Paper AS20

Beyond Toxicity : Accelerating Dose-Finding with Pharmacokinetic-Driven Bayesian Design PKBOIN-12

Anetta Xavier, eClinical Solution Pvt Ltd, Bengaluru, India

ABSTRACT

In early-phase clinical trials, especially those involving immunotherapies and targeted agents, the focus has shifted from identifying the Maximum Tolerated Dose (MTD) to determining the Optimal Biological Dose (OBD), which aims to achieve the best balance between therapeutic effect and safety. Although pharmacokinetic (PK) data—used to assess how a drug behaves in the body—are routinely collected, they are often overlooked in existing dose-finding strategies. To leverage this valuable information, we introduce PKBOIN-12, a model-assisted Bayesian design that incorporates PK data alongside toxicity and efficacy outcomes to improve OBD determination. This design can be expanded to handle late-onset treatment responses using time-to-event modeling. Simulation will be performed, to demonstrate that PKBOIN-12 enhances OBD selection accuracy, increases patient allocation to beneficial dose levels, and reduces the risk of underexposure. This design represents a significant step toward more precise and data-informed dosing strategies in early-phase clinical trials.

1. INTRODUCTION

A paradigm shifts in oncology with the introduction of molecularly targeted and immune-based therapies, including agents such as imatinib, trastuzumab, ipilimumab, and pembrolizumab. Unlike conventional cytotoxic chemotherapies, these treatments are designed to selectively interact with specific molecular abnormalities or immune pathways that are more prevalent in malignant cells than in normal tissues. As a result, targeted therapies and immune checkpoint inhibitors have become integral components of standard care across a wide range of malignancies, including melanoma, lung, renal, bladder, and hematologic cancers. Unlike conventional cytotoxic chemotherapies, these treatments are designed to selectively interact with specific molecular abnormalities or immune pathways that are more prevalent in malignant cells than in normal tissues. As a result, targeted therapies and immune checkpoint inhibitors have become integral components of standard care across a wide range of malignancies, including melanoma, lung, renal, bladder, and hematologic cancers.

Historically, dose-finding studies for cytotoxic agents focused on identifying the maximum tolerated dose (MTD), based on the assumption that both toxicity and efficacy increase monotonically with dose. In contrast, for immunotherapies and molecularly targeted agents, the relationship between dose, efficacy, and toxicity is often more complex and may be non-monotonic. Consequently, the emphasis has shifted toward identifying an optimal biological dose (OBD), which seeks to achieve a favorable balance between therapeutic activity and adverse effects by jointly considering efficacy and safety outcomes.

Existing dose-finding methodologies in early-phase clinical trials are commonly classified into rule-based, model-assisted, and model-based designs. Traditional rule-based approaches, most notably the 3+3 design, remain widely used due to their simplicity, although they are limited in efficiency and statistical rigor. More recently, model-based and model-assisted designs have been developed to improve dose selection by formally incorporating accumulating trial data. While many model-based designs were originally proposed to estimate the maximum tolerated dose (MTD), the emergence of targeted therapies and immunotherapies has motivated the development of approaches aimed at identifying the optimal biological dose (OBD) by jointly considering toxicity and efficacy outcomes. Model-assisted designs, in particular, have gained popularity due to their balance between operational simplicity and improved decision-making. Among these approaches, the BOIN-12 design is notable as the only model-assisted method that explicitly integrates both toxicity and efficacy to guide OBD selection and has received regulatory acceptance, including use in early-phase trials.

Despite its advantages, the BOIN-12 design has several important limitations. In particular, it relies solely on binary toxicity and efficacy outcomes observed at a fixed assessment time, without explicitly accounting for dose–exposure relationships or interpatient variability in drug pharmacokinetics. As a result, BOIN-12 may not fully capture delayed toxicities or heterogeneous exposure levels that are common in targeted therapies and immunotherapies, potentially leading to suboptimal dose selection. Moreover, the absence of pharmacokinetic information limits its ability to borrow mechanistic insight when efficacy and toxicity signals are sparse in early-stage trials.

In early phase dose findings one of the objective is to evaluate the pharmacokinetics (PK) exposure of the target drug. Pharmacokinetic data describes how a drug is processed within the body over time, encompassing absorption, distribution, metabolism, and elimination. This information is critical for understanding drug exposure in humans and provides valuable insight into treatment effects. PK measures are often closely associated with clinical efficacy endpoints, including tumor response, immune activation, and survival outcomes. By incorporating the PK outcomes into early phase dose-finding clinical trials could enhance the accuracy of OBD selection.

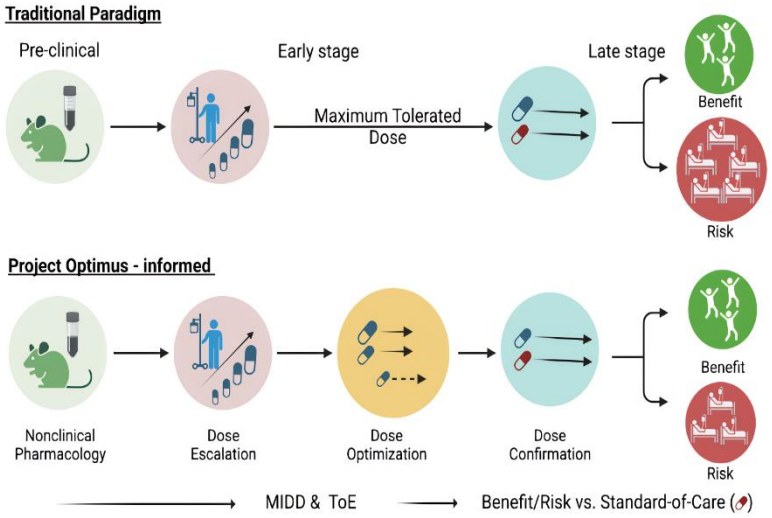
There are different dose-finding trial mostly the model-based designs in the early phase that has incorporated PK outcomes. CRM design by integrating PK data as a covariate into a parametric dose-response logit model (PKCOV). Hierarchical PK-toxicity model in a cross-over trial setting. The CRM design by incorporating an adjustment based on the latest AUC assessment instead of the standardized dose. The drawback of these designs was that they centred on finding the MTD strictly on the toxicity outcomes and did not include did not include efficacy outcomes to select the optimal dose considering the benefit risk balance.

