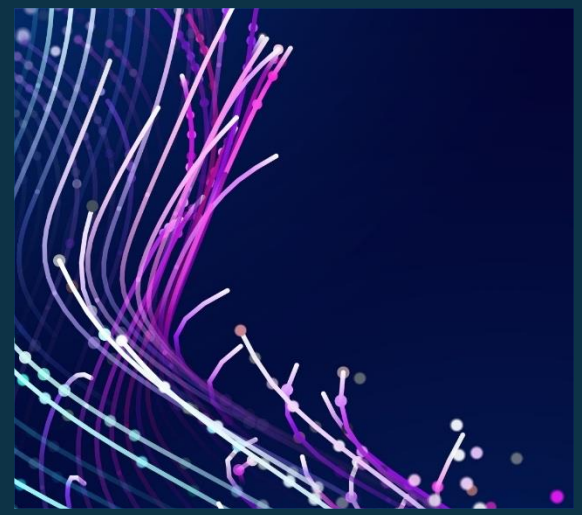

Beyond Toxicity : Accelerating Dose-Finding with Pharmacokinetic-Driven Bayesian Design PKBOIN-12

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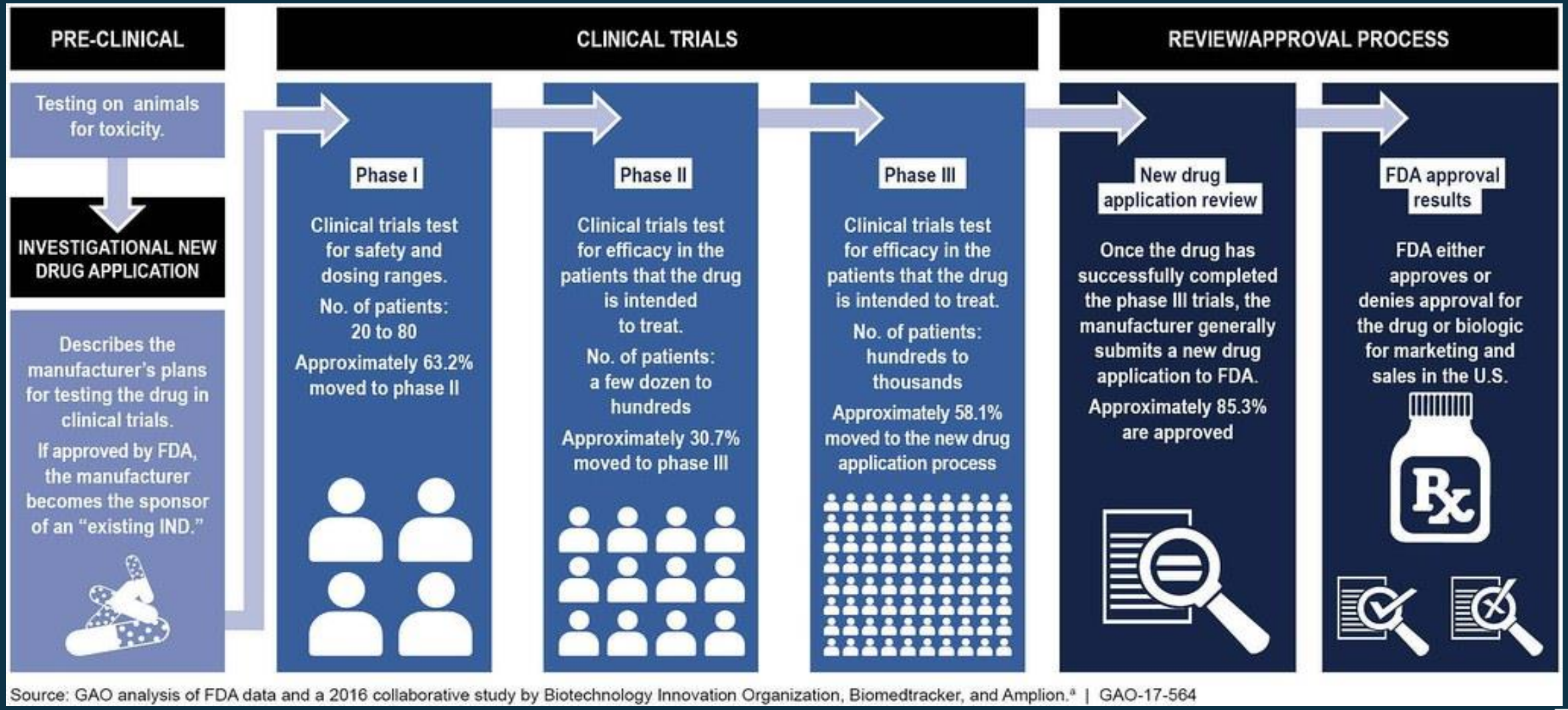
For PHUSE APAC Connect 2026

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 designs represents a significant step toward more precise and data-informed dosing strategies in early-phase clinical trials.

