BOIN) Design as a statistical methodology for phase I dose finding clinical trials. The submission states that as a model-assisted design, BOIN combines the simplicity of an algorithm-based design (for example, the convention 3+3 design), and superiority of a model-based design (for example, the continuous reassessment method).

The Applicant's submission document contained a brief introduction to the BOIN methodology and referred to the paper by Liu and Yuan (2015) for technical details and the derivation of the design. Therefore, our methodological review focused on the derivations presented by Liu and Yuan (2015). Liu and Yuan (2015) present two versions of the BOIN design, which they refer to as the local BOIN design, and the global BOIN design. The information presented in this FFP submission document applies only to the local BOIN design, and therefore, our review of this FFP submission applies only to the local BOIN design. Throughout this review document unless we explicitly mention the global BOIN design, we use the term BOIN design to refer to the local BOIN design as described by of Liu and Yuan (2015). The Applicant's submission document also presents a summary of simulation studies where several phase I trial designs were compared.

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During our review, we found some technical issues in the derivations presented in Liu and Yuan (2015) which needed to be corrected. As a result, we prepared detailed comments and sent them to the Applicant as an information request. The Applicant responded with an updated design and derivation, and we reviewed the revised design and derivation and provided additional comments to the Applicant. Through this iterative process, we sent a total of three sets of comments to the

Applicant, each time receiving a further revised version of the design and/or derivation, which improved the rigorousness of the methodological development of the BOIN design. In view of the iterative nature of these revisions, our determination applies to the most refined version of the revised BOIN design and derivation provided to us by the Applicant. This version of the revised BOIN design and derivation is summarized in Section 3.1 of this review.

Revised BOIN

The information presented in the original FFP submission document, including the simulation studies, focuses on the local BOIN design under the specific case where $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ (the quantities $\pi_{0j}, \pi_{1j}, \pi_{2j}$ are defined in Section 3.1 of this review), which is referred to as the case of the non-informative prior. Therefore, our FFP determination applies only to the local BOIN design under the non-informative prior, as the FFP review was requested for this specific form of the BOIN design. We focus here on the local BOIN design under the non-informative prior because versions of the BOIN design outside of these conditions are not within the scope of the present FFP submission, but this focus is not necessarily a reflection on the methodology itself. Further detailed information would be needed to make a determination on the BOIN design outside of the conditions of the local design and non-informative prior. In Section 3, however, we discuss the local BOIN design in the more general case where the non-informative prior is not required. Additional research may be useful to evaluate the properties of the BOIN design in cases when the non-informative prior condition is not required.

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Finally, with regards to the simulation results presented in the Applicant's submission document, where several phase I trial designs were compared, BOIN generally performed well in the simulation scenarios considered. This does not imply that other methods did not also perform well in the simulation scenarios. As is generally the case, findings from the simulation studies are driven by the specific parameters and models used to construct the simulation scenarios. Also, in the simulation studies of Zhou, Yuan, and Nie (2018), which are summarized in the Applicant's submission document, specific performance metrics were defined to evaluate accuracy, safety, and reliability of the designs, and the conclusions of their simulation studies are based on these metrics. If any underlying assumption is violated, the BOIN method may not be able to estimate the dose toxicity relationship accurately. For example, in instances with combination therapy, where the dose toxicity relationship may not be monotonically increasing or also in the case of therapies with delayed onset of toxicities.

BOIN的cond's

1.1 Recommendations

Under the non-informative prior, the local BOIN design, in its revised form, can be designated fit-for-purpose. Our determination is based on the Applicant's original submission, the Applicant's responses to our information requests (which present the revised form of the local BOIN design), and the relevant statistical literature, including the papers by Liu and Yuan (2015) and Zhou, Yuan, and Nie (2018). This recommendation does not preclude the availability and use of other methods for phase I dose finding clinical trials, including potentially the BOIN design itself outside of the local design and informative prior. In practice, one should carefully consider the requirements of

the specific situation when considering candidate designs for a dose finding clinical trial; and when deciding on the trial design, one should carefully evaluate the scientific validity of the candidate designs in the context of the intended application.

2 Background and Submission Overview

2.1 Background

A submission was received on March 9, 2020 from Dr. Ying Yuan and Dr. J. Jack Lee, The University of Texas MD Anderson Cancer Center, under the Fit-for-Purpose (FFP) initiative, intended to support the use of the Bayesian Optimal Interval (BOIN) Design as a statistical methodology for phase I dose finding clinical trials. The submission states that as a model-assisted design, BOIN combines the simplicity of an algorithm-based design (for example, the convention 3+3 design), and superiority of a model-based design (for example, the continuous reassessment method). During the review of this submission, the Agency sent information requests to Dr. Yuan on October 28, 2020, December 22, 2020, and March 18, 2021. The submitter provided responses to the information requests and questions posed by the Agency on November 2, 2020, January 7, 2021, and March 28, 2021. Those interactions led to revisions in the methodology that was evaluated and is referred to as the revised form of the BOIN design and derivation.

Previous interactions between the Agency and Dr. Ying Yuan include an initial face-to-face meeting with Dr. Yuan on September 26, 2019 to discuss the initial submission package. On December 13, 2019, the Agency invited Dr. Yuan to submit a package for FFP determination for the BOIN design.

2.2 Overview of Submission

The Applicant's submission document provides a brief introduction to the BOIN methodology and refers to the paper by Liu and Yuan (2015) for more technical details. Liu and Yuan (2015) describe the BOIN design as a method to find the maximum tolerated dose (MTD) of a new drug, where the MTD is defined as the dose with dose limiting toxicity (DLT) probability that is closest to the target toxicity probability. Liu and Yuan (2015) present two versions of the BOIN design, which they refer to as the local BOIN design, and the global BOIN design. The information presented in the FFP submission document applies only to the local BOIN design, and therefore, our review of this FFP submission applies only to the local BOIN design. Throughout this review document unless we explicitly mention the global BOIN design, we use the term BOIN design to refer to the local BOIN design as described by of Liu and Yuan (2015).

MTD定义

The submission document mentions examples of oncology trials where the BOIN design has been used, and presents an example demonstrating the implementation of the design. The submission

document summarizes simulation results from the paper by Zhou, Yuan, and Nie (2018). Zhou, Yuan, and Nie (2018) present simulation results evaluating several methods, including BOIN method to the continual reassessment method (CRM), dose escalation with overdose control (EWOC), Bayesian logistic regression model (BLRM), the modified toxicity probability interval (mTPI) and keyboard (equivalently mTPI-2) designs. Metrics for evaluating accuracy, safety, and reliability of these methods were assessed through numerical simulations. The submission document also briefly summarizes results of a simulation study by Ruppert and Shoben (2018) where the impact of some phase I trial designs on the overall outcome of the drug development process was evaluated for a drug considered to be safe and efficacious. Finally, the submission document mentions software implementations of the BOIN design for generating dose escalation and de-escalation rules and conducting simulations. The software implementations that are mentioned include an R package called BOIN, a BOIN Shiny app, and a Windows desktop program. 软件实施

2.3 Data Sources

The primary materials used to conduct this review include the Applicant's submission document, the responses to each of our three information requests, and the papers by Liu and Yuan (2015) and Zhou, Yuan, and Nie (2018).

3 Statistical Evaluation of the Methodological Development

The Applicant's original submission contains a description and brief introduction to the BOIN methodology and refers to Liu and Yuan (2015) for more technical details. Therefore, our methodological review focused on the derivation of the design as presented in Liu and Yuan (2015). During our review, we found that some technical issues in the derivations presented by Liu and Yuan (2015) which needed to be corrected. We prepared detailed comments and sent them to the Applicant as an information request, and the Applicant responded with an updated design and derivation. We reviewed the revised design and derivation and provided additional comments to the Applicant. Through this iterative process, we sent a total of three information requests to the Applicant, each time receiving a further revised version of the design and/or derivation, which improved the rigorousness of the methodological development of the BOIN design. In view of the iterative nature of these revisions, our determination applies to the most refined version of the revised BOIN design and derivation provided to us by the Applicant. This version of the revised BOIN design and derivation is summarized in Section 3.1.

3.1 Description of BOIN Methodology in its Revised Form

The following description of the BOIN methodology is based on information from Liu and Yuan (2015) while also incorporating the changes and additional information in the revised derivation provided by the Applicant in response to our information requests. This description summarizes the Applicant's revised design and derivation. As noted above, the revised design and derivation has been iteratively refined during this review, and the summary that follows is based on the most refined version of the BOIN methodology presented to us.

Assume that a total of J prespecified doses are under investigation in the study and let ϕ denote the target toxicity probability specified by physicians. It is assumed that the dose levels are ordered such that dose level $j = 1$ represents the lowest dose under investigation in the study, dose level $j = 2$ represents the second lowest dose under investigation in the study, and so on with dose level $j = J$ representing the highest dose under investigation in the study. At dose level j, let n_j denote the total number of patients treated, m_j denote the number of patients who had dose limiting toxicity (DLT), and define $\hat{p}_j = m_j/n_j$. Consider a class of designs as follows.

j=1 lowest
...
j=J highest

1. Patients in the first cohort are treated at the lowest dose level.

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2. Let j denote the current dose level. Assign a dose to the next cohort of patients as follows.
   - If $\hat{p}_j \leq \lambda_{1j}(n_j, \phi)$, then escalate the dose level to $j + 1$ (in the case $j = J$, if $\hat{p}_j \leq \lambda_{1j}(n_j, \phi)$, then the dose remains at level $j = J$).
   - If $\hat{p}_j > \lambda_{2j}(n_j, \phi)$, then de-escalate the dose to level $j - 1$ (in the case $j = 1$, if $\hat{p}_j > \lambda_{2j}(n_j, \phi)$, then the dose remains at level $j = 1$).
   - Otherwise, i.e., $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$, then retain the same dose level, which is level j.

   Here $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ are functions of j, n_j and ϕ such that $\lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi)$.

3. Repeat step 2 until the maximum sample size is reached or the trial is terminated due to excessive toxicity.

Reviewer's Comment. The design presented above, which is the revised version, differs from the design in Liu and Yuan (2015, page 509) in the following aspects.

- The condition for de-escalating the dose originally was $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$, but has been changed to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$.
- The condition for retaining the same dose level originally was $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$, but has been changed to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$.
- Originally it was stated that $0 \leq \lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi) \leq 1$; however, this condition has been replaced by the condition $\lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi)$.

The reasons for these changes will be explained in Section 3.2.1.

■

Next the Applicant considers how to choose $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ to minimize the probability of making an incorrect decision. For notational brevity, $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ are denoted as λ_{1j} and λ_{2j}. Let p_j denote the true toxicity probability of dose level j for $j = 1, \ldots, J$. For each $j = 1, \ldots, J$, the following point hypotheses H_{0j}, H_{1j}, and H_{2j} are formulated:

$$H_{0j}: p_j = \phi \text{ (on target)},$$

$$H_{1j}: p_j = \phi_1 \text{ (underdosing)},$$

$$H_{2j}: p_j = \phi_2 \text{ (overdosing)},$$

where $0 < \phi_1 < \phi < \phi_2 < 1$ and ϕ_1 denotes the highest toxicity probability that is deemed subtherapeutic such that dose escalation should be made, and ϕ_2 denotes the lowest toxicity probability that is deemed overly toxic such that dose de-escalation is required. Liu and Yuan (2015) recommend the default values

$$\phi_1 = 0.6\phi \text{ and } \phi_2 = 1.4\phi.$$

While the above are default recommendations for ϕ_1 and ϕ_2, the Applicant mentions that the values of ϕ_1 and ϕ_2 can be calibrated to achieve a particular requirement of the trial.

The probability of making an incorrect decision is formulated as follows. Let j denote the current dose level and let $\mathcal{R}$ denote the decision to retain the current dose level j, let $\mathcal{E}$ denote the decision to escalate the dose level to $j + 1$, and let $\mathcal{D}$ denote the decision to de-escalate the dose level to $j - 1$. Also let $\bar{\mathcal{R}}$ denote the decision not to retain the dose level j (that is, to to de-escalate the dose level to $j - 1$ or escalate the dose to level $j + 1$), let $\bar{\mathcal{E}}$ denote the decision not to escalate the dose level to $j + 1$ (that is to de-escalate the dose to level $j - 1$ or retain the dose level j), and let $\bar{\mathcal{D}}$ denote the decision not to de-escalate the dose level to $j - 1$ (that is to retain the dose level j or escalate the dose level to $j + 1$). Under each of the three hypotheses H_{0j}, H_{1j}, and H_{2j} the correct and incorrect decisions are assumed to be as follows.

- If the hypothesis $H_{0j}: p_j = \phi$ (on target) is true, then the correct decision is $\mathcal{R}$, and the incorrect decision is $\bar{\mathcal{R}}$.
- If the hypothesis $H_{1j}: p_j = \phi_1$ (underdosing) is true, then the correct decision is $\mathcal{E}$, and the incorrect decision is $\bar{\mathcal{E}}$.
- If the hypothesis $H_{2j}: p_j = \phi_2$ (overdosing) is true, then the correct decision is $\mathcal{D}$, and the incorrect decision is $\bar{\mathcal{D}}$.

Reviewer's Comment. The general form of the dose escalation/de-escalation/retainment rules, and the characterization of correct and incorrect decisions under each hypothesis H_{0j}, H_{1j}, H_{2j} are intuitively reasonable under the assumption of a monotonically increasing dose-toxicity relationship in the sense that $p_1 \leq p_2 \leq \cdots \leq p_J$.

