PREDOSE: **P**harmacometrically-**R**efined **E**arly-phase **D**ose **O**ptimization design for Oncology **S**tudy **E**nhancement

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Overview

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Why Project Optimus?

- Traditional oncology prioritized **MTD**, suited to cytotoxic chemotherapies where efficacy and toxicity increase monotonically with dose.
- For **targeted therapies and immunotherapies**, this breaks down: efficacy plateaus beyond a threshold while toxicity continues to escalate.
- Clinical evidence shows **sub-MTD doses** can achieve comparable efficacy with better tolerability, motivating the **Optimal Biological Dose (OBD)**.
- Fixed designs follow a predetermined schema and cannot locate the OBD. **Adaptive designs** continuously update dose-assignment rules from accumulating data, converging to the OBD in real time.

Common Adaptive design techniques include

- **BOIN / CRM** — Model-based dose-finding methods that continuously update the estimated dose–toxicity curve to obtain the OBD
- **Seamless Phase I/II designs** — Dose-finding and efficacy evaluation run as one continuous trial, eliminating the gap between phases
- **Response-adaptive randomisation** — Allocation shifts toward better-performing doses as evidence builds
- **Interim adaptations** — Pre-planned looks allow dropping of toxic or ineffective arms and expanding promising ones

The result: **fewer patients at wrong doses, faster OBD identification, and a richer evidence base** — exactly what Project Optimus demands!

FDA Dose Optimization Guidance (2024)

Collection and Interpretation of Clinical Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Data

- Integrate PK/PD/PG data with clinical data (safety and efficacy)
- Investigate effects in multiple populations when possible

Trial Designs to Compare Multiple Dosages

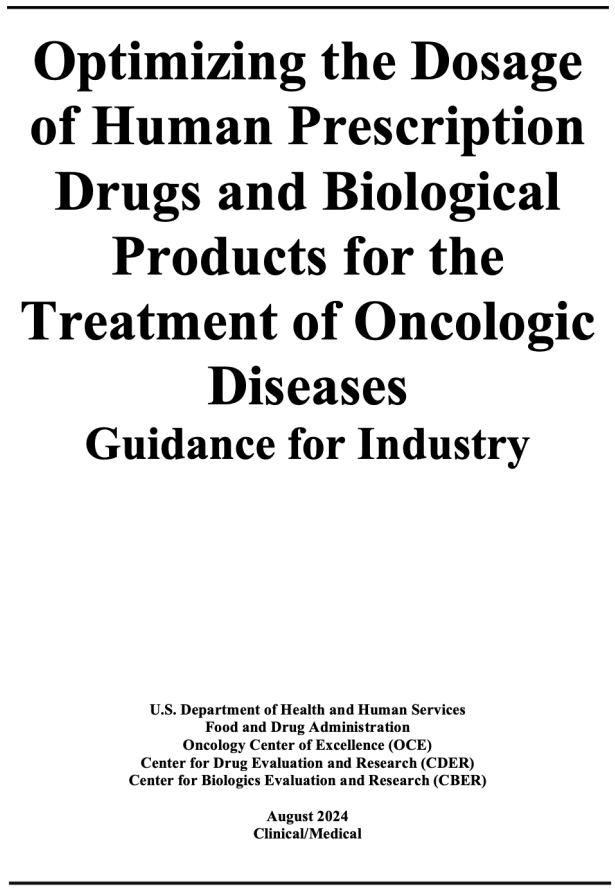
- Backfill patients on multiple doses before dose comparison
- Randomized dose comparison (adaptively and without considering frequentist error rates as the case for late-phase trials) – Bayesian?