Traditional Drug Development Process



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

Dose-finding designs

Rule Based Design

- 3+3 Design
- Transparent, easy to implement, but poor Performance

Model Based Design

- Continual Reassessment Method (CRM)
- Superior performance but functions as a “Blackbox” and difficult to implement

Model Assisted Design

- Bayesian Optimal Interval Design (BOIN),BOIN12, PKBOIN12
- Transparent and easy to implement with superior performance

Challenged in Targeted Oncology Drug Development

Category	Cytotoxic Chemotherapy	Targeted Therapy
Mechanism	General cell-cycle or DNA Damage	Specific Molecular target
Resistance	Usually none	Essential
Toxicity	Slower, less specific	Molecular, rapid adaptive
Trial Population	Broad, histology based	Small, molecularly defined
Dose Optimization	Defined by MTD	Complex (chronic use)

Dosing Approaches in Clinical Development

Maximum Tolerated Dose (MTD)

- The Maximum Tolerated Dose is the highest dose of a drug treatment that does not cause unacceptable adverse events.
- Useful for cytotoxic chemotherapies with steep dose response relationship and limited target specificity, typically not taken for ling durations.
- PK/PD and Dose/Exposure relationship largely ignored.
- Targeted oncology agents with wide therapeutic indices and intended longer term use have had their doses lowered post-approval with significant improvements in their tolerability and without decrease in efficacy.

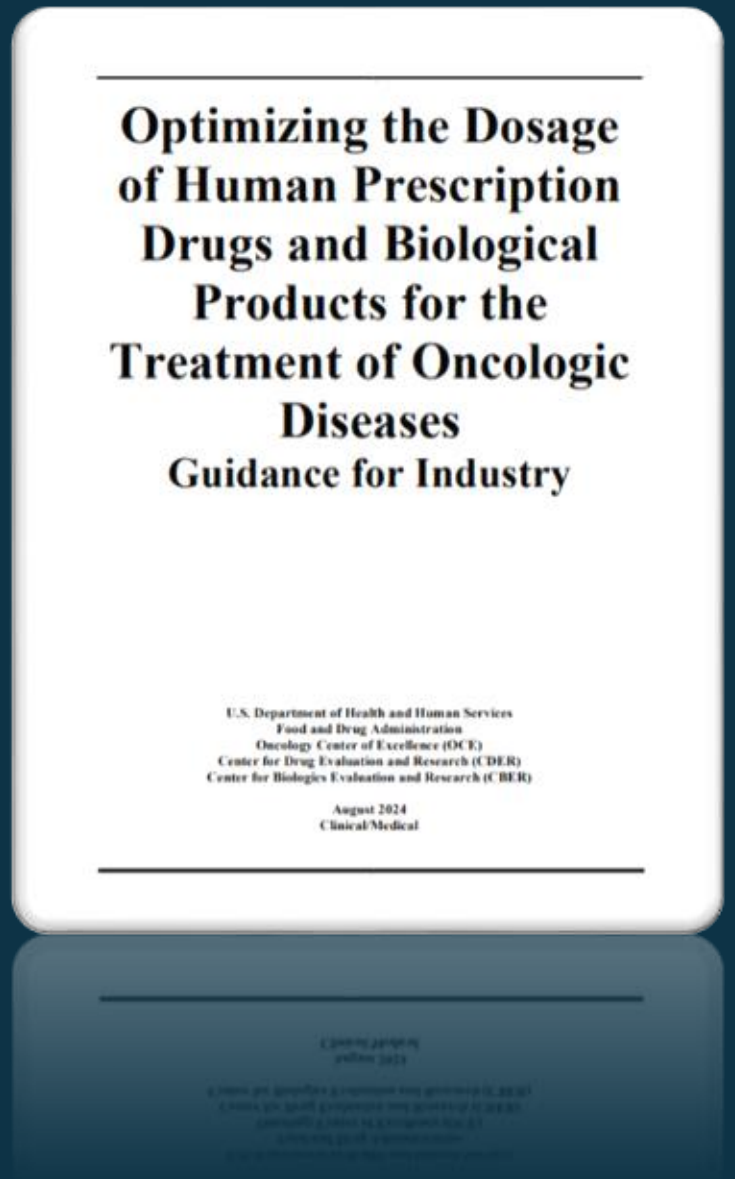
Optimal Biological Dose (OBD)