In this paper the objective is to provide information on the PKBOIN-12 design which is a Bayesian optimal interval design that integrates the toxicity, efficacy, and PK outcomes to select the optimal dose. PKBOIN-12, developed by Dr. Hao Sun of Bristol Myers Squibb and Tu Jieqi of the University of Illinois Chicago, is an innovative dose-finding method that enhances the established BOIN12 algorithm by incorporating Pharmacokinetic (PK) information into the Optimal Biological Dose (OBD) determination process. As a model-assisted approach, PKBOIN-12 avoids the need for complex real-time model estimation during trial conduct. The design builds directly upon the BOIN-12 framework and leverages its existing rank-based desirability score (RDS) table, which has already been applied in multiple clinical studies. This continuity enhances the practical feasibility of PKBOIN-12, making it easier to implement in real-world clinical settings compared with alternative dose-finding methods that incorporate pharmacokinetic information. By incorporating PK measures, PKBOIN-12 enables early identification and exclusion of pharmacologically insufficient dose levels during trial conduct, as well as more informed optimal biological dose selection at the conclusion of the study.

1.1 PROJECT OPTIMUS: A REGULATORY SHIFT TOWARD THE OBD

Project Optimus is a U.S. Food and Drug Administration (FDA) initiative aimed at reforming oncology drug development by shifting the focus from identifying the maximum tolerated dose (MTD) to determining the optimal biological dose (OBD). The central objective is to select doses that maximize therapeutic benefit while minimizing toxicity, ultimately improving patient outcomes.

To support this shift, the FDA released draft guidance titled “Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.” This guidance underscores that dose-finding can no longer rely solely on safety and tolerability endpoints. Instead, efficacy, pharmacokinetics, and exposure–response relationships must be systematically incorporated early in development.



Under the traditional paradigm, drug development progresses from preclinical studies into early clinical trials focused primarily on dose escalation to identify the MTD. This single dose is then advanced into late-stage trials under the assumption that higher exposure leads to greater efficacy. However, clinical experience has repeatedly shown that escalating to the MTD may increase toxicity without delivering proportional clinical benefit, leaving benefit–risk optimization to be addressed too late in development.

In contrast, a Project Optimus–informed approach reframes dose selection as an iterative, data-driven process. Following

nonclinical pharmacology and initial dose escalation, development explicitly incorporates dose optimization and dose confirmation stages. These stages leverage clinical pharmacology, exposure–response analyses, and Model-Informed Drug Development (MIDD) to characterize how different doses influence both efficacy and safety. Rather than defaulting to the MTD, multiple dose levels are evaluated to identify a dose or dose range that achieves the most favorable benefit–risk profile, particularly in comparison to standard of care. This paradigm shift ensures that dose selection is scientifically justified, patient-centric, and aligned with regulatory expectations.

2. METHODOLOGY

Consider an early-phase clinical trial evaluating D dose levels. For each patient, two binary outcomes are observed: toxicity Y_T, where $Y_T = \mathbf{1}$indicates a dose-limiting toxicity (DLT), and efficacy Y_E, where $Y_E = 1$indicates a treatment response. Let p_T and q_T denote the maximum acceptable toxicity probability and the minimum acceptable efficacy probability, respectively.
At dose level $\boldsymbol{d}$, the true toxicity and efficacy probabilities are denoted by $\boldsymbol{p_d}$and $\boldsymbol{q_d}$. Toxicity probabilities are assumed to increase monotonically with dose ($p_1 < \cdots < p_D$), while no monotonicity is assumed for efficacy. The maximum tolerated dose (MTD) is defined as

$$d_{MTD} = \arg max_d p_d I(p_d \leq p_T)$$

p_d : Observed toxicity probability at dose d
p_T: pre-specified toxicity threshold
If all the dose levels have $p_d > p_T$, the MTD does not exist, and the trial should be ended.

Let $n_{d,T}$ represent the number if patients who experience a DLT and $n_{d,E}$ denote the number of patients who saw efficacy response at dose level d. The outcomes based on toxicity and efficacy is categorized into four types:

O_1:No toxicity, Efficacy ($Y_T = 0, Y_E = 1$)
O_2: No toxicity, No efficacy (Y_T =0, Y_E =0)
O_3: Toxicity, Efficacy (Y_T =1, Y_E =1)
O_4: Toxicity, No efficacy (Y_T =1, Y_E =0)

Let $n_{d,i}$be the number of patients in category $O_i$at dose d, with total sample size $n_d = \sum_i n_{d,i}$. The total numbers of toxicities and responses are $n_{d,T} = n_{d,3} + n_{d,4}$ and $n_{d,E} = n_{d,1} + n_{d,3}$, respectively. The corresponding observed toxicity and efficacy rates are $\hat{p}_d = n_{d,T}/n_d and \hat{q}_d = n_{d,E}/n_d$.

2.1 BAYESIAN OPTIMAL INTERVAL DESIGN-12 (BOIN-12) DESIGN

BOIN12 is a model-assisted dose-finding design developed to identify the optimal biological dose (OBD) by explicitly balancing treatment efficacy and toxicity, particularly in settings with complex or non-monotonic dose–response relationships. Unlike traditional MTD-based approaches, BOIN12 quantifies the risk–benefit trade-off using a utility-based framework.

Patient outcomes are categorized into four toxicity–efficacy combinations, each assigned a utility score $u_i \in [0,100]$. The most desirable outcome (efficacy without toxicity) is assigned a utility of 100, while the least desirable outcome (toxicity without efficacy) is assigned a utility of 0. Utilities for the remaining outcomes are prespecified by clinical investigators to reflect clinical preferences.

