U.S. FOOD & DRUG ADMINISTRATION

DETERMINATION LETTER

Ying Yuan, Ph.D.
Bettyann Asche Murray Distinguished Professor
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1400 Pressler
Houston, Texas 77030

Dear Dr. Ying Yuan:

Please refer to the original submission received on March 9, 2020 under the Fit-for-Purpose (FFP) Initiative, and your amendments received November 2, 2020, January 7, 2021, and March 28, 2021, intended to support the use of the Bayesian Optimal Interval (BOIN) design as a statistical methodology for phase I dose finding clinical trials. We have completed our review of your submission, as amended, and have determined it is fit-for-purpose in the context outlined in this letter.

Goal and Intended Applications

The BOIN design is a statistical methodology for phase I dose finding clinical trials where the goal is to find the maximum tolerated dose (MTD) of a new drug. Here the MTD is defined as the dose with dose limiting toxicity (DLT) probability closest to a pre-specified target value. The submission states that phase I trial designs can be classified into three types: algorithm-based, model-based, and model-assisted; and it states that BOIN, a model-assisted design, combines an algorithm-based design (for example, the convention 3+3 design) and a model-based design (for example, the continuous reassessment method).

FDA Assessment

Based on an evaluation by a multidisciplinary review team, the following are noted.

1. The methodological review focused on the derivation of the BOIN design as presented in Liu and Yuan (2015)[1]. During the review, the team identified technical issues in the derivations presented in Liu and Yuan (2015). As a result of multiple information requests sent by the review team, the Applicant updated the design and derivation. This determination applies to the most refined version of the revised BOIN design summarized in Section 3 of the Biostatistics Review.

[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, 507-523.

2. 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 Applicant's 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 the Biostatistics Review). The condition $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$ is referred to as the non-informative prior. Therefore, our FFP determination applies only to the local BOIN design under the non-informative prior, as the FFP evaluation was requested for this specific form of the BOIN design. Additional research may be useful to evaluate the properties of the BOIN design in cases when the non-informative prior condition is not required.

3. In simulation studies presented in the Applicant's submission where several phase I trial designs were compared, BOIN generally performed well in the simulation scenarios considered. This statement does not imply that other phase I trial designs 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)[2], which are summarized in the Applicant's submission, 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.

A multidisciplinary team with representation from the Office of Biostatistics and the Office of Clinical Pharmacology in the Office of Translational Sciences, Center for Drug Evaluation and Research has reviewed all aspects of the submission. The review team finds that 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 multiple information requests (which present the revised form of the local BOIN design), and the relevant statistical literature. 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.

General Comments

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 described in Section 3 of the Biostatistics 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. In practice, one should carefully consider the requirements of the

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

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.

Sincerely,

Sylva H. Collins -S

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Sylva Collins, PhD
Director, Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research

Issam Zineh -S

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ENCLOSURE:

- Discipline Review: Biostatistics