- The Optimal Biological Dose is the lowest possible dose of the drug that offers the highest rate of efficacy and does not cause unacceptable adverse events.
- Exploration of border dose range including lower doses.
- Using OBD as the clinical dose for targeted therapies will usually de-risk confirmatory phase III trials, with a lower rate of adverse events and increased tolerability.
- Using the OBD may eliminate the need for post registrational dose adjustments.

Project Optimus (FDA): Driving Dose Optimization

Highlights

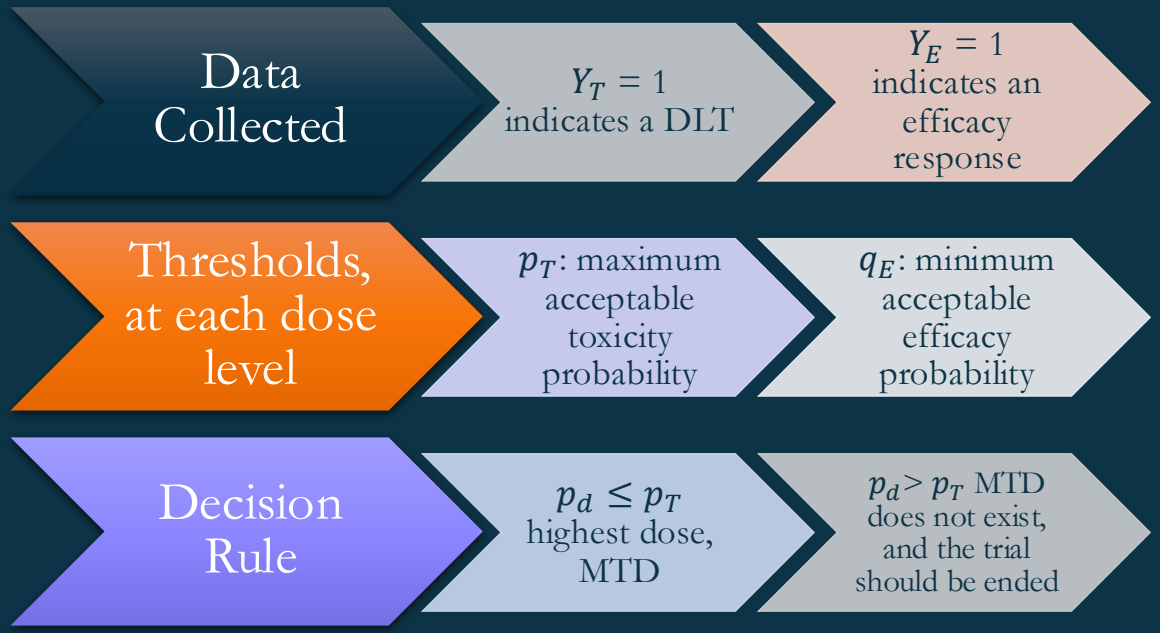
- Determine the optimal dose prior to confirmatory phase III trials
- Investigate at least two dose levels.
- Adaptive design to allow the dropping of a dose or doses.
- Characterize a dose-response relationship, not to prove statistical superiority or equivalence between doses.
- Inclusion of pharmacokinetic (PK) sampling and analysis plan in each protocol such that PK parameters and exposure-response relationship can be determined.



How can we achieve the goal of Dose Optimization?

Methodology

- Consider an early phase clinical trial with a total of D doses.



- Patient Counts at Dose d:
  - $n_{d,T}$ represent the number of patients who experience a DLT
  - $n_{d,E}$ denote the number of patients who show an efficacy response at dose level d.

Methodology (Cont.)