Safety and Tolerability -- Endpoints

- DLT and low grade toxicity should be considered – Toxicity burden
- PRO

Subsequent Indications and Usages

- Different doses for different diseases should be considered



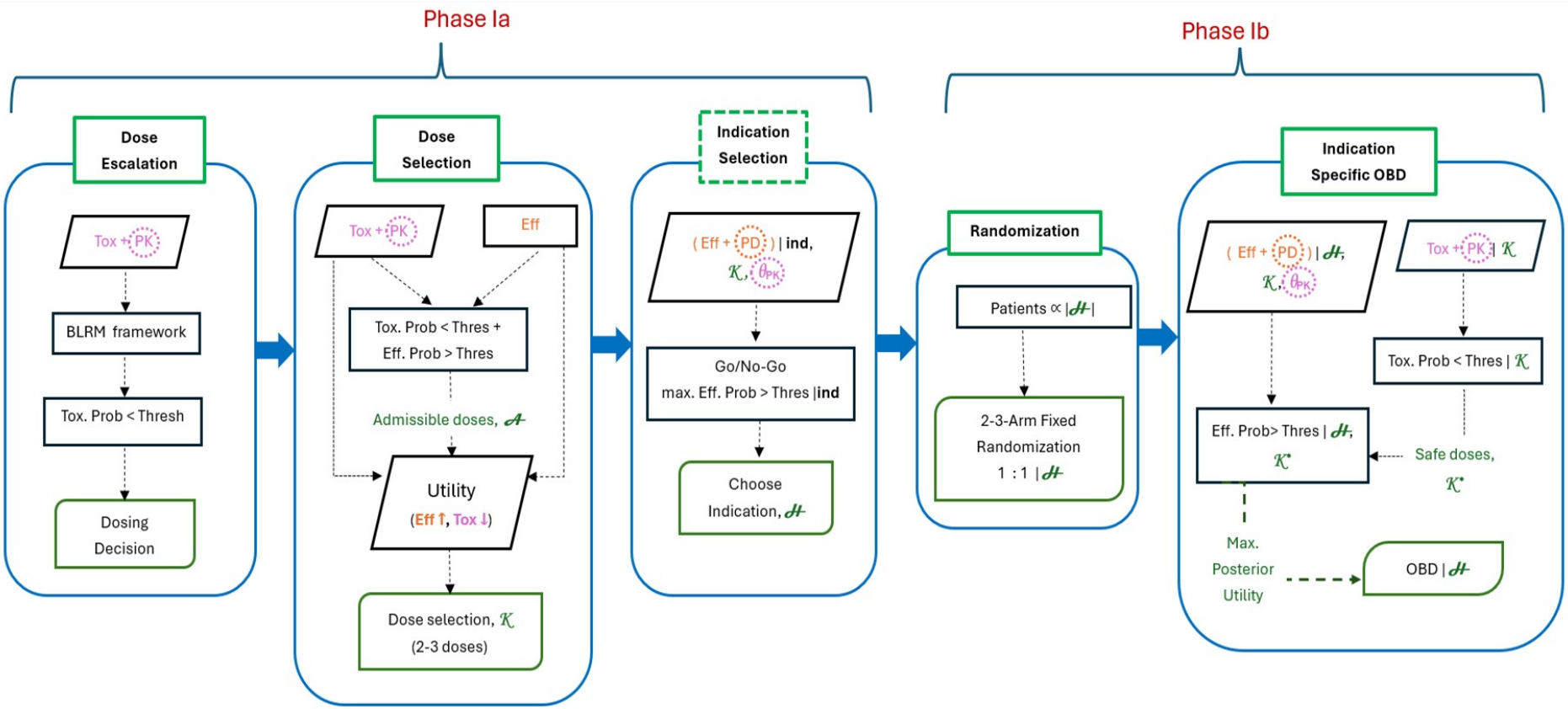
Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2024
Clinical/Medical