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Under the Bayesian paradigm, each of the hypotheses H_{0j}, H_{1j}, and H_{2j} is assigned a prior probability of being true, denoted by

假如考虑informative prior

$$\pi_{0j} = P(H_{0j}), \pi_{1j} = P(H_{1j}), \pi_{2j} = P(H_{2j}).$$

Then the Applicant obtains the probability of making an incorrect decision at each of the dose assignments, denoted by $\alpha(\lambda_{1j}, \lambda_{2j})$, as follows:

$$\begin{aligned}\alpha(\lambda_{1j}, \lambda_{2j}) &= P(H_{0j})P(\bar{\mathcal{R}}|H_{0j}) + P(H_{1j})P(\bar{\mathcal{E}}|H_{1j}) + P(H_{2j})P(\bar{\mathcal{D}}|H_{2j}) \\ &= P(H_{0j})P(m_j \le n_j\lambda_{1j} \text{ or } m_j > n_j\lambda_{2j}|H_{0j}) + P(H_{1j})P(m_j > n_j\lambda_{1j}|H_{1j}) \\ &\quad + P(H_{2j})P(m_j \le n_j\lambda_{2j}|H_{2j}) \\ &= \pi_{0j}\{\text{Bin}(n_j\lambda_{1j}; n_j, \phi) + 1 - \text{Bin}(n_j\lambda_{2j}; n_j, \phi)\} + \pi_{1j}\{1 - \text{Bin}(n_j\lambda_{1j}; n_j, \phi_1)\} \\ &\quad + \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2)\end{aligned}$$

where $\text{Bin}(b; n, p)$ denotes the cumulative distribution function of the $\text{Binomial}(n, p)$ distribution evaluated at the value b. The decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$ is then written as

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j}$$

Equation 1

where

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1)$$

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi).$$

Equation 2

Reviewer's Comment.

The formulas above for the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$ hold if $j \in \{2,3,\ldots,J-1\}$. However, adjustment is needed if $j = 1$ or $j = J$. Dose level $j = 1$ represents the lowest dose level under investigation in the study, and hence it is not possible to de-escalate the dose to level $j - 1$ if $j = 1$. Therefore, if $j = 1$, then the dose assignment rule in step 2 of the class of designs is the following.

When the current dose level is $j = 1$, assign a dose to the next cohort of patients as follows.

- If $\hat{p}_1 \le \lambda_{11}(n_1, \phi)$, then escalate the dose level to level 2.
- If $\hat{p}_1 > \lambda_{11}(n_1, \phi)$, then retain the same dose level which is level 1.

Thus, in the BOIN framework as presented above, if $j = 1$, then the decision error probability is

$$
\begin{aligned}
&P(H_{01})P(\bar{\mathcal{R}}|H_{01}) + P(H_{11})P(\bar{\mathcal{E}}|H_{11}) + P(H_{21})P(\bar{\mathcal{D}}|H_{21}) \\
&\qquad = P(H_{01})P(m_1 \le n_1\lambda_{11}\,|H_{01}) + P(H_{11})P(m_1 > n_1\lambda_{11}|H_{11}) + P(H_{21}) \\
&\qquad = \pi_{01}\mathrm{Bin}(n_1\lambda_{11}; n_1,\, \phi) + \pi_{11}\{1 - \mathrm{Bin}(n_1\lambda_{11}; n_1, \phi_1)\} + \pi_{21} \\
&\qquad = \pi_{01}\mathrm{Bin}(n_1\lambda_{11}; n_1,\, \phi) - \pi_{11}\mathrm{Bin}(n_1\lambda_{11}; n_1, \phi_1) + \pi_{11} + \pi_{21} \\
&\qquad = \alpha_1(\lambda_{11}) + \pi_{11} + \pi_{21}
\end{aligned}
$$

Equation 3

using $\alpha_1(\lambda_{1j})$ as defined in Equation 2. Dose level $j = J$ represents the largest dose under investigation in the study, and hence it is not possible to escalate the dose to level $j + 1$ if $j = J$. Therefore, if $j = J$, then the dose assignment rule in step 2 of the class of designs is the following.

When the current dose level is $j = J$, assign a dose to the next cohort of patients as follows.

- If $\hat{p}_J > \lambda_{2J}(n_J, \phi)$, then de-escalate the dose to level $J - 1$.
- If $\hat{p}_J \le \lambda_{2J}(n_J, \phi)$, then retain the same dose level, which is level J.

Thus, in the BOIN framework as presented above, if $j = J$, then the decision error probability is

$$
\begin{aligned}
&P(H_{0J})P(\bar{\mathcal{R}}|H_{0J}) + P(H_{1J})P(\bar{\mathcal{E}}|H_{1J}) + P(H_{2J})P(\bar{\mathcal{D}}|H_{2J}) \\
&\qquad = P(H_{0J})P(\, m_J > n_J\lambda_{2J}|H_{0J}) + P(H_{1J}) + P(H_{2J})P(m_J \le n_J\lambda_{2J}|H_{2J}) \\
&\qquad = \pi_{0J}\{1 - \mathrm{Bin}(n_J\lambda_{2J}; n_J, \phi)\} + \pi_{1J} + \pi_{2J}\mathrm{Bin}(n_J\lambda_{2J}; n_J, \phi_2) \\
&\qquad = \pi_{2J}\mathrm{Bin}(n_j\lambda_{2J}; n_J, \phi_2) - \pi_{0J}\mathrm{Bin}(n_J\lambda_{2J}; n_J, \phi) + \pi_{0J} + \pi_{1J} \\
&\qquad = \alpha_2(\lambda_{2J}) + \pi_{0J} + \pi_{1J}
\end{aligned}
$$

Equation 4

using $\alpha_2(\lambda_{2J})$ as defined in Equation 2. The Applicant's approach to minimize the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$ with respect to λ_{1j} and λ_{2j} is to minimize $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ separately, and therefore, it follows from Equation 3 and Equation 4, that this approach also applies to minimize the decision error in the cases $j = 1$ and $j = J$.

■

To minimize $\alpha(\lambda_{1j}, \lambda_{2j})$, the Applicant minimizes $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ separately with regard to λ_{1j} and λ_{2j}, respectively. Let $I(\cdot)$ denote an indicator function. The Applicant obtains that $\alpha_1(\lambda_{1j})$ is minimized when

$$
\lambda_{1j} \in \begin{cases} \left[1 - \dfrac{I(y^* = n_j)}{n_j},\ \infty\right) & \text{if } y^* \ge n_j \\ \left[\dfrac{\lceil y^* \rceil - 1}{n_j},\ \dfrac{\lfloor y^* \rfloor + 1}{n_j}\right) & \text{if } 0 < y^* < n_j \\ \left(-\infty,\ \dfrac{I(y^* = 0)}{n_j}\right) & \text{if } y^* \le 0 \end{cases}
$$

where

$$y^* = \frac{n_j \log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)},$$

and $\alpha_2(\lambda_{2j})$ is minimized when

$$\lambda_{2j} \in \begin{cases} \left[1 - \frac{I(y^{**} = n_j)}{n_j}, \infty\right) \text{ if } y^{**} \geq n_j \\ \left[\frac{\lceil y^{**} \rceil - 1}{n_j}, \frac{\lfloor y^{**} \rfloor + 1}{n_j}\right) \text{ if } 0 < y^{**} < n_j \\ \left(-\infty, \frac{I(y^{**} = 0)}{n_j}\right) \text{ if } y^{**} \leq 0 \end{cases}$$

where

$$y^{**} = \frac{n_j \log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)}.$$

As discussed in the Applicant's revised derivation, one specific values of λ_{1j} that minimizes $\alpha_1(\lambda_{1j})$ is

$$\lambda_{1j}^* = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)}$$

equation 5,6是一般形式

informative prior下参考这种形式。

Equation 5

and one specific value of λ_{2j} that minimizes $\alpha_2(\lambda_{2j})$ is

$$\lambda_{2j}^* = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)}.$$

Equation 6

This solution, namely λ_{1j}^* as defined in Equation 5 and λ_{2j}^* as defined in Equation 6, is the solution provided by Liu and Yuan (2015), as the values of λ_{1j} and λ_{2j}, respectively, that minimize the decision error probability.

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When the non-informative prior $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ is used (the default setting recommended by the Applicant), the optimal dose escalation and de-escalation boundaries λ_{1j}^* as defined in Equation 5 and λ_{2j}^* as defined in Equation 6 can be expressed as

$$\lambda_{1j}^* = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)}$$

Equation 7

and

$$\lambda_{2j}^* = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right)}.$$

Equation 8

The boundaries in Equation 7 and Equation 8 remain the same for all dose levels j and also remain the same for all n_j. Therefore, the same pair of boundaries can be used throughout the trial if the non-informative prior is used, and the boundaries λ_{1j}^* and λ_{2j}^* can be written as λ_1^* and λ_2^*, respectively. The Applicant notes that the boundaries in Equation 7 and Equation 8 are the ones recommended by Liu and Yuan (2015), implemented in current BOIN software, and used in practice.

If an informative prior is used (that is, if π_{0j}, π_{1j}, π_{2j} are chosen such that the condition $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ does not hold), then with λ_{1j}^* and λ_{2j}^* as defined in Equation 5 and Equation 6, respectively, it is possible that $\lambda_{1j}^* > \lambda_{2j}^*$. If $\lambda_{1j}^* > \lambda_{2j}^*$, then these boundaries cannot be used since they do not satisfy the condition $\lambda_{1j}^* \leq \lambda_{2j}^*$; and instead, a numerical search can be used to find values of λ_{1j} and λ_{2j} that minimize the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$ under the condition $\lambda_{1j} \leq \lambda_{2j}$. The Applicant notes that this issue will not occur when the non-informative prior is used (that is, when $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$). The issue does not occur when $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ because, the condition $0 < \phi_1 < \phi < \phi_2 < 1$, implies that

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$$0 < \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} < \phi < \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right)} < 1.$$

The Applicant has provided the following revised version of Theorem 1 of Liu and Yuan (2015).

Theorem 1. Under the non-informative prior $\pi_{0j} = \pi_{1j} = \pi_{2j}$, the optimal dose escalation boundary λ_1^* is the boundary at which $P(H_1|y_j, n_j) \geq P(H_0|y_j, n_j)$, and the optimal dose de-escalation boundary λ_2^* is the boundary at which $P(H_2|y_j, n_j) > P(H_0|y_j, n_j)$.

Reviewer's Comment. In the above statement of Theorem 1, the subscript j is dropped from λ_{1j}^*, λ_{2j}^*, H_{0j}, H_{1j}, and H_{2j}. Also, y_j is used instead of m_j to denote the number of patients who had DLT at the current dose level j.

■

添加剂量终止策略，保证受试者安全

The BOIN design also incorporates the following dose elimination rule (page 515 of Liu and Yuan, 2015):

If $P(p_j > \phi|m_j, n_j) > 0.95$ and $n_j \geq 3$, dose levels j and higher are eliminated from the trial, and the trial is terminated if the first dose level is eliminated, where $P(p_j > \phi|m_j, n_j) > 0.95$ can be evaluated on the basis of a beta-binomial model, assuming that m_j follows a binomial distribution (with size and probability parameters n_j and p_j) and p_j follows a vague beta prior, e.g. $p_j \sim \text{beta}(1,1)$. 终止策略下，还需指定prior

Once the trial is completed the maximum tolerated dose (MTD) needs to be selected. Let $\tilde{p}_1, \ldots, \tilde{p}_J$ denote the isotonically transformed values of the observed toxicity probabilities $\hat{p}_1, \ldots, \hat{p}_J$. The MTD is selected as the dose level j^* for which $\tilde{p}_{j^*}$ is closest to ϕ. In the case that there are ties for $\tilde{p}_{j^*}$, if $\tilde{p}_{j^*} < \phi$, then the highest dose level is selected from the ties as the MTD, and if $\tilde{p}_{j^*} > \phi$, then the lowest dose level is selected from the ties as the MTD.

ties是什么

Reviewer's Comment. The discussion in Liu and Yuan (2015, page 514) on selecting the MTD does not specify how to select the MTD if there are ties for $\tilde{p}_{j^*}$ and $\tilde{p}_{j^*} = \phi$.

■

3.2 Comments on the Methodological Development

The Applicant's revised methodology and derivations, as summarized above in Section 3.1 address some technical issues in the derivations in Liu and Yuan (2015) that were identified during this review. Detailed technical comments appear in the three information requests that were sent to the Applicant. In the following Section 3.2.1 we describe the technical issues and explain how the revised methodology and derivations address these issues. Then in Section 3.2.2 we present some additional comments on the methodology.

3.2.1 Comments Addressed by the Revised BOIN Methodological Development

The following comments describe some issues pertaining to the original version of the BOIN design as presented in Liu and Yuan (2015), and explain how the revised BOIN methodological development, as summarized in Section 3.1, addresses these issues.

1. There was an issue with the original expression of the decision error probability and its minimization as presented in Liu and Yuan (2015). As explained in Comment 1 of Information Request 1, the last equality of Equation (1) of Liu and Yuan (2015) does not hold in general. Furthermore, in Appendix A of Liu and Yuan (2015), the decision error probability is written as $\alpha(\lambda_{1j}, \lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j}$ where $\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1)$ and $\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi)$. Note that this definition of $\alpha_2(\lambda_{2j})$ from Appendix A of Liu and Yuan (2015) differs from the definition of $\alpha_2(\lambda_{2j})$ in the Applicant's revised derivation as summarized in Section 3.1 (see Equation 2). Comment 2 of Information Request 1 provides an example where the function $\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j} - 1; n_j, \phi)$ is not minimized at the value claimed in Liu and Yuan (2015). To correct these issues, the Applicant made the following revisions.

   a. The condition for de-escalating the dose originally was $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$, but has been changed to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$.
   b. The condition for retaining the same dose level originally was $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$, but has been changed to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$.