Outcome	Toxicity (Y_T)	Efficacy (Y_E)	Patient Count
O_1	0	1	$n_{d,1}$
O_2	0	0	$n_{d,2}$
O_3	1	1	$n_{d,3}$
O_4	1	0	$n_{d,4}$

Then,

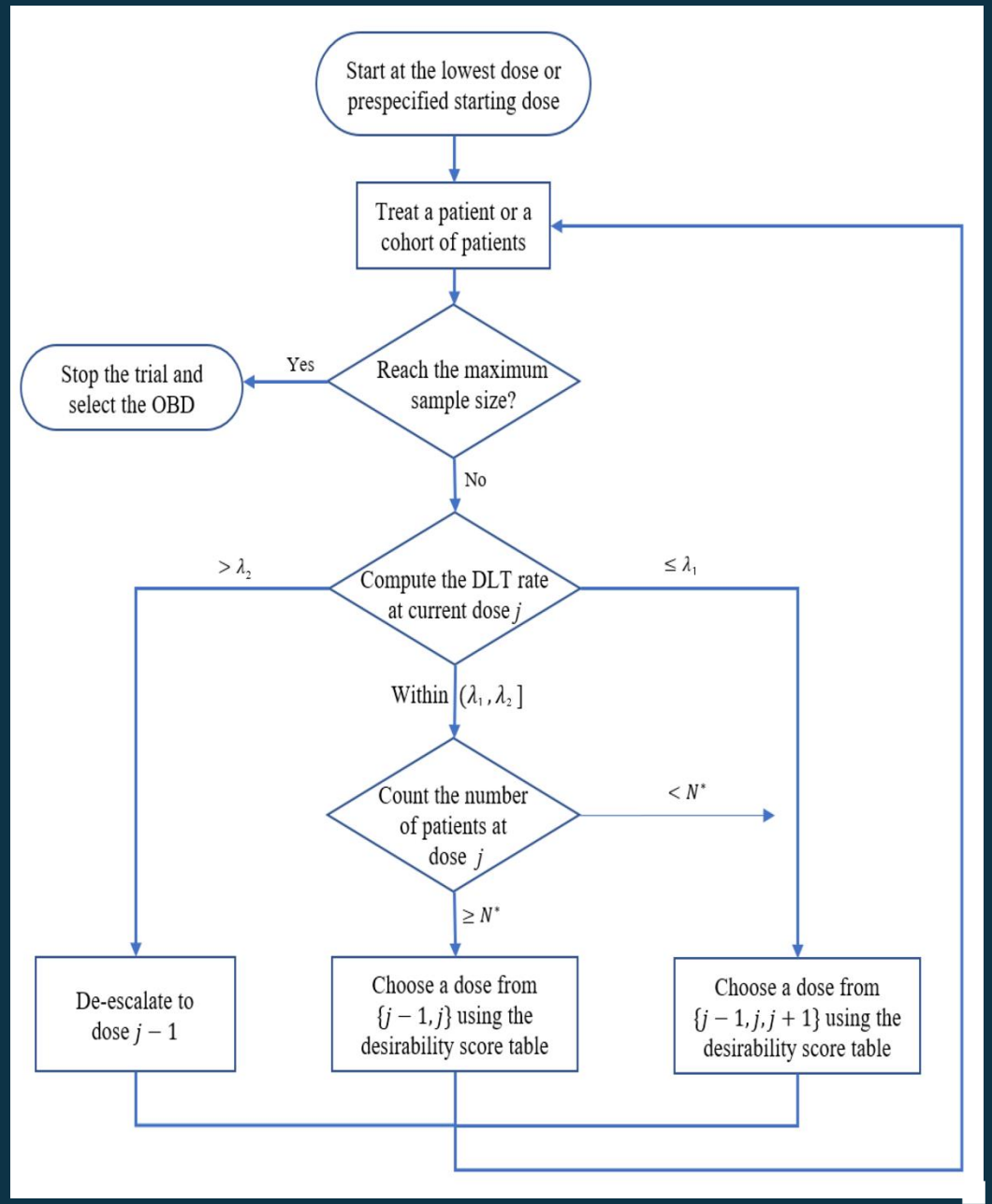
- $n_{d,T} = n_{d,3} + n_{d,4}$:Total toxicities
- $n_{d,E} = n_{d,1} + n_{d,3}$:Total Responses
- $n_d = \sum_{i=1}^{4} n_{d,i}$:Total dose at dose d