For dose level d, the expected utility is defined as

$$EU_d = \sum_{i=1}^{4} u\, \pi_{d,i}$$

where $\pi_{d,i}$ denotes the probability of outcome i. A higher expected utility indicates a more favorable benefit–risk profile. Under BOIN12, the OBD is defined as the dose with the maximum expected utility.

In the BOIN-12 framework, dose-level utility is characterized through a quasi beta–binomial formulation. To guide interim dose-assignment decisions, Lin et al. introduced a rank-based desirability score (RDS) that summarizes the combined evidence of efficacy and toxicity at each dose level. Let u_d denote the standardized desirability of dose d, defined as the expected utility scaled to the unit interval. A pseudo-event count, x_d, is constructed by aggregating patient-level utility indicators and rescaling them to mimic binomial-type data. Specifically, this quantity represents the effective number of "successes" among $n_d$treated patients and is assumed to follow a quasi-binomial distribution with success probability u_d .

Within a Bayesian setting, a noninformative Beta (1,1) prior is assigned to u_d . Given the observed pseudo-count x_d and sample size n_d, the resulting posterior distribution of the desirability parameter is

$$u_d | \, n_d, x_d \sim \text{Beta}\,(1+ x_d, 1+ n_d - x_d).$$

The Rank Desirability Score (RDS) is used to identify the most promising dose at each step of the trial. The rank-based desirability score (RDS) is defined by ordering the posterior probabilities.

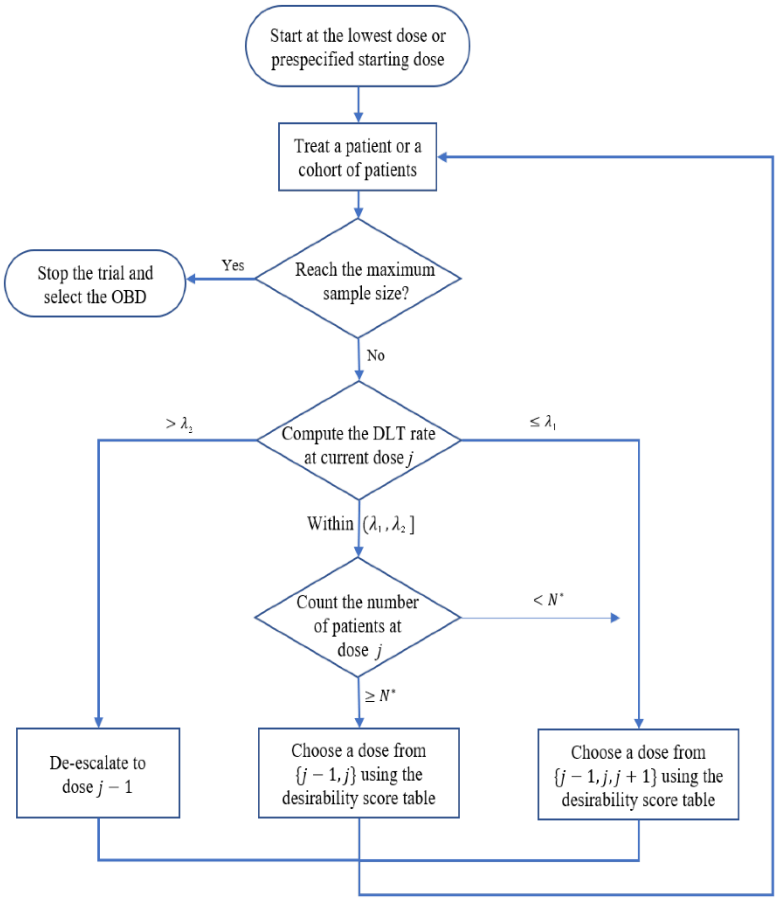
$$\Pr(u_d > u_b | n_d, x_d)$$

across all dose levels, where u_b denotes a prespecified utility benchmark. This benchmark is defined as the midpoint between the target utility and the maximum achievable utility, with the target utility given by

The dose with a higher RDS is equivalent to having a higher posterior probability.

2.1.1 STEPS OF BOIN 12 DESIGN

Let $c = 1$ denote the initial cohort and let d represent the lowest or a prespecified starting dose level. Let $N^* = 6$ be the predetermined minimum sample size required for stable dose evaluation. The BOIN-12 dose-finding procedure proceeds as follows.



1. Treatment Assignment

Enroll and treat cohort c at the current dose level d.

2. Toxicity Evaluation and Dose Decision

At dose level d, compute the observed toxicity rate $\hat{p}_d = n_{d,T}/n_d$, where $n_{d,T}$ and n_d denote the number of observed dose-limiting toxicities and the total number of treated patients, respectively. The value of $\hat{p}_d$ is then compared with two prespecified toxicity boundaries $0 < \lambda_1 < \lambda_2 < 1$, which are determined based on the target toxicity rate p_T.

The next dose level d' is selected according to the following rules:

(a) *Excessive toxicity:* If $\hat{p}_d \geq \lambda_2$, de-escalate to the next lower dose level, setting $d' = d - 1$.

(b) *Escalation condition:* If $\hat{p}_d < \lambda_2$, at least nine patients have been treated at dose d, and the next higher dose level $d + 1$ has not yet been explored, escalate to $d' = d + 1$.

(c) *Acceptable toxicity range:* If $\lambda_1 < \hat{p}_d < \lambda_2$:

- When $n_d \geq N^*$, select the next dose d' from the admissible set $\{d - 1, d\}$ based on the larger rank-based desirability score (RDS).
- When $n_d < N^*$, select d' from the admissible set $\{d - 1, d, d + 1\}$ with the highest RDS.

(d) Low toxicity: If $\hat{p}_d \leq \lambda_1$, select the next dose d' from the admissible set $\{d - 1, d, d + 1\}$ that maximizes the RDS.

3. Cohort Update

Increment the cohort index by one ($c = c + 1$) and update the current dose level to $d = d'$.

4. Iteration

Repeat Steps 1–3 until the maximum planned sample size is attained, at which point the optimal biological dose is selected based on accumulated trial data.