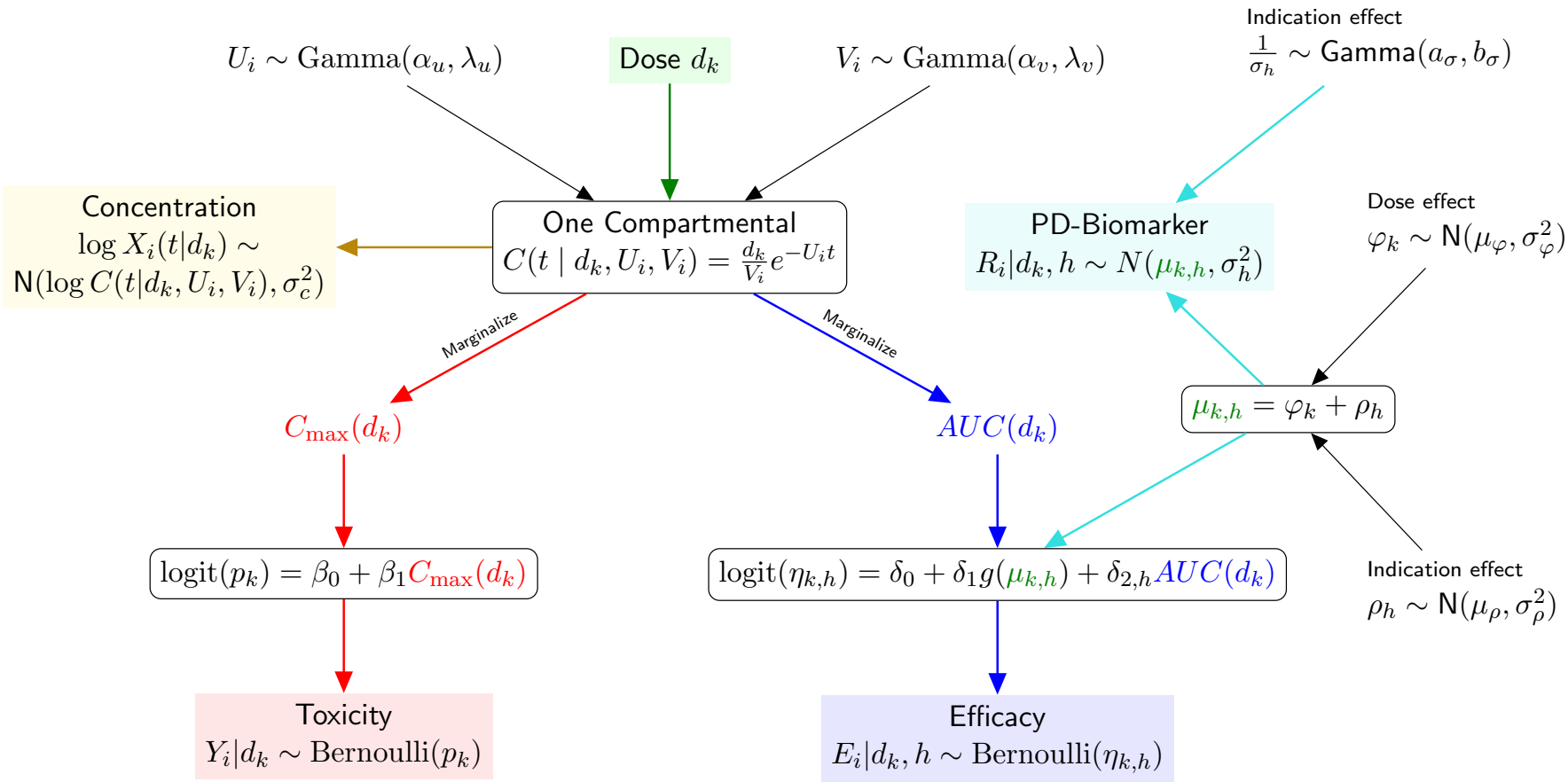
PREDOSE: Proposed Framework



Abbreviations : **BLRM**: Bayesian Logistic Regression Model, **Eff**: Efficacy, **ind**: Indication, **PK**: Pharmacokinetic, **PD**: Pharmacodynamic, **Prob**: Probability, **Tox**: Toxicity, **Thresh**: Threshold, **OBD**: Optimal Biological dose.

Symbols : θ_{PK} : PK hyperparameters, $\mathcal{A}$: Admissible set of doses, $\mathcal{H}$: Selected indications, $\mathcal{K}$: Selected Phase Ia doses, $\mathcal{K}^*$: Selected safe Phase Ia/b doses.

