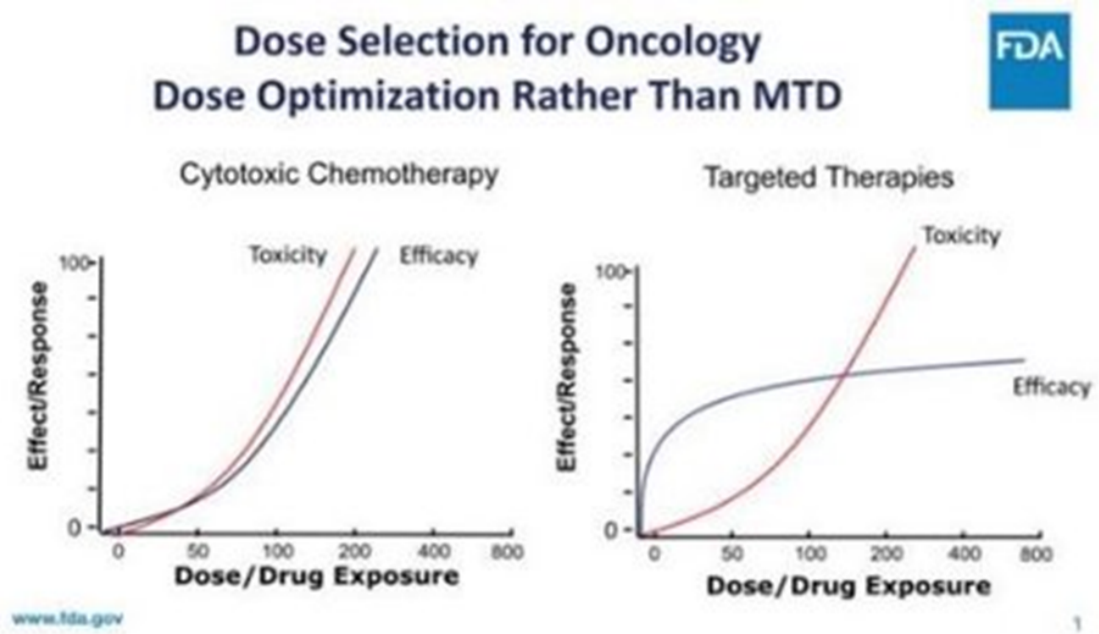
PREDOSE: **P**harmacometrically-**R**efined **E**arly-phase **D**ose **O**ptimization design for Oncology **S**tudy **E**nhancement

Presenter: Dr. Ayon Mukherjee (Project Lead)
Collaborators: Prof. Yuan Ji, Dr. Damitri Kundu, KyongJu Lee and **Dr. Arunava Chakravartty**

22nd October 2026



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)**.
- Common Adaptive design techniques include (i) Model based dose finding methods (e.g. **BOIN, CRM**) (ii) **Seamless Phase I/II designs** (iii) **Response-adaptive randomisation** (iv) **Interim adaptations**.

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

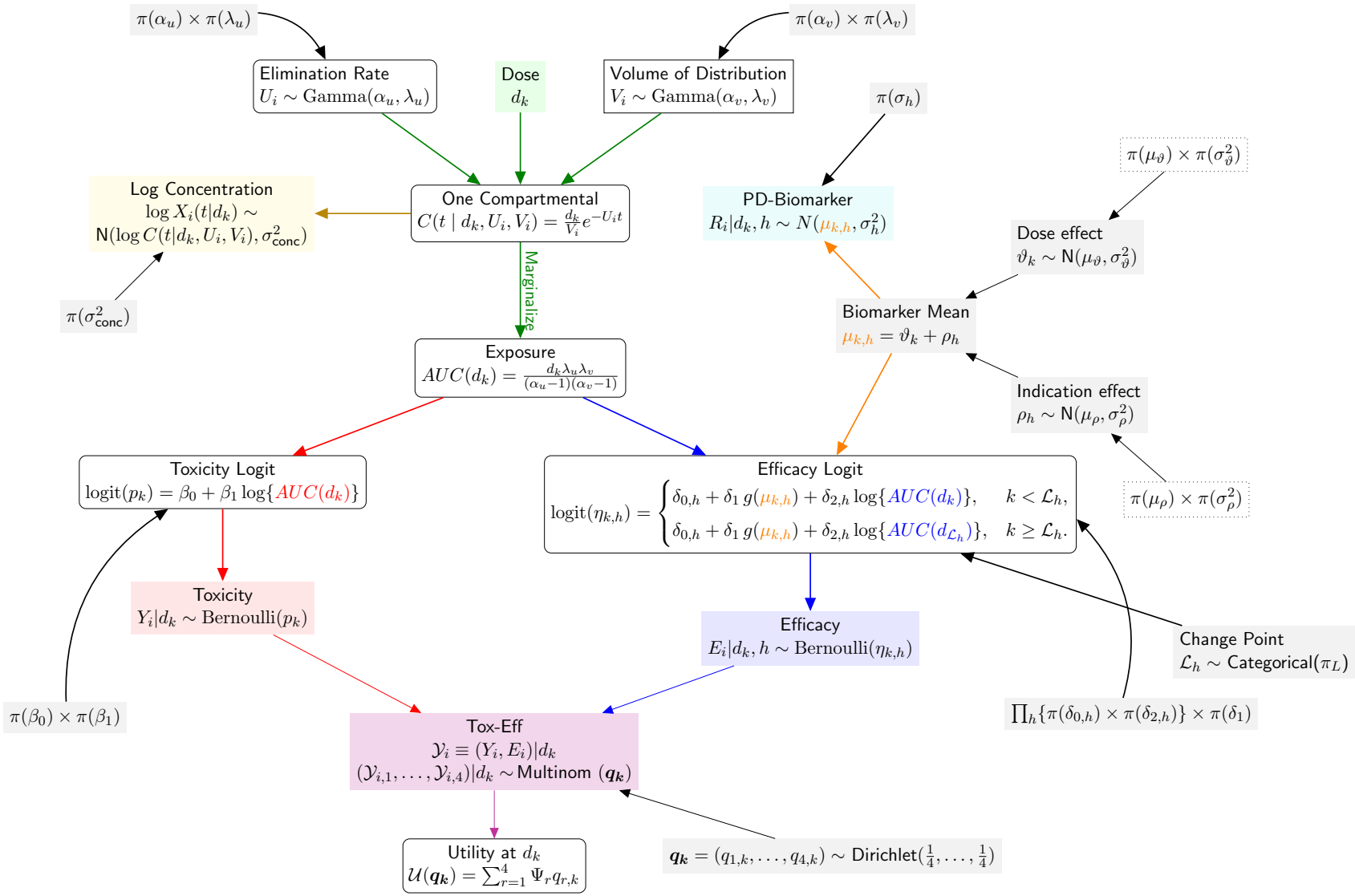
Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