2.1.2 OPTIMAL BIOLOGICAL DOSE DETERMINATION AND ELIMINATION CRITERIA

Upon completion of patient enrollment, BOIN-12 identifies the optimal biological dose through a two-stage post-trial decision procedure. First, the maximum tolerated dose (MTD) is estimated by applying isotonic regression to the observed dose-specific toxicity rates $\{\hat{p}_d\}_{d=1}^{D}$, yielding monotone-adjusted estimates $\{\tilde{p}_d\}_{d=1}^{D}$. The estimated MTD, denoted d_{MTD}^{*}, is defined as the dose level whose adjusted toxicity rate is closest to the prespecified target toxicity probability p_T.

In the second stage, the OBD is selected from the set of dose levels not exceeding the estimated MTD, that is, from $\{1, \ldots, d_{\text{MTD}}^{*}\}$, by choosing the dose with the highest estimated utility. To safeguard against exposing patients to overly toxic or insufficiently effective treatments, dose elimination rules are applied throughout the trial and during final dose selection. Specifically, a dose level $d$and all higher doses are removed from further consideration if the posterior probability that its toxicity rate exceeds the target level $p_T$surpasses a prespecified threshold C_T. Similarly, a dose level is excluded if the posterior probability that its efficacy rate falls below the target efficacy level $q_E$exceeds a prespecified cutoff C_E.

Noninformative Beta$(1, 1)$ priors are assumed for both toxicity and efficacy probabilities. Only dose levels that satisfy both safety and efficacy criteria remain eligible for assignment to subsequent cohorts. If all dose levels are eliminated based on these criteria, the trial is terminated early without recommending a dose.

2.2 PHARMACOKINETICS BAYESIAN OPTIMAL INTERVAL DESIGN-12 (PKBOIN-12) DESIGN

2.2.1 PHARMACOKINETIC COMPONENT OF THE PKBOIN-12 DESIGN

The PKBOIN-12 design extends the BOIN-12 framework by incorporating pharmacokinetic (PK) information to improve identification of the optimal biological dose (OBD) in early-phase trials. In early-phase, multiple pharmacokinetic (PK) endpoints may be collected, including measures such as area under the concentration–time curve, maximum concentration, time to maximum concentration, half-life, clearance, and volume of distribution. Within the PKBOIN-12 design, one clinically relevant continuous PK endpoint is prespecified for dose evaluation. Let $d = 1, \dots, D$ denote the dose levels, and let $r_d$represent the true mean value of the selected PK endpoint at dose level d, which is assumed to increase monotonically with dose. A target PK value $r_P$is specified to represent the minimum exposure required for biological activity, such that dose levels with $r_d < r_P$ considered to be an ineffective dose.However, excessive PK exposure does not necessarily imply improved efficacy and may be associated with increased toxicity; therefore, PK information is used to support dose selection rather than replace clinical outcomes.

For patient j treated at dose level d, the observed PK measurement is denoted by $r_{d,j}$, with $I_d$representing the set of patients assigned to that dose and $n_d = | I_d |$the corresponding sample size. The observed mean PK value at dose $d$is calculated as $\hat{r}_d = n_d^{-1} \sum_{j \in I_d} r_{d,j}$. Individual PK measurements are assumed to follow a normal distribution with mean $r_d$and variance σ_d^2, while the dose-specific mean $r_d$is assigned a weakly informative truncated normal prior with variance $\sigma_0^2$to ensure positivity.

The posterior distribution of r_d is given by

$$r_d | \hat{r}_d, \sigma_d^2 \sim \text{truncated-N}\left(\frac{n_d \hat{r}_d}{\sigma_d^2\left(\frac{1}{\sigma_d^2}+\frac{n_d}{\sigma_d^2}\right)}, \frac{1}{\frac{1}{\sigma_d^2}+\frac{n_d}{\sigma_d^2}}\right)$$

In the PKBOIN-12 design if the small term $\frac{1}{\sigma_0^2}$ is ignored, the maximum a posteriori (MAP) estimate of the dose-specific mean PK value serves as the Bayesian point estimate used to assess whether a dose achieves adequate pharmacokinetic exposure and to support dose selection decisions.

To classify pharmacokinetic (PK) adequacy, a cutoff value τ_1, satisfying $0 \le \tau_1 \le r_P$, is introduced, where $r_P$denotes the prespecified target mean PK value corresponding to adequate drug exposure. The cutoff is determined by minimizing the probability of incorrect PK classification under two competing hypotheses:

H_{P0}, which assumes sufficient exposure with true mean PK value $r_d = r_P$, and
H_{P1}, which assumes insufficient exposure with true mean PK value $r_d = r_I$, where $r_I$represents a prespecified ineffective PK level.

Assuming equal prior probabilities for the two hypotheses, the optimal cutoff is defined as the midpoint between $r_P$and r_I, such that $\tau_1 = (r_P + r_I)/2$. In practice, doses with an estimated mean PK value exceeding $\tau_1$are classified as achieving adequate PK exposure, providing a simple and interpretable decision rule for identifying doses with insufficient exposure.

The PK-based classification is integrated with toxicity and efficacy information within the BOIN-12 framework to guide dose escalation, de-escalation, and final OBD selection, thereby improving decision-making in small-sample early-phase trials.

2.2.2 DOSE FINDING ALGORITHM

The dosing algorithm of PKBOIN-12 is based on that of the BOIN12 design. The dose allocation algorithm of PKBOIN-12 is based on that BOIN12 design. The $d_{PK,min}$ as the lowest dose level such that its observed PK sample mean is greater than the cutoff point. The proposed design PKBOIN-12 uses quasi-events (x_d) and desirability scores for dose decisions, combining BOIN12's utility framework with PK data for more flexible OBD selection.

Unlike BOIN12, which limits the admissible set to 3 doses, PKBOIN-12 expands it to include more doses with effective PK. The set starts from d^*=min{d −1, $d_{PK,min}$}, such that the new constructed admissible set, A, is a subset of {d^*, . . . , d + 1}.