Toxicity-PK and Efficacy-PD Model



Simulation setup

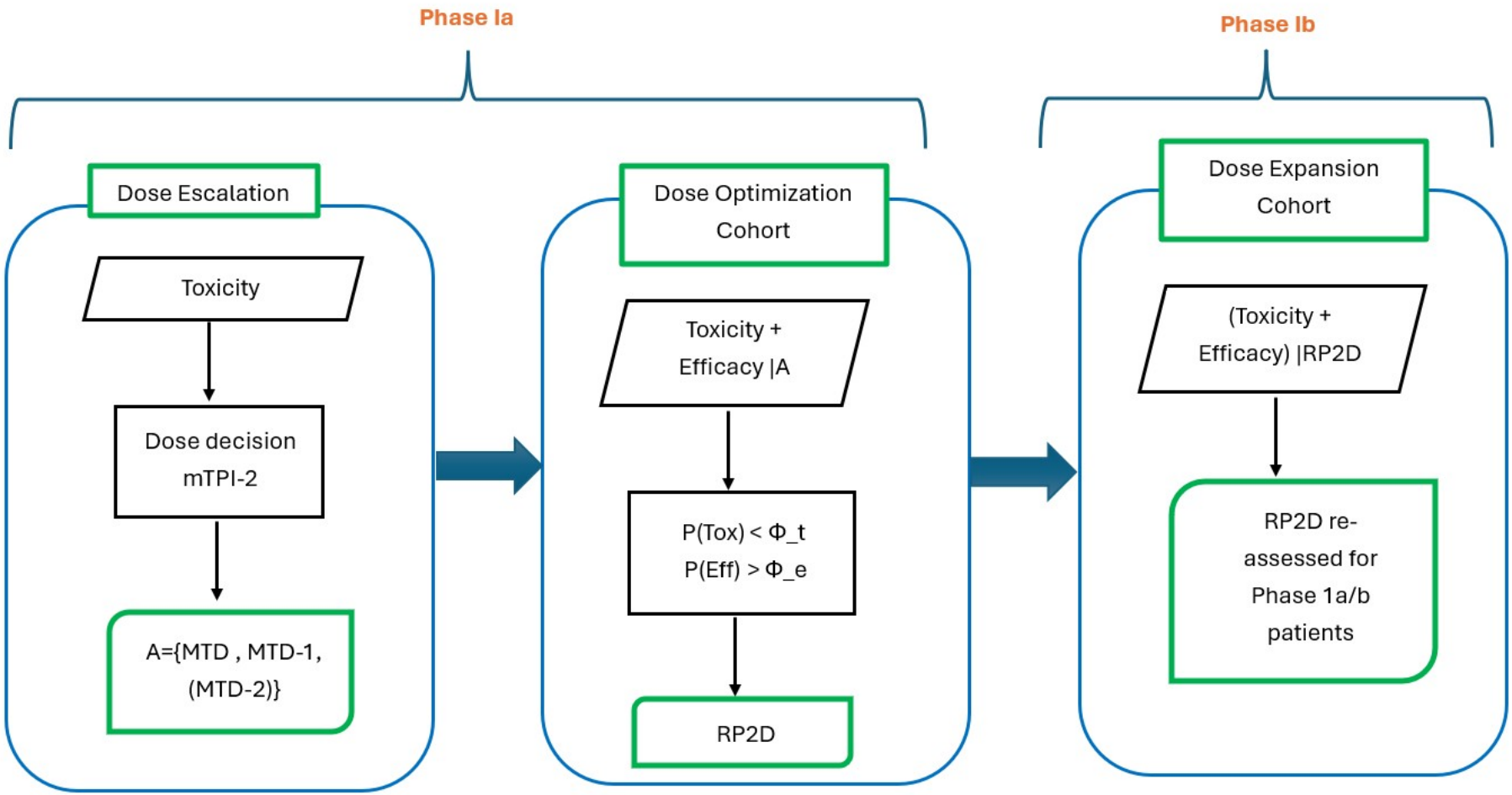
Five dose levels (*0.3, 1.0, 3.0, 5.0, and 10.0 mg/kg*) are investigated across a maximum of **120** patients, with up to 30 patients in Phase 1a and 90 in Phase 1b.

- Patient arrival times within each cohort in (i) Phase 1a $\sim$ Exp($\lambda = 1$), (ii) for Phase 1b patients $\sim$ Piece-wise Exponential($\boldsymbol{\Lambda}, \boldsymbol{\tau}$).
- *Plasma drug concentrations* are measured at 4, 8, 24, 48, and 72 hours post-dose for PK assessment, with cohort-level PK data assumed available at **8 weeks**.
- The *DLT* observation window is **4 weeks** post-dose, and tumor response (*efficacy*) is assessed radiological scans at **12 weeks** post-dose.