   The Applicant has re-derived and minimized the decision error probability under these revisions to the design, as summarized in Section 3.1, to address these issues.

2. Liu and Yuan (2015) originally stated the condition $0 \leq \lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi) \leq 1$. However, Example 2 in Information Request 2 presents an example where the decision error probability is minimized when $\lambda_1 \in (-\infty, 0)$ and $\lambda_2 \in [1, \infty)$; thus, demonstrating that the minimizing values can occur outside of the interval [0,1]. In view of this observation, and in view of the changes to the dose de-escalation and dose retainment conditions (discussed in the preceding comment) under which the situation $\lambda_{1j}(n_j, \phi) = \lambda_{2j}(n_j, \phi)$ would not cause a problem in the decision rules; the condition $0 \leq \lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi) \leq 1$ has been replaced by the condition $\lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi)$ in the revised BOIN methodological development. Note that in addition to changing $\lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi)$ to $\lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi)$, the revised condition also allows $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ to occur outside of the interval [0,1].

3. The revised BOIN methodological development clarifies that the decision error probability is minimized over a set of values for λ_{1j} and λ_{2j}, not just at a single point; and the Applicant has

formulated the general solution. Our information requests present some numerical examples that illustrate this point.

4. The revised BOIN methodological development clarifies that if the condition $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ does not hold, then the decision boundaries λ_{1j}^* and λ_{2j}^* defined by

$$\lambda_{1j}^* = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}}$$

and

$$\lambda_{2j}^* = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right\}}$$

can be such that $\lambda_{1j}^* > \lambda_{2j}^*$. If $\lambda_{1j}^* > \lambda_{2j}^*$, then these boundaries cannot be used since they do not satisfy the condition $\lambda_{1j}^* \leq \lambda_{2j}^*$; and instead, a numerical search can be used to find values of λ_{1j} and λ_{2j} that minimize the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$ under the condition $\lambda_{1j} \leq \lambda_{2j}$. An example to illustrate this situation is presented in Example 3 of Information Request 2. The revised derivation also points out that this issue will not occur when the non-informative prior is used (that is, when $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$). The issue does not occur when $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ because, the condition $0 < \phi_1 < \phi < \phi_2 < 1$, implies that

$$0 < \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} < \phi < \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right)} < 1.$$

5. In the revised BOIN methodological development, Theorem 1 is re-stated under the assumption that $\pi_{0j} = \pi_{1j} = \pi_{2j}$. The assumption $\pi_{0j} = \pi_{1j} = \pi_{2j}$ is included to ensure that $\lambda_{1j}^* \leq \lambda_{2j}^*$ (where λ_{1j}^* and λ_{2j}^* are defined by Equation 5 and Equation 6, respectively). If the assumption $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ is omitted from Theorem 1, then it is possible that $\lambda_{1j}^* > \lambda_{2j}^*$, and if $\lambda_{1j}^* > \lambda_{2j}^*$, then the conclusion of Theorem 1 may not hold.

6. The submission package describes simulation studies to assess the operating characteristics of phase I trial designs, including the BOIN design. The simulation results are discussed later in Section 4 of this review. These simulation results use the original version of the BOIN design as described in Liu and Yuan (2015), not the revised design described above in Section 3.1. However, the revisions to the BOIN design will not affect these specific simulation results because of the following reasons.

a. The simulation results presented in the submission package are for the case when $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$. As noted above, the condition $0 < \phi_1 < \phi < \phi_2 < 1$, implies that

$$0 < \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} < \phi < \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} < 1,$$

and hence the condition $0 < \lambda_{1j}^* < \lambda_{2j}^* < 1$ holds in the simulation scenarios. The simulation scenarios cannot result in $\lambda_{1j}^* > \lambda_{2j}^*$, which, as discussed above, is possible if $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ does not hold.

b. The simulation scenarios considered are such that λ_{2j}^* does not take any value in the finite set $\left\{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j-1}{n_j}, \frac{n_j}{n_j}\right\}$, and hence the event $\hat{p}_j = \lambda_{2j}^*$ has probability zero in the simulation scenarios. Also, as noted above, the condition $0 < \lambda_{1j}^* < \lambda_{2j}^* < 1$ holds in the simulation scenarios. Hence changing the de-escalation condition from $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$ and changing the retainment condition from $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$ to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$ will not change the escalation, de-escalation, or retainment decisions in the simulated trials.

3.2.2 Additional Comments

The following are some additional comments on the methodological development of the BOIN design.

剂量边界的先验与dose elimination的先验不同；不一致，dose elimination下，Pi是能取[0,1]内的任何值的。dose finding下Pi只能以不同概率去“离散地”取那三个值

7. The BOIN methodology is developed under a Bayesian paradigm, and we note that the prior distribution used to derive the values λ_{1j} and λ_{2j} (which determine the conditions for dose escalation, de-escalation, and retainment) differs from the prior distribution used to obtain the dose elimination rule. The values λ_{1j} and λ_{2j} are chosen to minimize the probability of making an incorrect decision under the Bayesian paradigm where the prior distribution of p_j is such that $P(p_j = \phi) = \pi_{0j}$, $P(p_j = \phi_1) = \pi_{1j}$, $P(p_j = \phi_2) = \pi_{2j}$, where $\pi_{0j} + \pi_{2j} + \pi_{2j} = 1$; that is, under this prior distribution p_j takes values ϕ, ϕ_1, ϕ_2 with probabilities π_{0j}, π_{1j}, π_{2j}, respectively. However, the dose elimination rule is obtained under the assumption that the prior distribution for p_j is the beta(1,1) distribution. The beta(1,1) distribution is equivalent to the continuous uniform distribution over the interval $(0,1)$

8. Let N_j denote the total number of patients that are treated at dose level j during the trial, for $j = 1, \ldots, J$. We note that $(N_1, \ldots, N_J)$ is a random vector. In contrast, at each decision-making

step, the BOIN design is derived by minimizing the decision error probability at the current step by treating the cumulative number of subjects treated at the current dose level j, namely n_j, as fixed.

9. There exist scenarios where there is more than one design that minimizes the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$. Two examples of such scenarios are presented below. The following Example 1 is also discussed in Comments 3 and 4 of Information Request 3, and Comment 4 of Information Request 3 specifically discusses the non-uniqueness situation.

有可能在同个优化条件下，有>1个优化方案

Example 1. Suppose $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$, $\pi_{2j} = 0.15$, $\pi_{0j} = (0.15)(1.4^3) = 0.4116$, $\pi_{1j} = 1 - \pi_{0j} - \pi_{2j} = 0.4384$, and suppose $j \in \{2,3,\dots,J\}$ so that $j > 1$. It can be shown here that $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ (as defined in Equation 2) are minimized, respectively, when $\lambda_{1j} \in [0,1/3)$ and $\lambda_{2j} \in [2/3,\infty)$, and observe the constraint $\lambda_{1j} \leq \lambda_{2j}$ is satisfied if $\lambda_{1j} \in [0,1/3)$ and $\lambda_{2j} \in [2/3,\infty)$. Hence, if one chooses $\lambda_{1j} \in [0,1/3)$ and $\lambda_{2j} \in [2/3,1)$, then if $\hat{p}_j = 1$, the current dose level would be de-escalated to level $j-1$; and if one chooses $\lambda_{1j} \in [0,1/3)$ and $\lambda_{2j} \in [1,\infty)$, then if $\hat{p}_j = 1$, the current dose would be retained. Thus, this example shows that minimizing $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$, may not lead to a unique design. Observe that in this case, applying Equation 5 and Equation 6 we obtain $\lambda_{1j}^* \approx 0.2299$ and $\lambda_{2j}^* = 1$; and hence if $\hat{p}_j = 1$, while minimization of $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$, allows for either retaining or de-escalation, the choice of the BOIN design would be to retain the current dose level.

Example 2. Suppose $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$, $\pi_{0j} = (0.6)\big(1-(0.6)(0.25)\big)^2 = 0.4335$, $\pi_{1j} = (1-0.25)^2 = 0.5625$, $\pi_{2j} = 1 - \pi_{0j} - \pi_{1j} = 0.004$, and suppose $j \in \{1,2,\dots,J-1\}$ so that $j < J$. It can be shown here that $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ (as defined in Equation 2) are minimized, respectively, when $\lambda_{1j} \in [0,2/3)$ and $\lambda_{2j} \in [1,\infty)$, and observe the constraint $\lambda_{1j} \leq \lambda_{2j}$ is satisfied if $\lambda_{1j} \in [0,2/3)$ and $\lambda_{2j} \in [1,\infty)$. Hence, if one chooses $\lambda_{1j} \in [0,1/3)$ and $\lambda_{2j} \in [1,\infty)$, then if $\hat{p}_j = 1/3$, the current dose level would be retained; and if one chooses $\lambda_{1j} \in [1/3,2/3)$ and $\lambda_{2j} \in [1,\infty)$, then if $\hat{p}_j = 1/3$, the dose level would be escalated to dose level $j+1$. Thus, this example shows that minimizing $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$, may not lead to a unique design. Observe that in this case, applying Equation 5 and Equation 6 we obtain $\lambda_{1j}^* = 1/3$ and $\lambda_{2j}^* \approx 3.5552$; and hence if $\hat{p}_j = 1/3$, while minimization of $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$, allows for either retaining or escalation, the choice of the BOIN design would be to escalate the dose to level $j+1$.

上面两个例子都是dose决策边界不唯一的，实际使用要注意。

The two examples above were carefully constructed to illustrate the point that minimization of the decision error probability $\alpha(\lambda_{1j}, \lambda_{2j})$, subject to $\lambda_{1j} \leq \lambda_{2j}$, might not lead to a unique

design. Nevertheless, in practice one may want to be aware of this possibility of non-uniqueness and one may want to verify if the chosen values of π_{0j}, π_{1j}, π_{2j}, ϕ, ϕ_1, ϕ_2, and the cohort size (noting that n_j can change throughout the trial) will result in a unique design.

4 Simulation

4.1 Description of Simulation

simulation study来源文献

The Applicant submitted simulation study results published by Zhou, Yuan, and Nie (ZYN, 2018). The simulation study performed by ZYN evaluated and compared the operating characteristics of the BOIN design with three model-based phase I designs, the continual reassessment method (CRM), dose escalation with overdose control (EWOC), and Bayesian logistic regression model (BLRM), and two model-assisted designs, the modified toxicity probability interval (mTPI) and keyboard (equivalently mTPI-2) designs. The results for each design were evaluated relative to the 3+3 design.

Model-Based Designs

CRM. The CRM (O'Quigley et al., 1990) is a model-based design that assumes a parametric model for the dose–toxicity curve. After each patient cohort is treated, the CRM updates the estimate of the dose–toxicity curve based on the accumulating DLT data across all dose levels and assigns the next cohort of patients to the "optimal" dose, defined as the dose whose posterior mean estimate of the DLT probability is closest to the target ϕ. The trial continues in this manner until the prespecified sample size is exhausted. At that point, the MTD is selected as the dose with an estimated DLT probability closest to φ. The particular CRM the Applicant considered is a modified version of CRM, sometimes referred as modified CRM, which does not allow dose skipping during the dose escalation.

EWOC. The EWOC is a modification of the CRM. The EWOC employs a two-parameter logistic regression model to provide extra flexibility to model the dose–toxicity curve. Similar to the CRM, the EWOC continuously updates the estimate of the dose–toxicity curve based on the accumulating data and assigns the next cohort of patients to the currently estimated "optimal" dose. EWOC uses a different definition of the optimal dose to actively control the risk of overdosing and defines the optimal dose as the highest dose whose posterior probability of being higher than the MTD is equal to or less than a prespecified threshold a, with the recommended value of 25%. In the EWOC, dose skipping is not allowed, and dose escalation and de-escalation are restricted to one level at a time.

BLRM. The BLRM uses the similar two-parameter logistic regression model as the EWOC, and similar to CRM and EWOC, the BLRM continuously updates the estimate of the dose – toxicity curve based on the accumulating data and assigns the next cohort of patients to the currently estimated “optimal” dose, where the “optimal” dose is defined as the dose that has the highest

posterior probability of being within (δ_1, δ_2), and (δ_1, δ_2) denotes the proper dosing interval meaning that any dose with the DLT probability within that interval can be approximately accepted as the MTD. Typically, BLRM imposes an overdose control rule similar to the EWOC. In the BLRM, dose skipping is not allowed.

Model-Assisted Designs

mTPI design. The mTPI design specified three intervals: the proper dosing interval (δ_1, δ_2), the underdosing interval $(0, \delta_1)$, and the overdosing interval $(\delta_2, 1)$. The Mtpi design uses a beta-binomial model locally to describe the toxicities at the current dose only and makes the decision of dose escalation and de-escalation based on the unit probability mass (UPM) of the three intervals. The UPM of an interval is defined as the posterior probability that the DLT probability of the current dose is within the interval divided by the length of the interval. Therefore, UPM of an interval is equal to the area under the posterior distribution curve within the interval divided by the interval length. Let UPM1, UPM2, and UPM3 denote the UPM for the underdosing, proper dosing, and overdosing intervals, respectively. The mTPI design determines dose escalation/de-escalation as follows:

- Escalate to the next higher dose if UPM1 is the maximum of the three UPMs.
- Stay at the current dose if UMP2 is the maximum of the three UPMs
- De-escalate to the next lower dose if UMP3 is the maximum of the three UPMs

The trial continues until the prespecified sample size is reached, and the MTD is selected as the dose for which the isotonic estimate of the DLT probability is closest to ϕ. In mTPI design, if the observed data suggest that the posterior probability that the DLT rate of the current dose is greater than the target ϕ exceeds 0.95, the current dose and higher doses are excluded from the trial, and if the lowest dose is excluded, the trial is terminated.