Let the sample size cutoff $N^* = 6$, c=1 and d as the lowest or a pre-specified dose level.

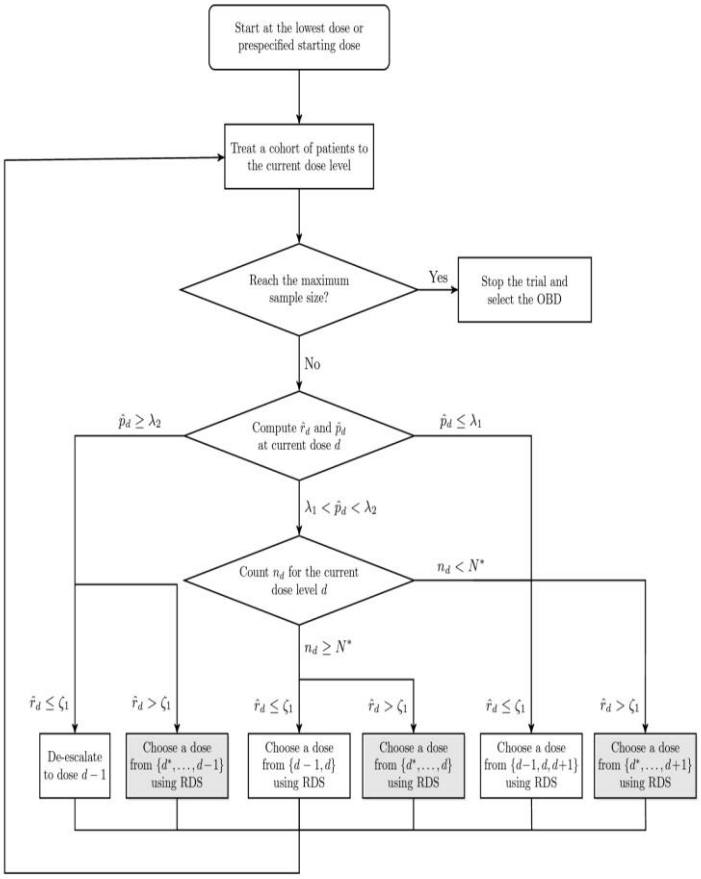
2.2.2.1 STEPS OF PKBOIN 12 DESIGN

1. Treatment Assignment

Enroll and treat a cohort of patients at the current dose level d, starting from the lowest dose or a prespecified starting dose.

2.Outcome Estimation

Using all accumulated data at dose level $\boldsymbol{d}$, calculate the observed toxicity rate $\widehat{\boldsymbol{p}}_{\boldsymbol{d}}$, the observed efficacy rate $\widehat{\boldsymbol{q}}_{\boldsymbol{d}}$, and the observed mean PK value $\widehat{\boldsymbol{r}}_{\boldsymbol{d}}$.



3: Dose Decision When PK Exposure Is Inadequate

If the estimated PK mean satisfies $\widehat{\boldsymbol{r}}_{\boldsymbol{d}} \leq \boldsymbol{\zeta_1}$, indicating insufficient PK exposure, determine the next dose based solely on toxicity and efficacy, following BOIN-12 rules:

(a) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} \geq \boldsymbol{\lambda_2}$, de-escalate to the next lower dose $\boldsymbol{d-1}$.

(b) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} < \boldsymbol{\lambda_2}$, at least nine patients have been treated at dose $\boldsymbol{d}$, and dose $\boldsymbol{d+1}$has not yet been explored, escalate to dose $\boldsymbol{d+1}$.

(c) If $\boldsymbol{\lambda_1} < \widehat{\boldsymbol{p}}_{\boldsymbol{d}} < \boldsymbol{\lambda_2}$, compare the number of treated patients $\boldsymbol{n_d}$with $\boldsymbol{N^*}$:

- When $\boldsymbol{n_d} \geq \boldsymbol{N^*}$, select the next dose from the admissible set $\{\boldsymbol{d-1}, \boldsymbol{d}\}$using randomized dose selection (RDS).
- Otherwise, select the next dose from $\{\boldsymbol{d-1}, \boldsymbol{d}, \boldsymbol{d+1}\}$using RDS.

(d) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} \leq \boldsymbol{\lambda_1}$, select the next dose from $\{\boldsymbol{d-1}, \boldsymbol{d}, \boldsymbol{d+1}\}$using RDS.

4: Dose Decision When PK Exposure Is Adequate

If $\widehat{\boldsymbol{r}}_{\boldsymbol{d}} > \boldsymbol{\zeta_1}$, indicating adequate PK exposure, incorporate PK information into dose selection and expand the admissible dose set downward:

(a) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} \geq \boldsymbol{\lambda_2}$, select the next dose from the expanded admissible set $\{\boldsymbol{d^*}, \ldots, \boldsymbol{d-1}\}$using RDS.

(b) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} < \boldsymbol{\lambda_2}$, at least nine patients have been treated at dose $\boldsymbol{d}$, and dose $\boldsymbol{d+1}$has not yet been explored, escalate to dose $\boldsymbol{d+1}$.

(c) If $\boldsymbol{\lambda_1} < \widehat{\boldsymbol{p}}_{\boldsymbol{d}} < \boldsymbol{\lambda_2}$, compare $\boldsymbol{n_d}$with $\boldsymbol{N^*}$:

- When $\boldsymbol{n_d} \geq \boldsymbol{N^*}$, select the next dose from $\{\boldsymbol{d^*}, \ldots, \boldsymbol{d}\}$using RDS.
- Otherwise, select the next dose from $\{\boldsymbol{d^*}, \ldots, \boldsymbol{d+1}\}$using RDS.

(d) If $\widehat{\boldsymbol{p}}_{\boldsymbol{d}} \leq \boldsymbol{\lambda_1}$, select the next dose from $\{\boldsymbol{d^*}, \ldots, \boldsymbol{d+1}\}$using RDS.

5: Update Dose and Cohort Index

Increment the cohort index $\boldsymbol{c = c+1}$and update the current dose to the selected dose $\boldsymbol{d = d'}$.