Model considerations

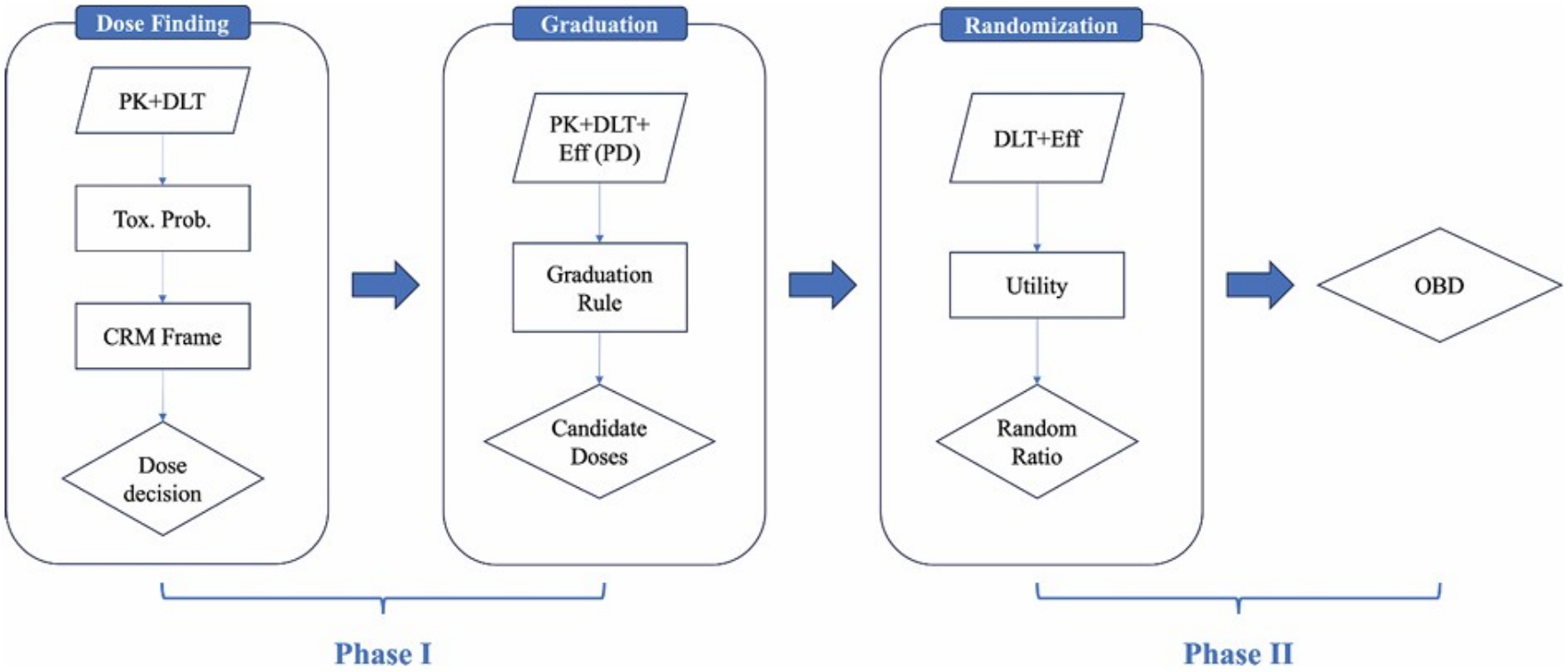
- Target toxicity $\varphi_T = 0.3$ and target efficacy $\varphi_E = 0.3$.
- We compare our model (*PREDOSE with PK*) with 3 other models (1) *PREDOSE with out PK* (2) *Standard design* and (3) *PEDOOP*.

Example design (Standard design)