Different from the model-based designs, the mTPI design determines the dose escalation and de-escalation decision at each of the dose levels before the onset of the trial.

Keyboard design. The Keyboard design is a modified version of mTPI design. The difference is that it constructs a series of equal-width dosing intervals, referred to as keys, to guide dose escalation and de-escalation. By eliciting a proper dosing interval (referred to as the target key) from clinicians, the keyboard design forms series of equal-width keys on both sides of the target key, then the decision of dose escalation and de-escalation is determined based on the location of the "strongest" key, relative to the target key, where "strongest" key is defined as the key that has the largest area under the posterior distribution curves of DLT probability under the current dose. The strongest key represents the interval in which the DLT probability under the current dose is most likely located. Therefore, if the strongest key is on the left side of (i.e., smaller than) the target key, it means that the current dose is underdosing patients, and the trial needs to escalate to the next higher dose. If the strongest key on the right side of (i.e., greater than) the target key, it

means that the current dose is overdosing patients, and the trial needs to de-escalate to the next lower dose. If the strongest key is the target key, stay at the current dose level.

Simulation Setting

In ZYN's simulation study, three target DLT probabilities ϕ = 0.2, 0.25, and 0.30 are considered, with 6 dose levels and maximum sample size of 36. The starting dose level is 1. For mTPI, Keyboard, and BLRM, the proper dosing interval $(\delta_1, \delta_2) = (\phi - 0.05, \phi + 0.05)$, while $(\phi_1, \phi_2) = (0.6\phi, 1.4\phi)$. If the 3+3 design selects the MTD before reaching it maximum sample size, an expansion cohort is assumed to be treated at the MTD to reach the total sample size of 36. The target DLT probability is assumed to be $\phi = 0.25$.

The design parameters for the six models are summarized in the figure below.

	CRM	CRM-DS	EWOC	BLRM	BLRM-NOC	mTPI	Keyboard	BOIN
Model	$p_j = a_j^{\exp(\alpha)}$		$logit(p_j) = \beta_0 + \beta_1 d_j$	$logit(p_j) = \log\alpha + \beta\log(d_j/d^*)$		$y_j \mid n_j \sim Binomial(p_j)$		
Prior	$\alpha \sim N(0, 2)$, $(a_1 \dots a_6)$§		$\gamma \sim Unif(d_1, 2d_j - d_{j-1})$ $p_1 \sim Unif(0, \phi)$‡	$(\log\alpha, \log\beta) \sim N\left(\begin{pmatrix}-0.847\\0.381\end{pmatrix}, \begin{pmatrix}2.015^2 & 0\\0 & 1.027^2\end{pmatrix}\right)$		$p_j \sim Beta(1,1)$*		
Proper dosing interval	N/A		N/A	$(\delta_1, \delta_2) = (\phi - 0.05, \phi + 0.05)$		$(\phi - 0.05, \phi + 0.05)$		N/A
Dose skipping	No	Yes	No	No	No	No	No	No
Starting dose	1	1	1	1	1	1	1	1
Overdose control rule	N/A	N/A	$\Pr(d_j > \gamma \mid data) \le 0.25$	$\Pr(p_j > \delta_2 \mid data) \le 0.25$	N/A	$\Pr(p_j > \phi \mid data) \le 0.95$		
Stopping rule	$\Pr(p_1 > \phi \mid data) > 0.95$			$\Pr(p_1 > \delta_2 \mid data) > 0.25$	$\Pr(p_1 > \phi \mid data) > 0.95$	$\Pr(p_1 > \phi \mid data) > 0.95$		

Notation: ϕ denotes the target DLT probability; p_j denotes the true DLT probability of dose level j; d_j is the dosage of dose level j; y_j denotes the number patients experienced DLTs at dose level j; n_j denotes the number of patients treated at dose level j; for $j = 1, \dots, J$, and d^* is the reference dose.

§ In our simulation, we used skeletons $(a_1 \dots a_6)$ = (0.032, 0.095, 0.2, 0.332, 0.470, 0.596), (0.062, 0.140, 0.25, 0.376, 0.502, 0.615), (0.095, 0.186, 0.3, 0.422, 0.540, 0.643) for target DLT probabilities 0.2, 0.25, 0.3, respectively, obtained using the method of Lee and Cheung (2009) from R package "dfcrm".

‡ $\gamma = \frac{1}{\beta_1}(\log(\phi) - \log(1-\phi) - \beta_0)$ and $p_1 = \frac{\exp(\beta_0 + \beta_1 d_1)}{1 + \exp(\beta_0 + \beta_1 d_1)}$.

* BOIN uses this prior only for overdose control, and its dose escalation/de-escalation rule does not require specifying a prior for p_j. mTPI and keyboard require this prior to determine dose escalation and de-escalation, and also for overdose control.

Source: Table S1, Supplementary Data, ZYN (2018).

The ZYN's simulation used 1000 randomly simulated dose-toxicity scenarios (or curves) using the pseudo-uniform scenario algorithm (Clertant and O'Quigley, 2017) as the basis for evaluating and comparing phase I dose escalation designs. Note that this algorithm generated scenarios where all doses have equal probability for being overly toxic.

In the simulation, if the DLT probability for the lowest dose > target DLT probability + 0.1, all doses are deemed as overly toxic, the trial is terminated early, and no doses are selected as the MTD.

Under each scenario, the Applicant conducted 2000 simulated trials, with patients recruited in cohort sizes of three with the target DLT probability of 0.25. The simulation results were evaluated based on accuracy, safety, and reliability. The definitions of these criteria are presented in the Table 1.

Table 1 Performance metrics for evaluating the operating characteristics of phase I designs

(A) Accuracy
A1. The percentage of correct selection (PCS), which is defined as the percentage of simulated trials in which the target dose is correctly selected as the MTD. When all the dose levels are above the MTD (e.g., the DLT probability of the lowest dose ≥ 0.33), PCS is defined as the percentage of early termination of trials. A2. The average percentage of patients who are assigned to the MTD across the simulated trials. When all the dose levels are above the MTD (e.g., the DLT probability of the lowest dose ≥ 0.33), we use the average percentage of patients not enrolled into the trial for this metric.
(B) Safety
B1. The percentage of simulated trials in which a toxic dose with the true DLT probability ≥ 0.33 is selected as the MTD. B2. The average percentage of patients assigned to the toxic doses with true DLT probability ≥ 0.33.
(C) Reliability
C1. The risk of overdosing, defined as the percentage of simulated trials with more than 50% of patients treated at doses above the MTD. C2. The risk of poor allocation, defined as the percentage of simulated trials in which fewer than six patients are treated at the MTD. C3. The risk of irrational dose assignment, defined the percentage of times that the design fails to de-escalate the dose when 2/3 or ≥ 3/6 patients had DLTs at a dose.

Source: Table 4, DDT-application-BOIN-YuanLee_V5, Applicant's submission.

Simulation Results

Accuracy

In terms of the percentage of correct selection, the BOIN design was found to be comparable to the CRM, mTPI, and Keyboard design. On an average these methods outperform the '3 + 3' design by about 15% - 20% . The '3+3' design outperforms the BLRM by about 5% - 10% but has comparable performance to EWOC. The BOIN design appears to have comparable variation with mTPI and Keyboard design, while BLRM and EWOC had larger variations.

For percentage of patients treated at MTD, BOIN design outperforms 3+3 design, BLRM and EWOC. The performance of BOIN is similar to the performance of the keyboard design. CRM and mTPI outperforms the BOIN design. The BOIN design appears to have comparable variation with mTPI and keyboard design, while BLRM and EWOC have larger variations.

Safety

In terms of percentage of selecting doses with DLT probability ≥ 0.33 as MTD, and percentage of patients treated at doses with DLT probability ≥ 0.33, BOIN was not able to outperform the 3+3 design, and BOIN has similar performance as mTPI, keyboard and CRM. The BLRM and EWOC

designs outperform 3+3 design, and the other novel phase I designs included in the comparison. BOIN has relatively comparable variation with CRM, BLRM, mTPI and keyboard design. On an average, BLRM outperforms 3+3 and all the other designs in terms of safety.

Reliability

In terms of the risk of overdosing 50% of the patients treated at doses above the MTD, the BOIN design was found to be comparable to Keyboard design, and both designs outperform 3+3 design. BLRM outperforms all the other designs in this metric. BOIN has relatively comparable variation with all the other design, except for EWOC which has larger variation.

In terms of risk of treating fewer than 6 patients at the MTD, on an average the designs including CRM, mTPI, BOIN and Keyboard designs have smaller risk than the 3 + 3 design, while BLRM and EWOC has a higher risk in this metric. Additionally, the BLRM and EWOC designs have larger variation than the other designs.

4.2 Comments on the Simulation Results

Simulation results, summarized above in Section 4.1, were submitted comparing the BOIN method to other model-based, model-assisted, and algorithmic trial designs. These simulations were evaluated and compared based on specific metrics of accuracy, reliability, and safety of the methods. There are several design parameters in each of the individual methods that need to be adjusted when the method is used in practice. Depending upon the settings of the parameters different simulation results can be observed in the operating characteristics. The submission document also briefly summarizes results of a simulation study by Ruppert and Shoben (2018) where the impact of some phase I trial designs on the overall outcome of the drug development process was evaluated for a drug considered to be safe and efficacious. Based on their analysis results, Ruppert and Shoben (2018) discuss some general guidelines on phase I design selection depending on whether or not there is a strong a prior belief in the general shape of the dose-toxicity curve.

As with other methods, the performance of BOIN is affected by the choice of design parameters. If any underlying assumption is violated, the BOIN method may not be able to estimate the dose toxicity relationship accurately. For example, in instances with combination therapy, where the dose-toxicity relationship may not be monotonically increasing or also in the case of therapies with delayed onset of toxicities.

5 Conclusion and Recommendations

The Applicant’s submission document contained a brief introduction to the BOIN methodology and referred to the paper by Liu and Yuan (2015) for the technical details and the derivation of the

design. Therefore, our methodological review focused on the derivations presented in Liu and Yuan (2015). Liu and Yuan (2015) present two versions of the BOIN design, which they refer to as the local BOIN design, and the global BOIN design. The information presented in this FFP submission document applies only to the local BOIN design, and therefore, our review of this FFP submission applies only to the local BOIN design.

During our review, we found some technical issues in the derivations presented in Liu and Yuan (2015) which needed to be corrected. As a result, we prepared detailed comments and sent them to the Applicant as an information request. The Applicant responded with an updated design and derivation, and we reviewed the revised design and derivation and provided additional comments to the Applicant. Through this iterative process, we sent a total of three sets of comments to the Applicant, each time receiving a further revised version of the design and/or derivation, which improved the rigorousness of the methodological development of the BOIN design. In view of the iterative nature of these revisions, our determination applies to the most refined version of the revised BOIN design and derivation provided to us by the Applicant. This version of the revised BOIN design and derivation is summarized in Section 3.1 of this review.

The information presented in the original FFP submission document, including the simulation studies, focuses on the local BOIN design under the specific case where $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ (the quantities $\pi_{0j}, \pi_{1j}, \pi_{2j}$ are defined in Section 3.1 of this review), which is referred to as the case of the non-informative prior. Therefore, our FFP determination applies only to the local BOIN design under the non-informative prior, as the FFP review was requested for this specific form of the BOIN design. We focus here on the local BOIN design under the non-informative prior because versions of the BOIN design outside of these conditions are not within the scope of the present FFP submission, but this focus is not necessarily a reflection on the methodology itself. Further detailed information would be needed to make a determination on the BOIN design outside of the conditions of the local design and non-informative prior. In Section 3, however, we discuss the local BOIN design in the more general case where the non-informative prior is not required. Additional research may be useful to evaluate the properties of the BOIN design in cases when the non-informative prior condition is not required.

Finally, with regards to the simulation results presented in the Applicant's submission document, where several phase I trial designs were compared, BOIN generally performed well in the simulation scenarios considered. This statement does not imply that other methods did not also perform well in the simulation scenarios. As is generally the case, findings from the simulation studies are driven by the specific parameters and models used to construct the simulation scenarios. Also, in the simulation studies of Zhou, Yuan, and Nie (2018), which are summarized in the Applicant's submission document, specific performance metrics were defined to evaluate accuracy, safety, and reliability of the designs, and the conclusions of their simulation studies are based on these metrics. If any underlying assumption is violated, the BOIN method may not be able to estimate the dose toxicity relationship accurately. For example, in instances with combination therapy, where the dose toxicity relationship may not be monotonically increasing or also in the case of therapies with delayed onset of toxicities.