6: Trial Continuation

Repeat Steps 1–5 until the prespecified maximum sample size is reached.

2.2.3 OBD SELECTION AND ELIMINATION CRITERIA

After completion of the trial, toxicity, efficacy, and pharmacokinetic (PK) outcomes are estimated for each dose level using all observed data. To enforce the assumed monotonic increasing relationship between dose level and both toxicity and PK outcomes, isotonic regression is applied to the observed toxicity rates $\{\hat{p}_d\}_{d=1}^{D}$and observed PK sample means $\{\hat{r}_d\}_{d=1}^{D}$. Specifically, the pool-adjacent-violators algorithm (PAVA) is used to obtain the monotone-adjusted estimates $\{\tilde{p}_d\}_{d=1}^{D}$for toxicity and $\{\tilde{r}_d\}_{d=1}^{D}$for PK exposure.

Consistent with the BOIN-12 framework, the isotonic estimates of toxicity are used to identify the maximum tolerated dose (MTD). However, PKBOIN-12 differs from BOIN-12 in determining the lower bound of the final admissible dose set. Whereas BOIN-12 defaults to the lowest tested dose as the lower limit, PKBOIN-12 incorporates isotonic PK estimates to ensure that only doses achieving sufficient PK exposure are considered.

The final optimal biological dose (OBD) is selected through the following three-step procedure:

1. **Identification of the MTD**
   Apply isotonic regression to the observed toxicity rates $\{\hat{p}_d\}_{d=1}^{D}$to obtain monotone estimates $\{\tilde{p}_d\}_{d=1}^{D}$. The MTD is defined as the dose level d_{MTD}^{*}that minimizes the absolute deviation between the isotonic toxicity estimate and the target toxicity rate p_T, that is,
   $$d_{\text{MTD}}^{*} = \arg\min_{d} \mid \tilde{p}_d - p_T \mid.$$

2. **Identification of the Minimum PK-Efficacious Dose**
   Apply isotonic regression to the observed PK sample means $\{\hat{r}_d\}_{d=1}^{D}$to obtain monotone PK estimates $\{\tilde{r}_d\}_{d=1}^{D}$. The minimum dose achieving adequate PK exposure, denoted $d_{\text{PK,min}}^{*}$, is defined as the dose level that minimizes the absolute deviation between the isotonic PK estimate and the target PK value r_P, that is,
   $$d_{\text{PK,min}}^{*} = \arg\min_{d} \mid \tilde{r}_d - r_P \mid.$$

3. **Final OBD Selection Using Utility**
   The final OBD is selected as the dose level with the highest estimated utility among the candidate set $\{d_{\text{PK,min}}^{*}, \ldots, d_{\text{MTD}}^{*}\}$.

By restricting the final candidate set to doses that demonstrate adequate PK exposure, PKBOIN-12 avoids selecting dose levels that are unlikely to be efficacious. This approach contrasts with BOIN-12, which may include doses with insufficient exposure in the final selection process. The more targeted admissible set used by PKBOIN-12 increases the likelihood of correctly identifying the OBD by excluding pharmacokinetically inadequate doses. Even when the exact OBD is not selected, this refined candidate set improves the probability of choosing a dose that is close to the true OBD. This advantage is illustrated in simulation scenarios 5 and 13, where PKBOIN-12 demonstrates improved performance by systematically excluding doses lacking sufficient efficacy.

3. SIMULATION AND RESULT

A simulation was conducted to evaluate and compare the operating characteristics of the PKBOIN-12 design with those of the BOIN-12 design. The simulations considered $D = 6$dose levels, with dose level 1 designated as the starting dose. Patients were enrolled in cohorts of three, and the maximum sample size for each simulated trial was set to 45 patients.

Both toxicity and efficacy outcomes were modeled as binary variables. The target toxicity probability was specified as $p_T = 0.30$, and the minimum acceptable efficacy probability was set to $q_E = 0.20$. Utility scores of $u_2 = 40$and $u_3 = 60$ were assigned to outcomes $O_2$and O_3, respectively. To ensure fair comparisons between designs, common tuning parameters were used across all simulations, including toxicity interval boundaries $\lambda_1 = 0.276$and $\lambda_2 = 0.419$, the upper utility bound $u_b = 0.705$, and identical randomized dose selection (RDS) tables.

3.1 PHARMACOKINETIC MODELING

For PKBOIN-12, the area under the concentration–time curve (AUC) was selected as the pharmacokinetic (PK) endpoint. The target PK value was fixed at $r_P = 6000$. While toxicity and efficacy probabilities were assumed to be constant for all patients treated at the same dose level, individual PK outcomes were allowed to vary across patients to reflect realistic inter-subject variability in drug exposure.
Specifically, individual-level PK values $r_{d,j}$were generated from a truncated normal distribution to ensure positivity:

$$r_{d,j} \sim \text{truncated-N}\,(r_d, (0.25\, r_d)^2),$$

corresponding to a coefficient of variation of 25%. Here, $\mathrm{r_d}$denotes the true mean PK value at dose level d.
To capture the influence of PK variability on clinical outcomes, individual-level toxicity and efficacy probabilities were linked to the realized PK values according to

$$p_{d,j} = min\left\{p_d\left(1+g_P\frac{r_{d,j}-r_d}{r_d}\right),\ 1\right\}, q_{d,j} = min\left\{q_d\left(1+g_P\frac{r_{d,j}-r_d}{r_d}\right),\ 1\right\},$$

where $g_P$quantifies the strength of the association between PK exposure and the individual toxicity and efficacy risks. In the primary simulations, $g_P$was set to 1, representing a moderate exposure–response relationship. Binary toxicity and efficacy outcomes were then generated based on these individual-level probabilities.

3.2 SIMULATION IMPLEMENTATION

The tables below summarize the operating characteristics of BOIN-12 and PKBOIN-12 across four simulation scenarios constructed to exhibit monotonic increasing relationships between dose level and toxicity, efficacy, and pharmacokinetic (PK) outcomes, with different dose levels prespecified as the true optimal biological dose (OBD).