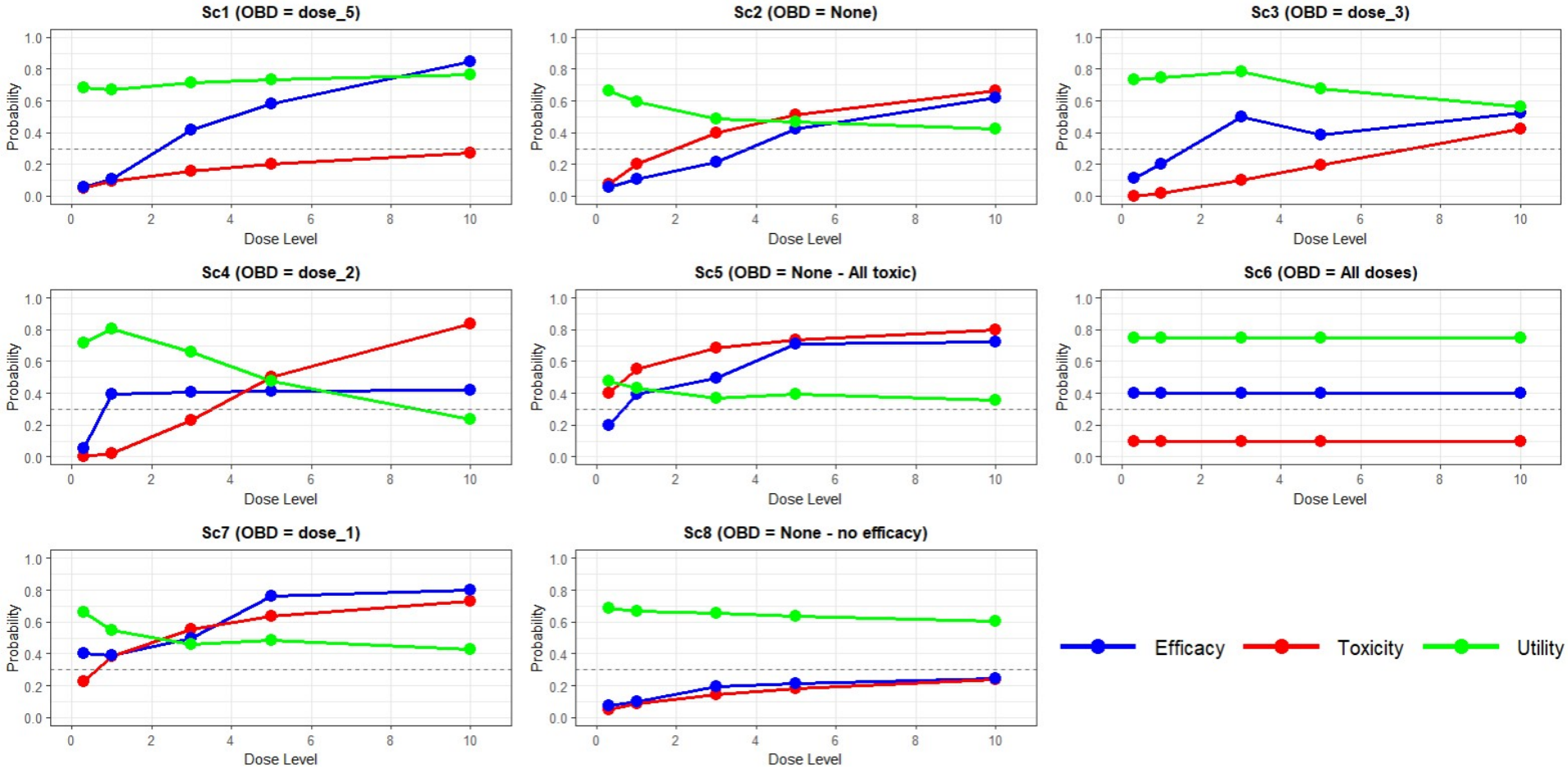
In Standard design: (i) dose optimization cohort randomizes $20 \times |\{\textit{selected doses}\}|$ *patients.*
(ii) total patients for Phase Ib $= 120 - (30 + 20 \times |\{\textit{selected doses}\}|)$.
(iii) RP2D obtained is indication agnostic. .