We recommend that the Applicant submit an erratum to Liu and Yuan (2015) to help communicate the revisions of the BOIN design and derivation (as summarized in Section 3.1 of this review) with the scientific community, and we recommend that the Applicant ensure that their software implementations of the BOIN design are in alignment with the revisions. Under the non-informative prior, the local BOIN design, in its revised form, can be designated fit-for-purpose. Our determination is based on the Applicant's original submission, the Applicant's responses to our information requests (which present the revised form of the local BOIN design), and the relevant statistical literature, including the papers by Liu and Yuan (2015) and Zhou, Yuan, and Nie (2018). This recommendation does not preclude the availability and use of other methods for phase I dose finding clinical trials, including potentially the BOIN design itself outside of the local design and informative prior. In practice, one should carefully consider the requirements of the specific situation when considering candidate designs for a dose finding clinical trial; and when deciding on the trial design, one should carefully evaluate the scientific validity of the candidate designs in the context of the intended application.

6 References

Clertant, M., O'Quigley, J. (2017). Semiparametric Dose Finding Methods. Journal of the Royal Statistical Society, Series B, 79, Part 5, 1487-1508.

Liu, S., Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society, Series C, 64, Part 3, 507-523.

O'Quigley, J., Pepe, M., Fisher, L. (1990). Continual Reassessment Method: A Practical Design for Phase I Clinical Trials in Cancer. Biometrics, 46, 1, 33-48.

Ruppert, A.S., Shoben, A.B. (2018). Overall Success Rate of a Safe and Efficacious Drug: Results Using Six Phase 1 Designs, Each Followed by Standard Phase 2 and 3 Designs. Contemporary Clinical Trials Communications, 12, 40-50.

Zhou, H., Yuan, Y., Nie, L. (2018). Accuracy, Safety, and Reliability of Novel Phase I Trial Designs. Clinical Cancer Research, 24, 18, 4357-4364.

Fit-For-Purpose Initiative: Request for Information

Submission: Bayesian optimal interval (BOIN) design as an efficient statistical methodology for phase I dose finding trials

The BOIN method proposed in your submission seems to be based on the article of Liu and Yuan (2015)[1]. We have the following questions after we reviewed the paper.

Given that Liu and Yuan (2015) forms the basis of the BOIN design, the effects of the following findings on the methods on the operating characteristics in terms of selecting the correct dose need to be addressed. Please respond at the earliest so that we can complete the review of your submission.

In the comments below, we utilize the notation of Liu and Yuan (2015).

Comment 1.

The final expression for the probability of making an incorrect decision in Equation (1) of Liu and Yuan (2015) does not hold in general. Equation (1) of Liu and Yuan (2015) states the following:

$$\alpha(\lambda_{1j}, \lambda_{2j}) = P(H_{0j})P(\bar{R}|H_{0j}) + P(H_{1j})P(\bar{E}|H_{1j}) + P(H_{2j})P(\bar{D}|H_{2j})$$

$$= P(H_{0j})P(m_j \le n_j\lambda_{1j} \text{ or } m_j \ge n_j\lambda_{2j}|H_{0j}) + P(H_{1j})P(m_j > n_j\lambda_{1j}|H_{1j}) + P(H_{2j})P(m_j < n_j\lambda_{2j}|H_{2j})$$

$$= \pi_{0j}\{Bin(n_j\lambda_{1j}; n_j, \phi) + 1 - Bin(n_j\lambda_{2j} - 1; n_j, \phi)\} + \pi_{1j}\{1 - Bin(n_j\lambda_{1j}; n_j, \phi_1)\} + \pi_{2j}Bin(n_j\lambda_{2j} - 1; n_j, \phi_2)$$

The last equality above does not hold in general because the equations

$$P(m_j \ge n_j\lambda_{2j}\,|H_{0j}\,) = 1 - Bin(n_j\lambda_{2j} - 1; n_j, \phi)$$

and

$$P(m_j < n_j\lambda_{2j}|H_{2j}) = Bin(n_j\lambda_{2j} - 1; n_j, \phi_2)$$

do not hold if $n_j\lambda_{2j} \in [0, n+1] \cap \{0,1,2, \ldots n+1\}^c$ (that is, $n_j\lambda_{2j}$ is a non-integer in the interval $[0, n+1]$). Please clarify.

[1] Liu, S., Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society, Series C, 64, Part 3, pp. 507-523.

Comment 2.

In view of Comment 1, clarification is needed regarding the values of $\lambda_{1j}$and λ_{2j} that minimize the probability of making an incorrect decision. Furthermore, the condition $0 \leq \lambda_{1j} < \lambda_{2j} \leq 1$ (Liu and Yuan (2015), page 509) may not hold if $\lambda_{1j}$and λ_{2j} are defined as in Equations (2) and (3) of Liu and Yuan (2015). We note that the condition $\lambda_{1j} < \lambda_{2j}$ is used in Equation (1) of Liu and Yuan (2015), in order to write

$$P\left(m_j \leq n_j\lambda_{1j} \; or \; m_j \geq n_j\lambda_{2j}|H_{0j}\right) = P\left(m_j \leq n_j\lambda_{1j}\middle|H_{0j}\right) + P(m_j \geq n_j\lambda_{2j}|H_{0j}).$$

Consider the following examples where $\alpha_1\left(\lambda_{1j}\right)$ and $\alpha_2\left(\lambda_{2j}\right)$ are the functions defined in Appendix A of Liu and Yuan (2015).

Example 1.

Consider the case when $\pi_{0j} = \pi_{1j} = \pi_{2j} = \frac{1}{3},\ n_j = 3\ ,\ \phi = 0.25, \phi_1 = 0.6\phi = 0.15,\ \phi_2 = 1.4\phi = 0.35.$

The expression for α_1 is given by the following expression:

$$\alpha_1\left(\lambda_{1j}\right) = \left(\frac{1}{3}\right) Bin\left(n_j\lambda_{1j}; n_j = 3, \phi = 0.25\right) - \left(\frac{1}{3}\right) Bin\left(n_j\lambda_{1j}; n_j = 3, \phi_1 = 0.15\right)$$

$$= \begin{cases} 0, \ \lambda_{1j} < 0 \\ -0.064, \ 0 \leq \lambda_{1j} < 1/3 \\ -0.032, \ 1/3 \leq \lambda_{1j} < 2/3 \\ -0.004, \ 2/3 \leq \lambda_{1j} < 1 \\ 0, \ \lambda_{1j} \geq 1 \end{cases}$$

According to Equation (2) of Liu and Yuan (2015), $\alpha_1\left(\lambda_{1j}\right)$ is minimized when

$$\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}} = 0.1968.$$

We observe here that $\alpha_1\left(\lambda_{1j}\right)$ is minimized for any $\lambda_{1j} \in [0, \frac{1}{3})$ and the value of 0.1968 belongs in this interval.

The corresponding expression for α_2 is:

$$\alpha_2(\lambda_{2j}) = \left(\frac{1}{3}\right) Bin\left(n_j\lambda_{2j} - 1; n_j = 3, \phi_2 = 0.35\right) - \left(\frac{1}{3}\right) Bin\left(n_j\lambda_{2j} - 1; n_j = 3, \phi = 0.25\right)$$

$$= \begin{cases} 0, & \lambda_{2j} < 1/3 \\ -0.049, & 1/3 \le \lambda_{2j} < 2/3 \\ -0.042, & 2/3 \le \lambda_{2j} < 3/3 \\ -0.009, & 3/3 \le \lambda_{2j} < 4/3 \\ 0, & \lambda_{2j} \ge 4/3 \end{cases}$$

According to Equation (3) of Liu and Yuan (2015), the value of λ_{2j} that minimizes $\alpha_2(\lambda_{2j})$ is $\lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}} = 0.2984$. However, based on the above expression we observe that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in \left[\frac{1}{3}, \frac{2}{3}\right)$ which contradicts the claim that it is minimized when $\lambda_{2j} = 0.2984$.

In view of Comment 1, we believe the expression for $\alpha_2(\lambda_{2j})$ needs to be modified to account for this discrepancy. In Appendix A of Liu and Yuan (2015) the decision error is written as $\alpha(\lambda_{1j}, \lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j}$.

We believe the above expression can be corrected by replacing $\alpha_2(\lambda_{2j})$ by the following:

$\alpha_2^*(\lambda_{2j}) = \pi_{2j}\left[Bin\left(n_j\lambda_{2j}; n_j, \phi_2\right) - bin\left(n_j\lambda_{2j}; n_j, \phi_2\right)\right] - \pi_{0j}[Bin\left(n_j\lambda_{2j}; n_j, \phi\right) - bin\left(n_j\lambda_{2j}; n_j, \phi\right)]$

where $bin(x; n, p)$ is the binomial(n, p) p.m.f. and $Bin(x; n, p)$ is the binomial(n, p) c.d.f., i.e.,

$$bin(x; n, p) = \begin{cases} \binom{n}{x} p^x (1-p)^{n-x}, if\ x = 0,1,2, \dots, n \\ 0, otherwise \end{cases}$$

and

$$Bin(x; n, p) = \begin{cases} 0, & if\ x < 0 \\ \sum_{i=0}^{k} bin(i; n, p), & if\ k \le x < k+1, k \in \{0,1,2, \dots, n-1\} \\ 1, & if\ x \ge n \end{cases}$$

Example 2.

Further, when we consider $\pi_{0j} = 0.6,\ \pi_{1j} = \pi_{2j} = 0.2,\ n_j = 3\ ,\ \phi = 0.25, \phi_1 = 0.6\phi = 0.15,$ $\phi_2 = 1.4\phi = 0.35$, Equations (2) and (3) of Liu and Yuan (2015) provide values of $\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}} = -0.379$ and $\lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}} = 1.062.$

In this instance, the condition $0 \leq \lambda_{1j} < \lambda_{2j} \leq 1$ (Liu and Yuan (2015), page 509) does not hold and the resulting decision rule is

If $\hat{p}_j \in \{0, \frac{1}{3}, \frac{2}{3}, 1\}$ (i.e. $\lambda_{1j} < \hat{p}_j < \lambda_{2j}$, which is always satisfied with $n_j = 3$), then retain the dose to level j.

Also, we find that

$$\alpha_2(\lambda_{2j}) = (0.2)Bin(n_j\lambda_{2j} - 1; n_j = 3, \phi_2 = 0.35) - (0.6)Bin(n_j\lambda_{2j} - 1; n_j = 3, \phi = 0.25)$$

$$= \begin{cases} 0, \ \lambda_{2j} < 1/3 \\ -0.198, \ 1/3 \leq \lambda_{2j} < 2/3 \\ -0.363, \ 2/3 \leq \lambda_{2j} < 3/3 \\ -0.399, \ 3/3 \leq \lambda_{2j} < 4/3 \\ -0.4, \ \lambda_{2j} \geq 4/3 \end{cases}$$

Therefore $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in \left[\frac{4}{3}, \infty\right)$ which contradicts the claim that it is minimized when $\lambda_{2j} = 1.062$.

Example 3.

In another example when we consider $\pi_{0j} = 0.25, \ \pi_{1j} = 0.45, \pi_{2j} = 0.30, \ n_j = 3 \ , \ \phi = 0.25, \phi_1 = 0.6\phi = 0.15, \ \phi_2 = 1.4\phi = 0.35$, Equations (2) and (3) of Liu and Yuan (2015) provide values of $\lambda_{1j} = 0.5049$ and $\lambda_{2j} = 0.1717$

In this instance, the condition $0 \leq \lambda_{1j} < \lambda_{2j} \leq 1$ (Liu and Yuan (2015), page 509) does not hold and the resulting decision rule is:

If $\hat{p}_j \in \left\{0, \frac{1}{3}\right\}$ (i.e., $\hat{p}_j \leq \lambda_{1j}$), then escalate the dose to level $j + 1$.

If $\hat{p}_j \in \left\{\frac{1}{3}, \frac{2}{3}, 1\right\}$ (i.e., $\hat{p}_j \geq \lambda_{2j}$), then de-escalate the dose to level $j - 1$.

The above rule is ambiguous when $\hat{p}_j = \frac{1}{3}$.

Also, we find that

$$\alpha_2(\lambda_{2j}) = (0.3)Bin(n_j\lambda_{2j} - 1; n_j = 3, \phi_2 = 0.35) - (0.25)Bin(n_j\lambda_{2j} - 1; n_j = 3, \phi = 0.25)$$

$$= \begin{cases} 0, \ \lambda_{2j} < 1/3 \\ -0.023, \ 1/3 \leq \lambda_{2j} < 2/3 \\ 0.005, \ 2/3 \leq \lambda_{2j} < 3/3 \\ 0.041, \ 3/3 \leq \lambda_{2j} < 4/3 \\ 0.05, \ \lambda_{2j} \geq 4/3 \end{cases}$$

Therefore $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in \left[\frac{1}{3}, \frac{2}{3}\right)$ which contradicts the claim that it is minimized when $\lambda_{2j} = 0.1717$.

As demonstrated in the examples above, the constraint $0 \leq \lambda_{1j} < \lambda_{2j} < 1$ which is assumed on page 509 of Liu and Yuan (2015) is not always satisfied. The examples show that λ_{1j} and λ_{2j} can fall outside of the interval $[0,1]$, and it is also possible to have $\lambda_{1j} > \lambda_{2j}$.

In the examples above, the stated value of λ_{2j} (Equation (3) of Liu and Yuan (2015)) does not minimize the function $\alpha_2(\lambda_{2j})$ as claimed in Appendix A of Liu and Yuan (2015). The functions $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are both stepwise constant functions. A precise and complete mathematical description/derivation of the minimizing values is needed, giving full consideration to the stepwise nature of these functions.