Scenario 1: True OBD = Dose Level 5

In Scenario 1, dose level 5 was designated as the true OBD and (by design) was the only dose achieving adequate PK exposure. PKBOIN-12 selected the true OBD with a probability of 41%, which is 10 percent higher than BOIN-12. In contrast, BOIN-12 showed a non-negligible chance of selecting lower PK-ineffective doses (dose levels 1–3), with a combined selection probability of 13.2%, whereas PKBOIN-12 did not select these doses. PKBOIN-12 also allocated slightly more patients to the true OBD (12.6 vs 11.5 on average) while reducing allocation to the lower dose levels.

	Selection Probability						*Number of Assigned Patients*					*Duration*
	1	*2*	*3*	*4*	*5*	*ET*	*1*	*2*	*3*	*4*	*5*	*Months*
BOIN12	*1.7*	*2.5*	*9*	*19*	***31***	*0.1*	*3.8*	*4.4*	*5.8*	*8.2*	***11.5***	*38.4*
PKBOIN12	*0.0*	*0.0*	*0*	*3.3*	***41***	*1.9*	*3*	*3.3*	*5.1*	*8.2*	***12.6***	*38.4*

Scenario 2: True OBD = Dose Level 4

In Scenario 2, dose level 4 was designated as the true OBD. PKBOIN-12 selected the true OBD with a probability of 53.4%, which is 3.4 percent than BOIN-12. In contrast, BOIN-12 exhibited a non-negligible probability of selecting lower dose levels (dose levels 1–3), with a combined selection probability of 10.1%, whereas PKBOIN-12 reduced this probability to 2.4%. PKBOIN-12 also showed a lower tendency to select the higher dose level 5 (15.4% vs 17.2%) and allocated slightly more patients to the true OBD (14.6 vs 14.5 on average).

	Selection Probability						*Number of Assigned Patients*					*Duration*
	1	*2*	*3*	*4*	*5*	*ET*	*1*	*2*	*3*	*4*	*5*	*Months*
BOIN12	*1.6*	*2.5*	*6*	***50***	*17.2*	*0.3*	*3.9*	*4.5*	*5.5*	***14.5***	*7.0*	*37.9*
PKBOIN12	*0.0*	*0.0*	*2.4*	***53.4***	*15.4*	*0.3*	*3.1*	*4.1*	*6.1*	***14.6***	*6.0*	*37*

Scenario 3: True OBD = Dose Level 2

In Scenario 3, dose level 2 was designated as the true OBD. PKBOIN-12 selected the true OBD with a probability approximately 13.4 percentage points higher than BOIN-12. In contrast, BOIN-12 more frequently selected higher dose levels despite the true OBD occurring at a lower dose, whereas PKBOIN-12 effectively limited escalation by incorporating PK information. As a result, PKBOIN-12 allocated more patients to the true OBD while reducing allocation to higher dose levels with less favorable safety profiles.

	Selection Probability						*Number of Assigned Patients*					*Duration*
	1	*2*	*3*	*4*	*5*	*ET*	*1*	*2*	*3*	*4*	*5*	*Months*
BOIN12	*35*	***43***	*14.3*	*2.3*	*0.1*	*1.5*	*17.3*	***17.5***	*7.5*	*1.9*	*0.5*	*36.7*
PKBOIN12	*18*	***59.2***	*17.0*	*2.4*	*0.2*	*2.4*	*16.2*	***18***	*7.4*	*1.8*	*0.3*	*36.5*

Scenario 4: True OBD = Dose Level 1

In Scenario 4, dose level 1 was designated as the true OBD, and all dose levels were assumed to achieve adequate PK exposure. Both BOIN-12 and PKBOIN-12 selected the true OBD with approximately 70% probability. PKBOIN-12 showed a marginal improvement of approximately 0.4 percentage points compared with BOIN-12. Patient allocation patterns were similar across the two designs, with most patients assigned to the lowest dose level.

	Selection Probability						*Number of Assigned Patients*					*Duration*
	1	*2*	*3*	*4*	*5*	*ET*	*1*	*2*	*3*	*4*	*5*	*Months*
BOIN12	***67***	*19.2*	*2.5*	*0.1*	*0*	*8.3*	***27.8***	*10*	*3.1*	*0.2*	*0.0*	*34.8*
PKBOIN12	***70***	*18.5*	*2.6*	*0.2*	*0.1*	*8.7*	***28***	*10*	*2.9*	*0.5*	*0.1*	*34.9*

The simulation studies demonstrate that incorporating pharmacokinetic (PK) information substantially improves the operating characteristics of the BOIN-12 design in selecting the Optimal Biological Dose. In multiple scenarios where ineffective dose levels were present, BOIN-12 exhibited a relatively high probability of selecting such doses as the optimal biological dose (OBD), which could result in advancing subtherapeutic doses to subsequent trial phases and jeopardizing clinical development. In contrast, PKBOIN-12 consistently reduced the likelihood of selecting PK-ineffective dose levels by explicitly excluding doses that failed to achieve adequate exposure. Across these scenarios, PKBOIN-12 maintained a comparable probability of avoiding overly toxic doses while improving the accuracy of OBD identification and allocating more patients to biologically relevant dose levels. These results indicate that integrating PK information into the BOIN-12 framework enhances dose selection without compromising safety or trial efficiency.

4. APPLICATION AND SOFTWARE

4.1 APPLICATION OF THE BOIN DESIGNS

The Bayesian Optimal Interval (BOIN) family of designs has been widely adopted in early-phase clinical trials, particularly in oncology, due to its simplicity, transparency, and operating characteristics comparable to model-based approaches. In 2021, the U.S. Food and Drug Administration (FDA) granted the BOIN design a fit-for-purpose designation for dose-finding under its Drug Development Tools (DDT) Fit-for-Purpose Initiative, further supporting its regulatory acceptance and increasing its use in drug development programs.