PEDOOP: Pharmacometrically enabled design



PEDOOP: (i) simultaneously models concentration, toxicity, efficacy for updating toxicity probability.
(ii) 10 - parameter posterior model, where PD biomarker is estimated from concentration, toxicity, efficacy.
(iii) utility-based adaptive randomization in Phase II.
(iv) OBD obtained indication agnostic. .

Indication agnostic Scenarios



Note: Utility$(d_k) = \Psi_3 \times (1 - P(\textit{Toxicity}|d_k) + \Psi_2 \times P(\textit{Efficacy}|d_k)$ *where,* $\Psi_3 = 1 - \Psi_2 = 0.7$.

% of Correctly Selected OBD

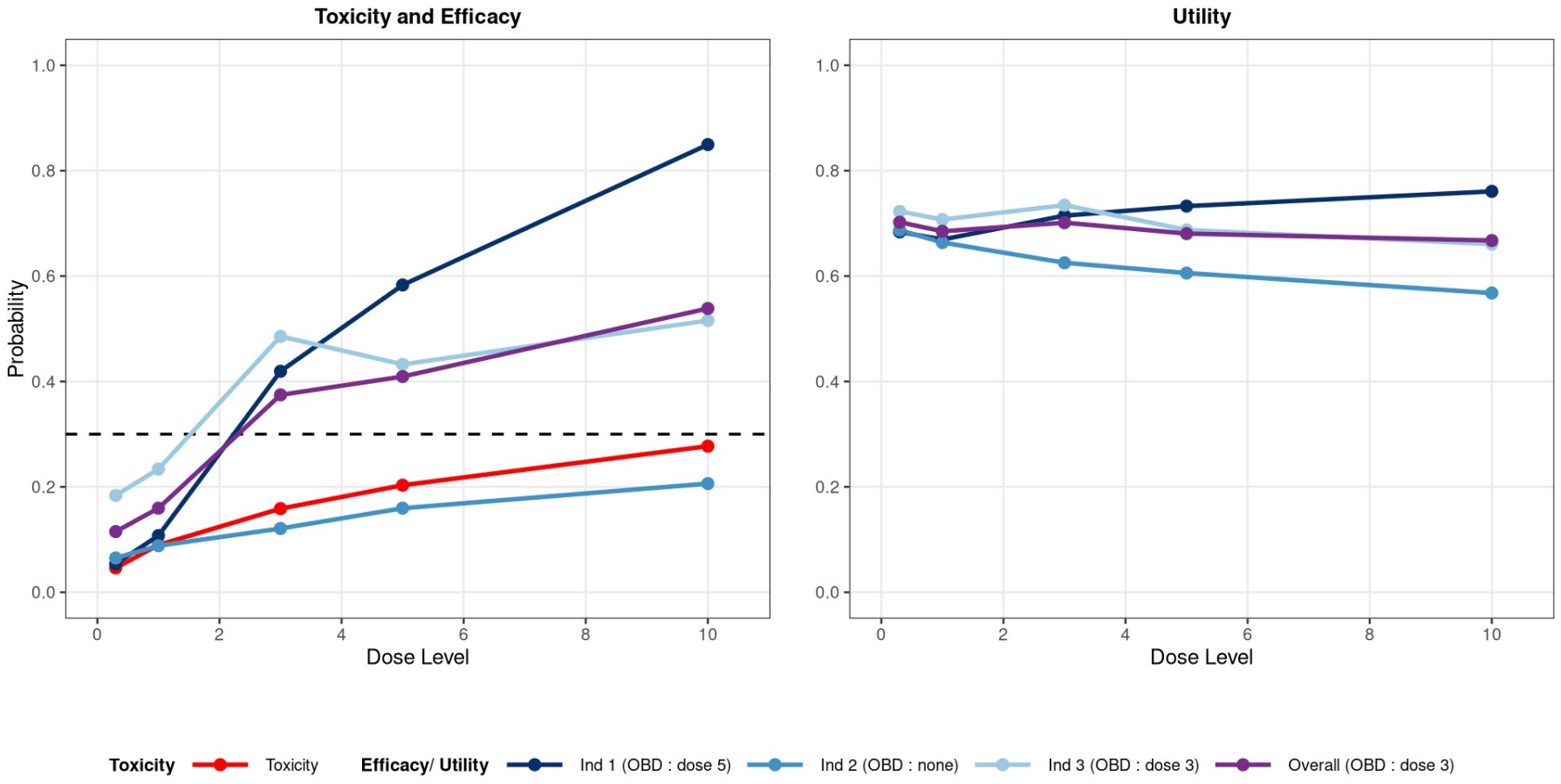
Scenario	True OBD	PREDOSE with PK	PREDOSE without PK	Standard Design	PEDOOP
1	DL5	**46.1**	44.7	36.0	27.7
2	None	**100.0**	99.9	98.0	99.9
3	DL3	**82.1**	77.1	40.5	46.0
4	DL2	68.3	56.8	**75.3**	11.1
5	None	**100.0**	**100.0**	99.6	**100.0**
6	All	98.4	**98.9**	98.1	82.4
7	DL1	57.8	62.4	**64.4**	24.4
8	None	94.19	95.0	78.0	**99.6**

Note: Values represent % of correctly selected OBD across 1,000 replications per scenario.

For (i) Scenario 6 (All dose are OBD), values represent %age of times **OBD is reached** by each design.

(ii) Scenario 2, 5 and 8 (No dose is OBD), values represent %age of times designs led to **no OBD**.

Indication specific Scenario



Note: Utility$(d_k) = \Psi_3 \times (1 - P($*Toxicity*$|d_k) + \Psi_2 \times P($*Efficacy*$|d_k)$, *where,* $\Psi_3 = 1 - \Psi_2 = 0.7$.

OC for Indication specific case

								Patient Allocation %				
Model	**Ind.**	**Time**	**Size**	**E.Stop**	**Sel.%**	**No OBD**	**C.OBD**	**DL1**	**DL2**	**DL3**	**DL4**	**DL5**
Standard design	1	160.8	114.5	15.2	100.0	24.0	20.0	21.2	16.4	22.0	18.1	22.3
	2				100.0	24.0	24.0	21.2	16.1	21.9	18.2	22.6
	3				100.0	24.0	32.9	20.4	16.6	21.9	18.4	22.8
PREDOSE with PK	1	123.2	**90.8**	**7.2**	87.7	20.4	30.8	11.3	15.5	24.7	23.2	25.3
	2				**38.1**	**96.7**	**96.7**	15.4	15.2	17.1	20.3	32.0
	3				**90.8**	**20.5**	**33.2**	10.7	15.5	24.7	23.7	25.4
PREDOSE without PK	1	**117.7**	91.6	10.1	**88.7**	**17.8**	**35.5**	10.7	14.4	25.0	24.8	25.2
	2				48.5	85.7	85.7	16.1	14.6	19.3	20.2	29.8
	3				80.6	30.8	18.3	10.2	14.4	23.1	23.9	28.4

Note: Values represent % of correctly selected OBD across 1,000 replications per scenario.