The observed probabilities for category O_i

- $\hat{p}_d = n_{d,T}/n_d$
- $\hat{q}_d = n_{d,E}/n_d$

BOIN 12

- BOIN12 is a flexible phase I/II model-assisted design to determine the OBD by optimizing the risk-benefit tradeoff and maximizing expected clinical utility using already defined outcome categories O_1 to O_4.
- Utility provides an intuitive approach to evaluating risk-benefit tradeoff. The BOIN12 model the dose utilities using a quasi-beta-binomial model.
- Under the Bayesian framework, each dose utility (u_d) is modelled with a non-informative prior, Beta(1,1),) which leads to the posterior distribution - $u_d \mid n_d, x_d \sim$ Beta (1+ x_d,1+ n_d- x_d).
- The Rank Desirability Score (RDS) is used to rank the posterior probabilities using the benchmark utility. Higher RDS is equivalent to having a higher posterior probability of being the best dose.
- The dosing is based of the two pre-specified DLT intervals i.e. the lower boundary $\boldsymbol{\lambda_1}$ and upper boundary $\boldsymbol{\lambda_2}$ depending on p_T from the BOIN design.



Selection and Elimination Process for BOIN12 Design

Selection

- MTD- Isotonic Regression to the regression to the observed toxicity rates and choose the MTD
- OBD - Select one dose from $\{1, \ldots, d_{MTD}\}$ as OBD with the highest estimated utility.

Elimination

- If $P(p_d > p_T \mid \hat{p}_d, n_d) > C_T$ Eliminate the dose level d and all above
- If $P(q_d < q_E \mid \hat{q}_d, n_d) > C_E$ Eliminate the dose level d and all above

Example:BOIN12 Combination Trial

Methotrexate(MTX)+erlotinib (150 mg)+celecoxib trial (200 mg)

- Dose Level :
  - MTX- (3–15 mg/m²)
- Cohort size:3, Sample size = 30 Thresholds: p_T=0.35 $q_E = 0.25$
- Boundaries: λ_1 = 0.276 and λ_2= 0.419
- Process: Start at lowest dose, make a decision based on the rule.
- Results: Final utilities (by dose levels 1–5) = 40, 46.7, 53.3, 60, 50
- Outcome: Dose level 4 (12 mg/m² MTX) selected as OBD