The BOIN-12 design—an extension of BOIN that jointly considers toxicity and efficacy outcomes—has been implemented in real clinical studies, especially in the context of novel immunotherapies. For example, BOIN-12 has been applied in a Phase I/II study of enhanced CD33-directed CAR-T cells in adult patients with relapsed or refractory acute myeloid leukemia (ClinicalTrials.gov Identifier: NCT04835519) and in a Phase I trial evaluating CD5 CAR-T cell therapy in subjects with relapsed or refractory T-cell acute lymphoblastic leukemia. These applications demonstrate that BOIN-12 is feasible in contemporary dose-finding trials and can be integrated into standard trial operations while providing interpretable and transparent decision rules for investigators. Despite these successful implementations, BOIN-12 relies solely on clinical toxicity and efficacy outcomes and does not formally incorporate pharmacokinetic (PK) information, even though PK data are routinely collected in many early-phase studies. Integrating PK outcomes can help identify dose levels that not only meet safety and efficacy criteria but also achieve adequate systemic exposure, thereby reducing the risk of advancing pharmacokinetically ineffective doses into later-stage development.

The proposed PKBOIN-12 design builds upon the established BOIN-12 framework by incorporating PK measurements into both interim dose-allocation decisions and final optimal biological dose (OBD) selection. PKBOIN-12 preserves the operational simplicity and interval-based rules that have facilitated real-world use of BOIN-12, while augmenting them with PK-based screening to prioritize biologically relevant doses. Although PKBOIN-12 has not yet been reported in a completed clinical trial, its formulation directly addresses a practical challenge encountered in many dose-finding studies and is readily implementable using routinely collected PK data.

PKBOIN-12 is particularly well suited for early-phase oncology trials in which PK data are collected alongside toxicity and preliminary efficacy outcomes. For example, in a phase I/II dose-escalation study of a novel anticancer agent, patients may be treated sequentially at increasing dose levels with PK endpoints such as area under the concentration–time curve (AUC) measured after initial dosing. In such settings, substantial inter-patient variability in drug exposure is common, and reliance on clinical outcomes alone may result in selection of doses that fail to achieve adequate exposure.

Under PKBOIN-12, a clinically relevant PK endpoint is prespecified, and a target PK value is defined based on preclinical or early clinical evidence. During the trial, PK information is incorporated into dose-allocation decisions by excluding dose levels that do not achieve sufficient exposure, while maintaining the interval-based escalation structure of BOIN-12. At trial completion, isotonic regression is applied to toxicity and PK outcomes to identify candidate doses that are both safe and pharmacokinetically adequate, from which the OBD is selected using a utility-based criterion.

Overall, PKBOIN-12 maintains the simplicity and transparency of BOIN-type designs while explicitly addressing the risk of advancing pharmacokinetically ineffective doses to later-stage studies. As demonstrated by the simulation studies, this approach can improve dose-selection accuracy and patient allocation without increasing trial duration, making PKBOIN-12 a practical and clinically relevant extension for early-phase trials where PK considerations are critical.

4.2 SOFTWARE AVAILABILITY AND IMPLEMENTATION

User-friendly software is available to support the practical implementation of BOIN-type designs. In particular, the BOIN-12 design is implemented in the BOIN software hosted at www.trialdesign.org, an interactive web-based platform developed to facilitate the design and conduct of early-phase clinical trials. The platform allows investigators to specify design parameters, generate dose-escalation decision rules, and evaluate operating characteristics through simulation, making BOIN-12 readily accessible to clinicians and trial statisticians.

The proposed PKBOIN-12 design is implemented in an R-based framework developed by the authors that extends BOIN-12 by incorporating pharmacokinetic information into dose selection.

5. CONCLUSION

This paper introduces PKBOIN-12, a practical extension of the BOIN-12 design that formally incorporates pharmacokinetic (PK) information into early-phase dose-finding studies. By integrating PK outcomes with toxicity and efficacy data, PKBOIN-12 directly addresses a key limitation of existing approaches—the risk of selecting dose levels that are clinically acceptable but pharmacokinetically inadequate. Extensive simulation studies demonstrate that PKBOIN-12 improves the accuracy of optimal biological dose (OBD) selection, allocates more patients to biologically relevant doses, and reduces exposure to subtherapeutic dose levels, all while preserving the transparency, simplicity, and efficiency that have enabled the widespread adoption of BOIN-type designs.

The proposed design is motivated by real clinical practice, where PK data are routinely collected but rarely incorporated into formal dose-allocation decisions. PKBOIN-12 leverages this information through interpretable, rule-based decision criteria that are compatible with standard trial operations and existing BOIN-12 software infrastructure. As such, PKBOIN-12 represents a natural and implementable extension of a regulatorily accepted framework for early-phase clinical development.

Several directions for future research warrant further investigation. First, the framework could be extended to incorporate multiple PK endpoints or exposure–response relationships, enabling a more comprehensive use of PK–PD information. Second, adaptations to accommodate non-binary efficacy endpoints or time-to-event outcomes would broaden the applicability of the design. Third, incorporating patient-specific covariates or hierarchical PK models may further improve dose selection in heterogeneous populations. Finally, prospective evaluation of PKBOIN-12 in clinical trials will be an important step toward assessing its practical performance and facilitating broader adoption.

In summary, PKBOIN-12 provides a clinically relevant and methodologically sound approach to dose optimization by bridging safety, efficacy, and pharmacokinetic considerations, and offers a promising direction for the design of future early-phase trials.

6. REFERNCE

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7. ACKNOWLEDGMENTS

I would like to thank my manager and friends for their valuable feedback in improvising the paper. Last but not the least my family who has been my support system throughout.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Anetta Mary Xavier
Company: eClinical Solutions Pvt Ltd
Address: : 1st floor, Creator Building,
International Tech Park, ITPL Main Rd,
Pattandur Agrahara, of, Bengaluru,
Karnataka 560066
Work Phone: (+91) 9730442388
Email: axavier@eclinicalsol.com
Website: https://www.eclinicalsol.com/
LinkedIn: https://www.linkedin.com/in/anettaxavier/