(i) C.OBD = Correct OBD; E.Stop = Early Stop

(ii) Indication 2, values mean %age of times no OBD is obtained

(iii) True Indication allocation (Ind 1: 35%, Ind 2: 25%, Ind 3: 45%)

(iv) True OBD (Ind 1 : DL5, Ind 2: None, Ind 3: DL3) .

Discussion

1. Our method recommends **pharmacometrically informed dosing strategies** that integrate efficacy and toxicity to guide dose escalation and selection of the optimal biologic dose (OBD), adapting dynamically as PK/PD data become available.

2. Our method **identifies indications suitable for cohort expansion** in Phase 1b. and reduces both sample size and trial duration significantly as compared to Typical design.

3. Adaptively **recommend OBDs under varying data availability**, accounting for presence or absence of **PK and PD biomarker information**, without increasing the trial time as compared to the Typical design.

4. It can be used to identify pharmacometrically informed indication-specific OBD for complex dosing strategies like **step-up dosing**.

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THANK YOU

OC for Indication agnostic case

							Patient Allocation %				
Sc.	**Model**	**Time**	**Size**	**E.Stop**	**No OBD**	**C.OBD**	**DL1**	**DL2**	**DL3**	**DL4**	**DL5**
Sc1	Standard design	162.2	115.4	12.7	12.7	36.0	20.7	15.7	19.5	17.9	**26.2**
	PEDOOP	365.8	**103.7**	27.3	27.7	27.7	4.6	8.9	26.3	30.3	**30.0**
	PREDOSE with PK	130.0	115.1	5.5	7.2	46.1	7.3	11.5	27.7	28.0	**25.5**
	PREDOSE without PK	**126.6**	115.7	4.9	**6.3**	44.7	7.0	11.7	29.2	27.0	**25.2**
Sc3	Standard design	162.7	116.3	12.1	12.1	40.5	22.2	18.9	**22.4**	24.7	11.8
	PEDOOP	345.7	**97.1**	29.9	31.3	46.0	4.2	5.4	**35.1**	37.2	18.1
	PREDOSE with PK	132.4	119.3	1.6	**5.2**	82.1	10.3	15.9	**33.3**	26.5	14.0
	PREDOSE without PK	**127.9**	118.7	1.6	7.3	77.1	10.4	17.1	**32.7**	26.9	12.9
Sc4	Standard design	164.2	117.4	6.8	**6.8**	75.3	22.4	**40.9**	25.6	9.3	1.8
	PEDOOP	270.7	**72.9**	55.5	57.3	11.1	6.3	**17.1**	56.7	17.4	2.5
	PREDOSE with PK	127.9	113.9	7.9	12.1	68.3	7.3	**42.7**	39.9	9.0	1.1
	PREDOSE without PK	**123.4**	113.3	8.9	18.1	56.8	7.4	**41.6**	40.7	9.1	1.1
Sc7	Standard design	131.7	91.4	31.9	**31.9**	64.4	**78.7**	15.7	4.3	1.1	0.2
	PEDOOP	223.4	**58.1**	72.1	74.6	24.4	**61.8**	32.8	4.5	0.8	0.1
	PREDOSE with PK	108.1	89.3	39.9	42.0	57.8	**75.2**	21.8	2.4	0.5	0.1
	PREDOSE without PK	**105.0**	92.8	34.6	37.4	62.4	**76.4**	20.6	2.5	0.4	0.1

Note: Values represent % of correctly selected OBD across 1,000 replications per scenario.

(i) C.OBD = Correct OBD; E.Stop = Early Stop.

No. of times OBD Selected by Model and Indication

			No. of Times OBD Selected					
Model	**Ind.**	**OBD**	**DL1**	**DL2**	**DL3**	**DL4**	**DL5**	**No OBD**
Standard design	1	DL5	0	1	329	230	200	240
	2	None	0	1	329	230	200	240
	3	DL3	0	1	329	230	200	240
PREDOSE with PK	1	DL5	0	4	220	264	308	204
	2	None	1	1	2	3	26	**967**
	3	DL3	11	31	**332**	196	225	205
PREDOSE without PK	1	DL5	0	0	127	340	**355**	178
	2	None	10	15	53	37	28	857
	3	DL3	5	4	183	225	275	308

Ind 1 OBD: DL5 Ind 2 OBD: None Ind 3 OBD: DL3

Trial time, size and early stopping %