Furthermore, the constraint $0 \leq \lambda_{1j} < \lambda_{2j} < 1$ should be accounted for in the theoretical development. Clarification is needed regarding conditions under which the procedure leads to a well-defined design. In view of Comment 1, the function $\alpha_2(\lambda_{2j})$ needs adjustment, or the set of possible values of λ_{2j} would need to be appropriately restricted. The effect of this adjustment on the operating characteristics needs to be characterized.

Comment 3.

Please clarify Theorem 1 of Liu and Yuan (2015) because the values of λ_{1j} and λ_{2j} fall in a continuous space, while $\hat{p}_j$ falls in a discrete space.

Specifically, Theorem 1 of Liu and Yuan (2015) states that

$\lambda_{1j} = \arg\max_{\hat{p}_j}\{P(H_1|n_j, m_j) > P(H_0|n_j, m_j)\}$ (*)

$\lambda_{2j} = \arg\min_{\hat{p}_j}\{P(H_2|n_j, m_j) > P(H_0|n_j, m_j)\}$ (**)

where

$\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}}$ and $\lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right\}}$ (***)

Clarification is needed because $\hat{p}_j \in \{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j}{n_j}\}$, hence, according to (*) and (**), $\lambda_{1j} \in \{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j}{n_j}\}$ and $\lambda_{2j} \in \{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j}{n_j}\}$, but based on (***), λ_{1j} and λ_{2j} are not necessarily in the set $\left\{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j}{n_j}\right\}$.

Comment 4.

The cumulative number of subjects treated at a given dose seems to be a random variable but is treated as a fixed variable in the calculation and minimization of the decision error probability. Please clarify.

Comment 5.

According to the paper the dose elimination rule is given as follows: If $P(p_j > \phi | m_j, n_j) > 0.95$ and $n_j \geq 3$, dose levels j and higher are eliminated from the trial, and the trial is terminated if the first dose level is eliminated, where $P(p_j > \phi | m_j, n_j) > 0.95$ can be evaluated on the basis of a beta-binomial model, assuming that m_j follows a binomial distribution (with size and probability parameters n_j and p_j) and p_j follows a vague beta prior, e.g. $p_j \sim beta(1,1)$.

We note that the prior distribution used to derive the design boundaries (which is that p_j takes values ϕ, ϕ_1, ϕ_2 with probabilities $\pi_{0j}, \pi_{1j}, \pi_{2j}$, respectively) differs from the prior distribution used for the early stopping rule. Please comment on the implications of using two different prior distributions.

Fit-For-Purpose Initiative: Request for Information
Submission: Bayesian Optimal Interval (BOIN) Design

We have reviewed your revised derivation, and have the following comments. These comments use the BOIN design and notations as defined in the revised derivation. Please note that Section 1 of this document contains our comments, and Section 2 presents a set of examples (Examples 1-5) along with detailed calculations for each example. Some of the comments in Section 1 refer to examples in Section 2.

We note that in Example 1 of Section 2, it is observed that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [0, 1/3)$, and $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [0, 1/3)$. When we apply the formulas from the revised derivation, the results are in agreement with these observations.

We also note that in Example 3 of Section 2, it is observed that $\lambda_{1j} > \lambda_{2j}$ when λ_{1j} and λ_{2j} are computed using equations (1) and (3) in the revised derivation, respectively. Therefore, a numerical search is needed to find the values of λ_{1j} and λ_{2j} that minimize $\alpha(\lambda_{1j}, \lambda_{2j})$ under the constraint that $\lambda_{1j} \leq \lambda_{2j}$. In Example 3 we enumerated all possible values of $\alpha(\lambda_{1j}, \lambda_{2j})$ in order to find the minimum value under this constraint.

The remaining examples from Section 2 are discussed in the following comments. Please provide detailed responses so that we can proceed with the review of your submission.

1 Comments

Comment 1

We recommend that you publish an errata to Liu and Yuan (2015)[1] and ensure that the BOIN software packages are in alignment with the errata.

(a) Please discuss any plans you may have to communicate your revised derivation, and changes to the BOIN design, with the scientific community.

(b) Please discuss which, if any, of the currently available BOIN software packages have been, or will be updated to reflect the changes in the design presented in your revised derivation.

Comment 2

(a) In Example 2, we observe that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in (-\infty, 0)$. When we apply the formulas from the revised derivation, we obtain that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [0, -1/3)$, which differs from our observation that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in (-\infty, 0)$, and the meaning of the interval $[0, -1/3)$ is unclear. The formulas in the revised derivation further yield that an optimal bound is $\lambda_{1j} = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)+n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx -0.3790$, and because this value is negative, the revised derivation states that one should take $\lambda_{1j} = 0$. However, the value $\lambda_{1j} = 0$ is not contained in the interval $(-\infty, 0)$ on which $\alpha_1(\lambda_{1j})$ is minimized; and $\lambda_{1j} = 0$ will yield a different design than $\lambda_{1j} \in (-\infty, 0)$. If $\lambda_{1j} = 0$ then the dose would be escalated if $\hat{p}_j = 0$, but if $\lambda_{1j} \in (-\infty, 0)$ then $\hat{p}_j = 0$ would not lead to dose escalation.

[1] Liu, S., Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society, Series C, 64, Part 3, pp. 507-523.

(b) In Example 2, we observe that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [1, \infty)$. When we apply the formulas from the revised derivation, we obtain that $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval $[1, 1)$, which differs from our observation that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [1, \infty)$, and the meaning of the interval $[1, 1)$ is unclear. The formulas in the revised derivation further yield that an optimal bound is $\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)+n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 1.0620$, and because this value is greater than 1, the revised derivation states that one should take $\lambda_{2j} = 1$. The value $\lambda_{2j} = 1$ is contained in the interval $[1, \infty)$ on which $\alpha_2(\lambda_{2j})$ is minimized.

Please clarify the details of the revised derivation in view of the comments (a) and (b) above, and provide a precise and complete mathematical derivation that covers the complete range of scenarios, including those noted above. Regarding (a), if the value $\lambda_{1j} = 0$ results from the restriction $0 \leq \lambda_{1j} \leq 1$, please justify why this value is more appropriate than choosing $\lambda_{1j} < 0$ which minimizes $\alpha_1(\lambda_{1j})$.

Comment 3

(a) In Example 4, observe that because of the choice of values $\pi_{0j} = \pi_{1j}$, $\phi = \frac{1-0.6^{-1/2}}{0.6-0.6^{-1/2}}$, and $\phi_1 = 0.6\phi$, we obtain $y^* = 1$, and hence the function $\alpha_1(\lambda_{1j})$ takes the same value when $\lambda_{1j} \in [0, 1/3)$ and when $\lambda_{1j} \in [1/3, 2/3)$, and is minimized at this value. Therefore, we observe here that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [0, 2/3)$. Applying the formulas provided in the revised derivation we obtain that $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [\max\{0, \text{floor}(y^*)/n_j\}, \min\{1, (\text{floor}(y^*) + 1)/n_j\}) = [1/3, 2/3)$, which does not describe the full set of minimizing values. In this case we also observe that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [1/3, 2/3)$, which agrees with the results obtained from the formulas in the revised derivation. Because $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [0, 2/3)$, it appears that if $\hat{p}_j = 1/3$, one could either retain the dose (take $\lambda_{1j} \in [0, 1/3)$) or escalate the dose (take $\lambda_{1j} \in [1/3, 2/3)$), and both design choices would minimize the decision error probability.

(b) In Example 5, observe that because of the choice of values $\pi_{0j} = \pi_{2j}$, $\phi = \frac{1-1.4^{-1/2}}{1.4-1.4^{-1/2}}$, and $\phi_2 = 1.4\phi$, we obtain $y^{**} = 1$, which leads to a similar situation as Example 4. The situation in Example 5 is that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [0, 2/3)$, but applying the formulas in the revised derivation one obtains that $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [\max\{0, \text{floor}(y^{**})/n_j\}, \min\{1, (\text{floor}(y^{**}) + 1)/n_j\}) = [1/3, 2/3)$, which does not describe the full set of minimizing values. Because $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [0, 2/3)$, it appears that if $\hat{p}_j = 1/3$, one could either de-escalate the dose (take $\lambda_{2j} \in [0, 1/3)$) or retain the dose (take $\lambda_{2j} \in [1/3, 2/3)$), and both design choices would minimize the decision error probability.

While Examples 4 and 5 use a careful setting of design parameters, nevertheless, it is desirable that the theoretical development, as well as software implementations of the design, can properly handle all cases. Please clarify the details of the revised derivation in view of the comment above, and provide a precise and complete mathematical derivation that covers the complete range of scenarios, including those discussed in Examples 4 and 5. In Example 4 it appears if $\hat{p}_j = 1/3$ one can either retain or escalate the dose, and both options minimize the decision error probability; please clarify how this scenario is handled by the theoretical derivation of the design, and software

implementations of the design. In Example 5 it appears that if $\hat{p}_j = 1/3$, one could either de-escalate the dose or retain the dose, and both design choices would minimize the decision error probability; please clarify how this scenario is handled by the theoretical derivation of the design, and software implementations of the design.

Comment 4

In Example 5, we also observe that because of the choice of values $\pi_{0j} = \pi_{2j}$, $\phi = \frac{1-1.4^{-1/2}}{1.4-1.4^{-1/2}}$, and $\phi_2 = 1.4\phi$, we obtain $\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)+n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} = \frac{1}{3}$. In this example, if $\lambda_{2j} = 1/3$, then the change in the design in the revised derivation (change $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$, and change $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$ to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$) will have an effect since when $\hat{p}_j = 1/3$ the decision under the original design is de-escalate the dose, but in the revision, the decision is to retain the dose. This example illustrates that the likelihood of the event $\hat{p}_j = \lambda_{2j}$ depends on the choice of the design parameters π_{0j}, π_{2j}, ϕ, ϕ_2.

We note that the revised derivation (page 4) states: "One potential concern is that in the revised derivation, the de-escalation rule is $\hat{p}_j > \lambda_{2j}$, rather than $\hat{p}_j \geq \lambda_{2j}$, presented in the submission. This difference has negligible impact on the operating characteristics of the design because λ_{2j} is a continuous variable and the probability of $\hat{p}_j = \lambda_{2j}$ is ignorable."

In view of Example 5 and the discussion above, the probability of the event $\hat{p}_j = \lambda_{2j}$ may be nonzero (in Example 5 if $\lambda_{2j} = 1/3$ we have $P(\hat{p}_j = \lambda_{2j}) = P(m_j = 1) \approx 0.81, 0.93, 0.66$, when $p_j = \phi, \phi_1, \phi_2$, respectively), depending on the choice of design parameters. However, if $\lambda_{2j} \notin \{\frac{0}{n_j}, \frac{1}{n_j}, \frac{2}{n_j}, \ldots, \frac{n_j}{n_j}\}$, then the probability of the event $\hat{p}_j = \lambda_{2j}$ equals zero. Please discuss this issue and provide a precise analysis of the effect the change will have on the operating characteristics.

Comment 5

Please provide a precise statement of Theorem 1 of Liu and Yuan (2015). In case equations (2) and (3) of Liu and Yuan (2015) yield $\lambda_{1j} > \lambda_{2j}$, and therefore a numerical search is needed to find the minimizing values subject to $\lambda_{1j} \leq \lambda_{2j}$, will the statement of the theorem be affected? Also, will this theorem be affected by the change to the design presented in your revised derivation? If any adjustment is needed to the proof of the theorem, please also provide the details.

Comment 6

In view of your revised derivation, including the key changes (change $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$, and change $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$ to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$), please discuss if any adjustment is needed to Theorem 2 and Theorem 3 of Liu and Yuan (2015). In case an adjustment is needed to the theorems, please provide the precise mathematical statement. If any adjustment is needed to the proofs of the theorems, please also provide the details.

Comment 7

Please confirm if all numerical results presented in the submission package are for the case $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$.

Comment 8

If the equations (1) and (3) in the revised derivation yield $\lambda_{1j} > \lambda_{2j}$, do the currently available BOIN software packages implement a numerical search to minimize $\alpha(\lambda_{1j}, \lambda_{2j})$ under the constraint that $\lambda_{1j} \leq \lambda_{2j}$?

Comment 9

Do the currently available BOIN software packages enable users to specify values of the prior probabilities π_{0j}, π_{1j}, π_{2j}, or do the software packages only allow users to specify designs with equal prior probabilities $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$? Please discuss this for each of the available BOIN software packages.

Comment 10

Currently, are there any published evaluations of the BOIN design in cases other than $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$? If so, do these studies ensure that $\lambda_{1j} \leq \lambda_{2j}$?

Comment 11

Please confirm whether or not the changes to the BOIN design presented in your revised derivation (change $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ to $\hat{p}_j > \lambda_{2j}(n_j, \phi)$, and change $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$ to $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$) will have any effect on the numerical results presented in the submission package. If the changes have no effect on these numerical results, then please provide an appropriate justification. If the changes will have an effect on these numerical results, please present an updated set of results.

Comment 12

(a) On page 2 of the revised derivation, please clarify the meaning of the summation $\sum_{y=0}^{n_j\lambda_{1j}}$ because the upper limit of the summation, $n_j\lambda_{1j}$, may not be an integer. Also, in this equation, is $n_j\lambda_{1j} < 0$ considered, in which case $\alpha_1(\lambda_{1j}) = 0$?

(b) On page 3 of the revised derivation, in the equations on Line 2, Line 4, and Line 17, it appears that the "=" should be "$\in$". Please also see our comments above about these formulas.