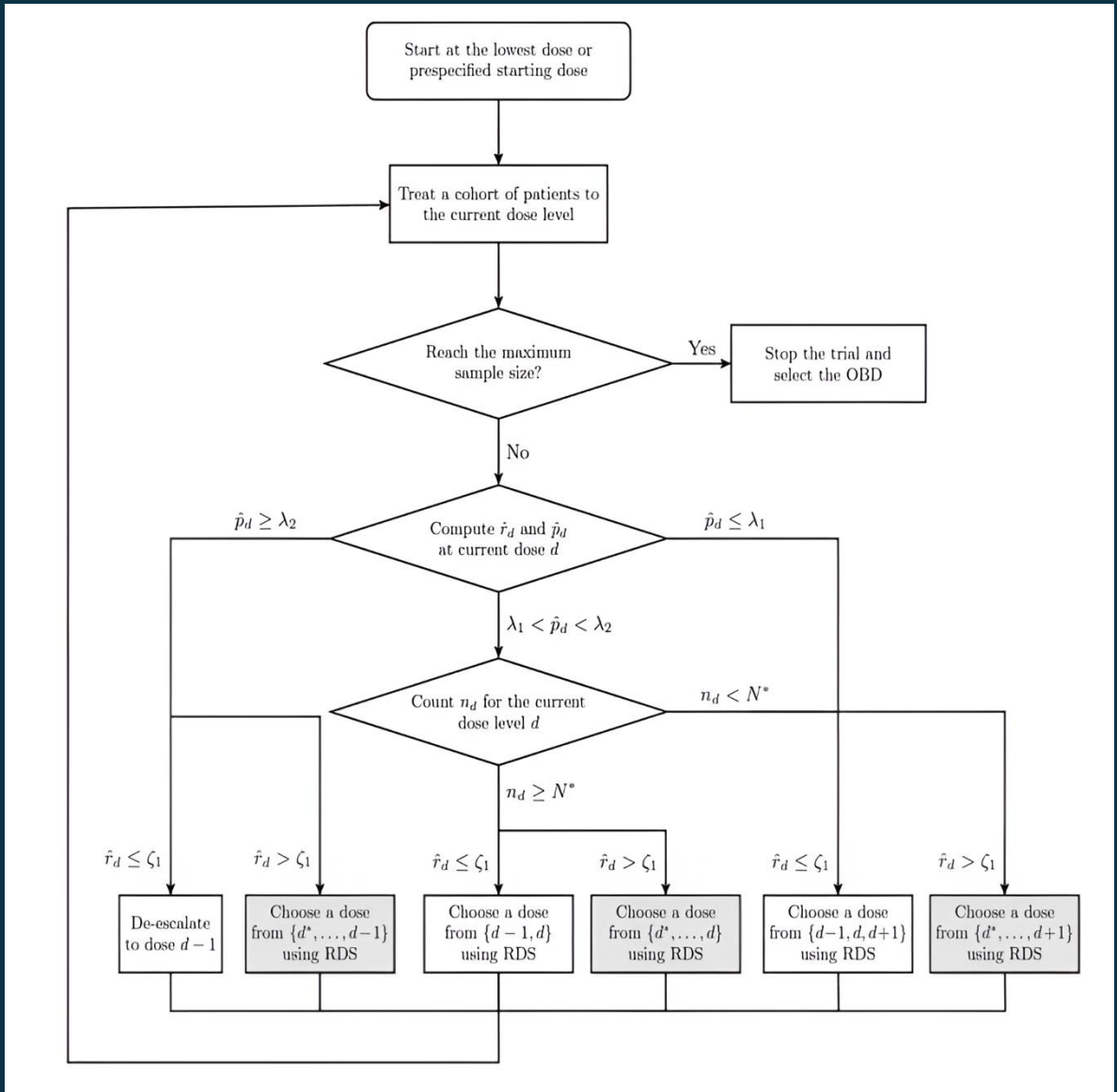
PKBOIN12

- Early-phase trials collect pharmacokinetic (PK) data describing how a drug is absorbed, distributed, metabolized, and eliminated.
- Given the small samples and sparse safety/efficacy readouts in early-phase trials, leveraging PK outcomes helps identify exposure-adequate doses and select the OBD.
- There are many continuous PK outcomes, such as AUC, Cmax which provides early exposure signals that guide the PK gate in PKBOIN12 design.
- Suppose,
  - r_d be the true mean of the targeted continuous PK outcome at dose level d
  - r_p be the target continuous PK value, a dose with PK outcome $r_n < r_p$
- Under Bayesian framework, ,r_d follows truncated normal distribution $(0, \sigma_0^2)$to guarantee that r_d is positive (σ_0^2= 1000 –default), which leads to the posterior distribution

$$r_d \mid \hat{r}_d, \sigma_d^2 \sim \text{truncated-N}\left(\frac{n_d \hat{r}_d}{\sigma_d^2\left(\frac{1}{\sigma_d^2}+\frac{n_d}{\sigma_d^2}\right)}, \frac{1}{\frac{1}{\sigma_d^2}+\frac{n_d}{\sigma_d^2}}\right)$$, where $\hat{r}_d$ denotes the observed PK sample mean

- The MAP estimate of r_d can be approximated by $\hat{r}_d$ if the small term $\frac{1}{\sigma_0^2}$ is ignored.
- A PK exposure cutoff τ_1 in PKBOIN12 that screens out under-exposed doses before utility-based allocation.

Steps of PKBOIN12 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.
- 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 $\{d^*, \ldots, d+1\}$.
- Let the sample size cutoff $N^* = 6$, c=1 and d as the lowest or a pre-specified dose level.

Selection and Elimination Process for PKBOIN12 Design

- To maintain monotonic trends in toxicity and PK, isotonic regression with pool-adjacent-violators algorithm (PAVA) is applied to $\{\hat{p}_i\}_{d=1}^{D}$ and PK samples $\{\hat{r}\}_{d=1}^{D}$, producing the transformed values $\{\tilde{p}_d\}_{d=1}^{D}$ and $\{\tilde{r}_d\}_{d=1}^{D}$

Selection

- MTD- Isotonic Regression to the regression to the observed toxicity rates $\{\tilde{p}_d\}_{d=1}^{D}$ and choose the MTD
- PK - Isotonic regression to the observed PK sample means $\{\tilde{r}_d\}_{d=1}^{D}$ and obtain the minimum efficacious PK exposure.
- OBD - Select one dose from $\{1, \ldots, d_{MTD}\}$ as OBD with the highest estimated utility.