(c) On page 3 of the revised derivation, in the equation on Line 17, it appears that $\min\left(n_j, \frac{\text{floor}(y^{**})+1}{n_j}\right)$ should be $\min\left(1, \frac{\text{floor}(y^{**})+1}{n_j}\right)$. Please also see our comments above about this formula.

2 Examples

In the revised derivation, the decision error $\alpha(\lambda_{1j}, \lambda_{2j})$ is written as

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j}$$

where

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1)$$
$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi).$$

Example 1

Let $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$, $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$.

We have,

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.064, & \text{if } 0 \le \lambda_{1j} < 1/3 \\ -0.032, & \text{if } 1/3 \le \lambda_{1j} < 2/3 \\ -0.004, & \text{if } 2/3 \le \lambda_{1j} < 1 \\ 0, & \text{if } \lambda_{1j} \ge 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.049, & \text{if } 0 \le \lambda_{2j} < 1/3 \\ -0.042, & \text{if } 1/3 \le \lambda_{2j} < 2/3 \\ -0.009, & \text{if } 2/3 \le \lambda_{2j} < 1 \\ 0, & \text{if } \lambda_{2j} \ge 1 \end{cases}$$

and hence $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are minimized, respectively, when

$$\lambda_{1j} \in \left[0, \frac{1}{3}\right) \text{ and } \lambda_{2j} \in \left[0, \frac{1}{3}\right).$$

Applying the definitions of y^* and y^{**} provided in the revised derivation, we obtain

$$y^* = \frac{n_j \log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.5904, \quad y^{**} = \frac{n_j \log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.8952.$$

Therefore, according to the theoretical development presented in the revised derivation, $\alpha_1(\lambda_{1j})$ is minimized when λ_{1j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^*)}{n_j}\right), \min\left(1, \frac{\text{floor}(y^*)+1}{n_j}\right)\right) = \left[\max\left(0, \frac{0}{3}\right), \min\left(1, \frac{1}{3}\right)\right) = \left[0, \frac{1}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{1j} = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.1968.$$

Also, according to the theoretical development presented in the revised derivation, $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^{**})}{n_j}\right), \min\left(1, \frac{\text{floor}(y^{**})+1}{n_j}\right)\right) = \left[\max\left(0, \frac{0}{3}\right), \min\left(1, \frac{1}{3}\right)\right) = \left[0, \frac{1}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.2984.$$

Example 2

Let $\pi_{0j} = 0.6$, $\pi_{1j} = \pi_{2j} = 0.2$, $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$.

We have,

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ 0.130, & \text{if } 0 \le \lambda_{1j} < 1/3 \\ 0.318, & \text{if } 1/3 \le \lambda_{1j} < 2/3 \\ 0.391, & \text{if } 2/3 \le \lambda_{1j} < 1 \\ 0.4, & \text{if } \lambda_{1j} \ge 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.198, & \text{if } 0 \le \lambda_{2j} < 1/3 \\ -0.363, & \text{if } 1/3 \le \lambda_{2j} < 2/3 \\ -0.399, & \text{if } 2/3 \le \lambda_{2j} < 1 \\ -0.4, & \text{if } \lambda_{2j} \ge 1 \end{cases}$$

and hence $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are minimized, respectively, when

$$\lambda_{1j} \in (-\infty, 0) \text{ and } \lambda_{2j} \in [1, \infty).$$

Applying the definitions of y^* and y^{**} provided in the revised derivation, we obtain

$$y^* = \frac{n_j\log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx -1.1370, \quad y^{**} = \frac{n_j\log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 3.1860.$$

Therefore, according to the theoretical development presented in the revised derivation, $\alpha_1(\lambda_{1j})$ is minimized when λ_{1j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^*)}{n_j}\right), \min\left(1, \frac{\text{floor}(y^*)+1}{n_j}\right)\right) = \left[\max(0, -\frac{2}{3}), \min\left(1, -\frac{1}{3}\right)\right) = \left[0, -\frac{1}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{1j} = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx -0.3790.$$

Since the value above is negative, according to the restriction described under equation (1) in the revised derivation, λ_{1j} will be set to zero, that is, set $\lambda_{1j} = 0$.

Also, according to the theoretical development presented in the revised derivation, $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^{**})}{n_j}\right), \min\left(1, \frac{\text{floor}(y^{**})+1}{n_j}\right)\right) = \left[\max(0, \frac{3}{3}), \min\left(1, \frac{4}{3}\right)\right) = [1, 1)\,,$$

and one specific value located in the above interval is

$$\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 1.0620.$$

Since the value above is greater than 1, according to the restriction described under equation (3) in the revised derivation, λ_{2j} will be set to one, that is, set $\lambda_{2j} = 1$.

Example 3

Let $\pi_{0j} = 0.25$, $\pi_{1j} = 0.45$, $\pi_{2j} = 0.30$, $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$.

We have

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.171, & \text{if } 0 \le \lambda_{1j} < 1/3 \\ -0.212, & \text{if } 1/3 \le \lambda_{1j} < 2/3 \\ -0.202, & \text{if } 2/3 \le \lambda_{1j} < 1 \\ -0.2, & \text{if } \lambda_{1j} \ge 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.023, & \text{if } 0 \le \lambda_{2j} < 1/3 \\ 0.005, & \text{if } 1/3 \le \lambda_{2j} < 2/3 \\ 0.041, & \text{if } 2/3 \le \lambda_{2j} < 1 \\ 0.05, & \text{if } \lambda_{2j} \ge 1 \end{cases}$$

Here we have,

$$\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.5049, \quad \lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.1717,$$

and therefore, according to the revised derivation, because $\lambda_{1j} > \lambda_{2j}$, a numerical search is necessary to find the optimal boundary. We have

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j} \approx \begin{cases} 0.7, & \text{if } \lambda_{1j} < 0, \lambda_{2j} < 0 \\ 0.677, & \text{if } \lambda_{1j} < 0, 0 \le \lambda_{2j} < 1/3 \\ 0.705, & \text{if } \lambda_{1j} < 0, 1/3 \le \lambda_{2j} < 2/3 \\ 0.741, & \text{if } \lambda_{1j} < 0, 2/3 \le \lambda_{2j} < 1 \\ 0.75, & \text{if } \lambda_{1j} < 0, \lambda_{2j} \ge 1 \\ 0.529, & \text{if } 0 \le \lambda_{1j} < 1/3, \lambda_{2j} < 0 \\ 0.506, & \text{if } 0 \le \lambda_{1j} < 1/3, 0 \le \lambda_{2j} < 1/3 \\ 0.534, & \text{if } 0 \le \lambda_{1j} < 1/3, 1/3 \le \lambda_{2j} < 2/3 \\ 0.570, & \text{if } 0 \le \lambda_{1j} < 1/3, 2/3 \le \lambda_{2j} < 1 \\ 0.579, & \text{if } 0 \le \lambda_{1j} < 1/3, \lambda_{2j} \ge 1 \\ 0.488, & \text{if } 1/3 \le \lambda_{1j} < 2/3, \lambda_{2j} < 0 \\ 0.465, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 0 \le \lambda_{2j} < 1/3 \\ 0.493, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 1/3 \le \lambda_{2j} < 2/3 \\ 0.529, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 2/3 \le \lambda_{2j} < 1 \\ 0.538, & \text{if } 1/3 \le \lambda_{1j} < 2/3, \lambda_{2j} \ge 1 \\ 0.498, & \text{if } 2/3 \le \lambda_{1j} < 1, \lambda_{2j} < 0 \\ 0.475, & \text{if } 2/3 \le \lambda_{1j} < 1, 0 \le \lambda_{2j} < 1/3 \\ 0.502, & \text{if } 2/3 \le \lambda_{1j} < 1, 1/3 \le \lambda_{2j} < 2/3 \\ 0.539, & \text{if } 2/3 \le \lambda_{1j} < 1, 2/3 \le \lambda_{2j} < 1 \\ 0.548, & \text{if } 2/3 \le \lambda_{1j} < 1, \lambda_{2j} \ge 1 \\ 0.5, & \text{if } \lambda_{1j} \ge 1, \lambda_{2j} < 0 \\ 0.477, & \text{if } \lambda_{1j} \ge 1, 0 \le \lambda_{2j} < 1/3 \\ 0.505, & \text{if } \lambda_{1j} \ge 1, 1/3 \le \lambda_{2j} < 2/3 \\ 0.541, & \text{if } \lambda_{1j} \ge 1, 2/3 \le \lambda_{2j} < 1 \\ 0.550, & \text{if } \lambda_{1j} \ge 1, \lambda_{2j} \ge 1. \end{cases}$$

Therefore, we observe that the unconstrained minimum of $\alpha(\lambda_{1j}, \lambda_{2j})$ occurs when $\lambda_{1j} \in [1/3, 2/3)$ and $\lambda_{2j} \in [0, 1/3)$. We also observe that under the constraint $\lambda_{1j} \le \lambda_{2j}$, $\alpha(\lambda_{1j}, \lambda_{2j})$ is minimized when $1/3 \le \lambda_{1j} \le \lambda_{2j} < 2/3$.

Example 4

Let $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$, $n_j = 3$, $\phi = \dfrac{1 - 0.6^{-1/2}}{0.6 - 0.6^{-1/2}} \approx 0.4211$, $\phi_1 = 0.6\phi \approx 0.2527$, $\phi_2 = 1.4\phi \approx 0.5896$.

We have

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.074, & \text{if } 0 \le \lambda_{1j} < 1/3 \\ -0.074, & \text{if } 1/3 \le \lambda_{1j} < 2/3 \\ -0.020, & \text{if } 2/3 \le \lambda_{1j} < 1 \\ 0, & \text{if } \lambda_{1j} \ge 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.042, & \text{if } 0 \le \lambda_{2j} < 1/3 \\ -0.083, & \text{if } 1/3 \le \lambda_{2j} < 2/3 \\ -0.043, & \text{if } 2/3 \le \lambda_{2j} < 1 \\ 0, & \text{if } \lambda_{2j} \ge 1 \end{cases}$$

and hence $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are minimized, respectively, when

$$\lambda_{1j} \in \left[0, \frac{2}{3}\right) \text{ and } \lambda_{2j} \in \left[\frac{1}{3}, \frac{2}{3}\right).$$

Applying the definitions of y^* and y^{**} provided in the revised derivation, we obtain

$$y^* = \frac{n_j \log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} = 1, \quad y^{**} = \frac{n_j \log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 1.5164.$$

Therefore, according to the theoretical development presented in the revised derivation, $\alpha_1(\lambda_{1j})$ is minimized when λ_{1j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^*)}{n_j}\right), \min\left(1, \frac{\text{floor}(y^*)+1}{n_j}\right)\right) = \left[\max(0, \frac{1}{3}), \min\left(1, \frac{2}{3}\right)\right) = \left[\frac{1}{3}, \frac{2}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{1j} = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} = \frac{1}{3}.$$

Also, according to the theoretical development presented in the revised derivation, $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^{**})}{n_j}\right), \min\left(1, \frac{\text{floor}(y^{**})+1}{n_j}\right)\right) = \left[\max(0, \frac{1}{3}), \min\left(1, \frac{2}{3}\right)\right) = \left[\frac{1}{3}, \frac{2}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.5055.$$

Example 5

Let $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$, $n_j = 3$, $\phi = \dfrac{1 - 1.4^{-1/2}}{1.4 - 1.4^{-1/2}} \approx 0.2791$ $\phi_1 = 0.6\phi \approx 0.1674$, $\phi_2 = 1.4\phi \approx 0.3907$.

We have

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.067, & \text{if } 0 \le \lambda_{1j} < 1/3 \\ -0.038, & \text{if } 1/3 \le \lambda_{1j} < 2/3 \\ -0.006, & \text{if } 2/3 \le \lambda_{1j} < 1 \\ 0, & \text{if } \lambda_{1j} \ge 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.049, & \text{if } 0 \le \lambda_{2j} < 1/3 \\ -0.049, & \text{if } 1/3 \le \lambda_{2j} < 2/3 \\ -0.013, & \text{if } 2/3 \le \lambda_{2j} < 1 \\ 0, & \text{if } \lambda_{2j} \ge 1 \end{cases}$$

and hence $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are minimized, respectively, when

$$\lambda_{1j} \in \left[0, \frac{1}{3}\right) \text{ and } \lambda_{2j} \in \left[0, \frac{2}{3}\right).$$

Applying the definitions of y^* and y^{**} provided in the revised derivation, we obtain

$$y^* = \frac{n_j \log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.6596, \quad y^{**} = \frac{n_j \log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} = 1.$$

Therefore, according to the theoretical development presented in the revised derivation, $\alpha_1(\lambda_{1j})$ is minimized when λ_{1j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^*)}{n_j}\right), \min\left(1, \frac{\text{floor}(y^*)+1}{n_j}\right)\right) = \left[\max(0, \frac{0}{3}), \min\left(1, \frac{1}{3}\right)\right) = \left[0, \frac{1}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{1j} = y^*/n_j = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.2199.$$

Also, according to the theoretical development presented in the revised derivation, $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval

$$\left[\max\left(0, \frac{\text{floor}(y^{**})}{n_j}\right), \min\left(1, \frac{\text{floor}(y^{**})+1}{n_j}\right)\right) = \left[\max(0, \frac{1}{3}), \min\left(1, \frac{2}{3}\right)\right) = \left[\frac{1}{3}, \frac{2}{3}\right),$$

and one specific value located in the above interval is

$$\lambda_{2j} = y^{**}/n_j = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} = \frac{1}{3}.$$

Fit-For-Purpose Initiative: Request for Information
Submission: Bayesian Optimal Interval (BOIN) Design

We have reviewed your revised derivation (January 2021 version), and have the following comments.