Elimination

- If $P(p_d > p_T \mid \hat{p}_d, n_d) > C_T$ Eliminate the dose level d and all above
- If $P(q_d < q_E \mid \hat{q}_d, n_d) > C_E$ Eliminate the dose level d and all above
- If $P(r_d < r_P \mid \hat{r}_d, n_d) > C_P$ Eliminate the dose level d and all above

Simulation

- Objective: To Evaluate how integrating PK data improves OBD selection under realistic variability.
- The simulation results shows include both the proportion of selections as the OBD and the average number of patients assigned to each dose level.
- Setup:
  - 5 dose Levels, 3 patients per cohort, max 45 patients
  - Binary toxicity & efficacy outcomes; AUC used as PK outcome
  - Assessment windows: 28 days (toxicity), 56 days (efficacy)
  - Common parameters:
    - *a)* p_T=0.30, q_E=0.20,
    - b) Cutoffs:C_T=0.90 , C_E=0.85, C_P=0.95

SCENARIO 1

	Selection Probability						Number of Assigned Patients					Duration
	1	2	3	4	5	ET	1	2	3	4	5	Months
BOIN 12	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

	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

Results

- In the four scenarios, a monotonically increasing dose-response relationship with different dose levels designated as the true OBD.
- Scenario 1: True OBD = Dose 5 (only dose with effective PK),PKBOIN-12 OBD selection: 41% (13.2% over BOIN-12)
- Scenario 2 – True OBD = Dose 4 PKBOIN-12 OBD selection: 53.4% (↑ 3.4% over BOIN-12) Lower toxic dose selection: ↓ 1.5% vs BOIN-12
- Scenario 3 – True OBD = Dose 2 PKBOIN-12 OBD selection: ↑ 13.4% compared to BOIN-12
- Scenario 4 – True OBD = Dose 1 (all doses effective PK)

All designs ≈ 70% correct OBD selection PKBOIN-12 slightly higher: ↑ 0.4% vs BOIN-12

SCENARIO 3

	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

	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

Application of the BOIN Design

Clinical Trial Applications Using BOIN-12

- Phase I/II trial of enhanced CD33 CAR-T cells
  - Population: Relapsed/refractory acute myeloid leukemia (AML)
  - BOIN-12 used to jointly evaluate toxicity and efficacy and select the OBD
- Phase I trial of CD5 CAR-T cells
  - BOIN-12 framework applied for early-phase dose optimization

•Demonstrates feasibility of BOIN-12 in real oncology dose-finding trials

Example Scenario: PK-BOIN-12 Application

- Trial Setting
  - Phase I/II dose-escalation study of a novel anticancer agent
  - Patients treated sequentially at increasing dose levels
  - Pharmacokinetic (PK) endpoints (e.g., AUC) measured after initial dosing
- Motivation
  - Substantial inter-patient variability in drug exposure
  - Clinical outcomes alone may lead to selection of doses with inadequate exposure
  - Need for exposure-informed dose optimization

Discussion/Summary

- Dose optimization should extend beyond safety to include efficacy, especially for targeted and immunologic therapies.
- BOIN-12 uses a Bayesian utility-based framework to guide adaptive dose selection.
- PKBOIN-12 extends BOIN-12 by incorporating pharmacokinetic (PK) exposure to inform dose decisions.
- Doses with inadequate PK exposure are filtered out before final OBD selection.
- Simulation studies show PKBOIN-12:
  - improves correct OBD selection
  - reduces selection of ineffective doses
- This approach supports FDA Project Optimus by integrating safety, efficacy, and PK data.
- PKBOIN-12 currently uses one clinically selected PK endpoint, prioritizing simplicity and interpretability. Extensions to multiple PK measures are possible.

Beyond the Current Framework

- Targeted therapies, often administered long-term, carry a risk of late-onset and persistent low-grade toxicities.
- To address late-onset toxicity and efficacy outcomes: TITE-BOIN12 and TITE-PKBOIN12 designs can be introduced
- Software implementation:
  - User-friendly tool available for BOIN12
  - Generates trial outputs, including OBD determination and trial protocol
- Future directions:
  - Current work focuses on a single drug
  - Framework can be expanded to combination therapies with appropriate extensions

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Question&Answer

Thank you