Comment 1

Liu and Yuan (2015)[1] describe the BOIN method for the general case where the condition $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ is not required. However, based on your responses to the previous information requests, it seems that the method is currently implemented and recommended for the non-informative prior case, namely $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$. Furthermore, your submission document focuses on the non-informative prior case, and currently, it appears that published evaluations of the operating characteristics of BOIN also focus on the non-informative prior case. Please confirm that for this submission, the fit-for-purpose designation for the BOIN method is desired only for the case of the non-informative prior $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$.

Comment 2

The last paragraph on page 5 of your revised derivation states the following.

> "When an informative prior is used, under certain setting of π_{0j}, π_{1j} and π_{2j}, it is possible that $\lambda_{1j}^* > \lambda_{2j}^*$. Let λ_{1j}^L and λ_{1j}^U respectively denote the lower and upper boundaries of the interval solution of λ_{1j} given by equation (1), and define λ_{2j}^L and λ_{2j}^U similarly for λ_{2j} given by equation (2). $\lambda_{1j}^* > \lambda_{2j}^*$ occurs only when (a) $\lambda_{1j}^U > \lambda_{2j}^L$ or (b) $\lambda_{1j}^L \geq \lambda_{2j}^U$. In case (a), any pair of $(\lambda_{1j}, \lambda_{2j}) \in [\lambda_{2j}^L, \lambda_{1j}^U)$ and satisfying $\lambda_{1j} \leq \lambda_{2j}$ can be used. In case (b), there is no closed form solution. Numerical search can be employed to find the solution that minimizes the error."

Consider the following example. This is the same as Example 3 in our previous set of comments. Let $\pi_{0j} = 0.25$, $\pi_{1j} = 0.45$, $\pi_{2j} = 0.30$, $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$. We have

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.171, & \text{if } 0 \leq \lambda_{1j} < 1/3 \\ -0.212, & \text{if } 1/3 \leq \lambda_{1j} < 2/3 \\ -0.202, & \text{if } 2/3 \leq \lambda_{1j} < 1 \\ -0.2, & \text{if } \lambda_{1j} \geq 1 \end{cases}$$

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.023, & \text{if } 0 \leq \lambda_{2j} < 1/3 \\ 0.005, & \text{if } 1/3 \leq \lambda_{2j} < 2/3 \\ 0.041, & \text{if } 2/3 \leq \lambda_{2j} < 1 \\ 0.05, & \text{if } \lambda_{2j} \geq 1 \end{cases}$$

[1] Liu, S., Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. Journal of the Royal Statistical Society, Series C, 64, Part 3, pp. 507-523.

and

$$\alpha(\lambda_{1j},\lambda_{2j}) = \alpha_1(\lambda_{1j}) + \alpha_2(\lambda_{2j}) + \pi_{0j} + \pi_{1j} \approx \begin{cases} 0.7, & \text{if } \lambda_{1j} < 0, \lambda_{2j} < 0 \\ 0.677, & \text{if } \lambda_{1j} < 0, 0 \le \lambda_{2j} < 1/3 \\ 0.705, & \text{if } \lambda_{1j} < 0, 1/3 \le \lambda_{2j} < 2/3 \\ 0.741, & \text{if } \lambda_{1j} < 0, 2/3 \le \lambda_{2j} < 1 \\ 0.75, & \text{if } \lambda_{1j} < 0, \lambda_{2j} \ge 1 \\ 0.529, & \text{if } 0 \le \lambda_{1j} < 1/3, \lambda_{2j} < 0 \\ 0.506, & \text{if } 0 \le \lambda_{1j} < 1/3, 0 \le \lambda_{2j} < 1/3 \\ 0.534, & \text{if } 0 \le \lambda_{1j} < 1/3, 1/3 \le \lambda_{2j} < 2/3 \\ 0.570, & \text{if } 0 \le \lambda_{1j} < 1/3, 2/3 \le \lambda_{2j} < 1 \\ 0.579, & \text{if } 0 \le \lambda_{1j} < 1/3, \lambda_{2j} \ge 1 \\ 0.488, & \text{if } 1/3 \le \lambda_{1j} < 2/3, \lambda_{2j} < 0 \\ 0.465, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 0 \le \lambda_{2j} < 1/3 \\ 0.493, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 1/3 \le \lambda_{2j} < 2/3 \\ 0.529, & \text{if } 1/3 \le \lambda_{1j} < 2/3, 2/3 \le \lambda_{2j} < 1 \\ 0.538, & \text{if } 1/3 \le \lambda_{1j} < 2/3, \lambda_{2j} \ge 1 \\ 0.498, & \text{if } 2/3 \le \lambda_{1j} < 1, \lambda_{2j} < 0 \\ 0.475, & \text{if } 2/3 \le \lambda_{1j} < 1, 0 \le \lambda_{2j} < 1/3 \\ 0.502, & \text{if } 2/3 \le \lambda_{1j} < 1, 1/3 \le \lambda_{2j} < 2/3 \\ 0.539, & \text{if } 2/3 \le \lambda_{1j} < 1, 2/3 \le \lambda_{2j} < 1 \\ 0.548, & \text{if } 2/3 \le \lambda_{1j} < 1, \lambda_{2j} \ge 1 \\ 0.5, & \text{if } \lambda_{1j} \ge 1, \lambda_{2j} < 0 \\ 0.477, & \text{if } \lambda_{1j} \ge 1, 0 \le \lambda_{2j} < 1/3 \\ 0.505, & \text{if } \lambda_{1j} \ge 1, 1/3 \le \lambda_{2j} < 2/3 \\ 0.541, & \text{if } \lambda_{1j} \ge 1, 2/3 \le \lambda_{2j} < 1 \\ 0.550, & \text{if } \lambda_{1j} \ge 1, \lambda_{2j} \ge 1. \end{cases}$$

Therefore, we observe that the unconstrained minimum of $\alpha(\lambda_{1j},\lambda_{2j})$ occurs when $\lambda_{1j} \in [1/3, 2/3)$ and $\lambda_{2j} \in [0, 1/3)$. We also observe that under the constraint $\lambda_{1j} \le \lambda_{2j}$, $\alpha(\lambda_{1j},\lambda_{2j})$ is minimized when $1/3 \le \lambda_{1j} \le \lambda_{2j} < 2/3$.

Here we note that,

$$\lambda^*_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right) + n_j^{-1}\log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.5049, \quad \lambda^*_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right) + n_j^{-1}\log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.1717,$$

and therefore in this case the discussion in the last paragraph of page 5 of the revised derivation applies because the boundaries do not satisfy the constraint $\lambda^*_{1j} \le \lambda^*_{2j}$. Note that

$$y^* = \frac{n_j\log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 1.5146, \quad y^{**} = \frac{n_j\log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} \approx 0.5150.$$

Therefore, applying equations (1) and (2) in the revised derivation, we obtain

$$[\lambda_{1j}^L, \lambda_{1j}^U) = \left[\frac{1}{3}, \frac{2}{3}\right), \quad [\lambda_{2j}^L, \lambda_{2j}^U) = \left[0, \frac{1}{3}\right),$$

and the above intervals are in agreement with the unconstrained minimizing values observed based on the expressions above for $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$.

However, applying the discussion in the last paragraph of page 5 of the revised derivation, we observe that conditions (a) $\lambda_{1j}^U > \lambda_{2j}^L$ and (b) $\lambda_{1j}^L \geq \lambda_{2j}^U$ are both satisfied. That is, conditions (a) and (b) are not mutually exclusive. Furthermore, according to the description in the last paragraph of page 5, since (a) is satisfied, any pair $\lambda_{1j}, \lambda_{2j} \in [\lambda_{2j}^L, \lambda_{1j}^U) = [0, 2/3)$ and satisfying $\lambda_{1j} \leq \lambda_{2j}$ can be used. But the solution interval $[0, 2/3)$ appears to be too large, and it disagrees with our observation above, based on enumeration of all values of $\alpha(\lambda_{1j}, \lambda_{2j})$, that under the constraint $\lambda_{1j} \leq \lambda_{2j}$, $\alpha(\lambda_{1j}, \lambda_{2j})$ is minimized when $1/3 \leq \lambda_{1j} \leq \lambda_{2j} < 2/3$. There are values $\lambda_{1j}, \lambda_{2j} \in [\lambda_{2j}^L, \lambda_{1j}^U) = [0, 2/3)$ satisfying $\lambda_{1j} \leq \lambda_{2j}$ that do not minimize $\alpha(\lambda_{1j}, \lambda_{2j})$ under the constraint $\lambda_{1j} \leq \lambda_{2j}$, for example $\lambda_{1j} = 0$, $\lambda_{2j} = 1/3$. Please clarify, and as needed, provided an updated derivation that covers all cases, as well as numerical examples to validate the derivation.

Comment 3

Consider the following example. Let $n_j = 3$, $\phi = 0.25$, $\phi_1 = 0.6\phi = 0.15$, $\phi_2 = 1.4\phi = 0.35$, $\pi_{2j} = 0.15$, $\pi_{0j} = (0.15)(1.4^3) = 0.4116$, $\pi_{1j} = 1 - \pi_{0j} - \pi_{2j} = 0.4384$. We have,

$$\alpha_1(\lambda_{1j}) = \pi_{0j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi) - \pi_{1j}\text{Bin}(n_j\lambda_{1j}; n_j, \phi_1) \approx \begin{cases} 0, & \text{if } \lambda_{1j} < 0 \\ -0.096, & \text{if } 0 \leq \lambda_{1j} < 1/3 \\ -0.064, & \text{if } 1/3 \leq \lambda_{1j} < 2/3 \\ -0.032, & \text{if } 2/3 \leq \lambda_{1j} < 1 \\ -0.027, & \text{if } \lambda_{1j} \geq 1 \end{cases}$$

and

$$\alpha_2(\lambda_{2j}) = \pi_{2j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi_2) - \pi_{0j}\text{Bin}(n_j\lambda_{2j}; n_j, \phi) \approx \begin{cases} 0, & \text{if } \lambda_{2j} < 0 \\ -0.132, & \text{if } 0 \leq \lambda_{2j} < 1/3 \\ -0.240, & \text{if } 1/3 \leq \lambda_{2j} < 2/3 \\ -0.262, & \text{if } 2/3 \leq \lambda_{2j} < 1 \\ -0.262, & \text{if } \lambda_{2j} \geq 1 \end{cases}$$

and hence $\alpha_1(\lambda_{1j})$ and $\alpha_2(\lambda_{2j})$ are minimized, respectively, when

$$\lambda_{1j} \in \left[0, \frac{1}{3}\right) \text{ and } \lambda_{2j} \in \left[\frac{2}{3}, \infty\right).$$

Applying the definitions of y^* and y^{**} provided in the revised derivation, we obtain

$$y^* = \frac{n_j \log\left(\frac{1-\phi_1}{1-\phi}\right) + \log\left(\frac{\pi_{1j}}{\pi_{0j}}\right)}{\log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)} \approx 0.6896, \quad y^{**} = \frac{n_j \log\left(\frac{1-\phi}{1-\phi_2}\right) + \log\left(\frac{\pi_{0j}}{\pi_{2j}}\right)}{\log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right)} = 3.$$

According to the theoretical development presented in your revised derivation, since $y^{**} = n_j$, $\alpha_2(\lambda_{2j})$ is minimized when λ_{2j} is in the interval $[1, \infty)$; however, according to our observation above, $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [2/3, \infty)$. Therefore, it appears the minimizing interval in the revised derivation does not include all minimizing values.

Please clarify this issue and provide a precise and complete mathematical derivation that covers the complete range of scenarios, including the scenario discussed above. Please demonstrate that the mathematical development covers special cases such as in the example above, and our previous set of examples, and if necessary, present additional examples demonstrating the validity of the mathematical development.

Comment 4

In some scenarios there may be more than one design that minimizes $\alpha(\lambda_{1j}, \lambda_{2j})$. The example presented in Comment 3 provides one such scenario because in that example $\alpha_1(\lambda_{1j})$ is minimized when $\lambda_{1j} \in [0, 1/3)$ and $\alpha_2(\lambda_{2j})$ is minimized when $\lambda_{2j} \in [2/3, \infty)$; therefore if $\hat{p}_j = 1$ the current dose could either be retained or de-escalated and both choices yield a design that minimizes $\alpha(\lambda_{1j}, \lambda_{2j})$. It appears the issue of non-uniqueness of the design may occur if $y^* \in \{0, 1, \ldots, n_j\}$ or $y^{**} \in \{0, 1, \ldots, n_j\}$. The revised derivation uses the design with λ^*_{1j} and λ^*_{2j} defined by equation (3) and (4) (in the revised derivation) if $\lambda^*_{1j} \leq \lambda^*_{2j}$, even if there are other choices that also minimize $\alpha(\lambda_{1j}, \lambda_{2j})$. Please clarify the conditions under which the design that minimizes $\alpha(\lambda_{1j}, \lambda_{2j})$ is unique, and the conditions under which the design that minimizes $\alpha(\lambda_{1j}, \lambda_{2j})$ is not unique. For cases when the design that minimizes $\alpha(\lambda_{1j}, \lambda_{2j})$ is not unique, please describe, with justification, which design should be used. Also, in the discussion please indicate if any special consideration is needed when $\lambda^*_{1j} > \lambda^*_{2j}$.