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)

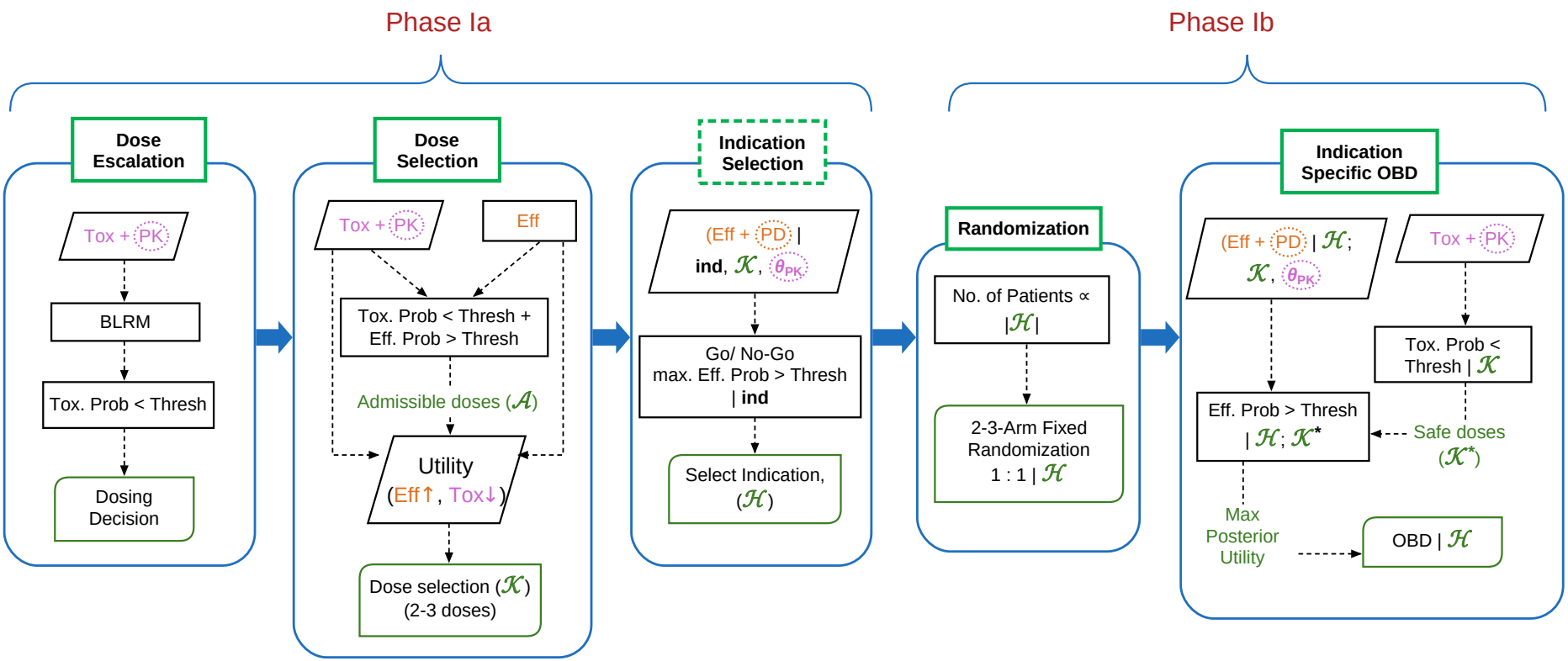
August 2024
Clinical/Medical

PK-Toxicity, PD-Efficacy and Utility DAG



Note: Prior ⋮⋮ Hyperprior. Subscripts represent: i-th patient, k-th dose and h-th indication

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.

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($\lambda = 3$), (ii) for Phase 1b patients $\sim$ Piece-wise Exponential($\boldsymbol{\Lambda} = (1, 4, 2, 3, 0.5), \boldsymbol{\tau} = (0, 25, 50, 75, 100)$ in weeks).
- *Blood samples* are collected at 4, 8, 24, 48, and 72 hours post-dose for PK assessment, with the labs reporting the PK data at **8 weeks**.
- The *DLT* observation window is **4 weeks** post-dose. Tumour response (*efficacy*) is assessed by radiological scans at **12 weeks** post-dose, and biomarker data, where available, arrive at **10 weeks**.

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) *Reference design* and (3) *PEDOOP* (Yuan et. al. 2024).

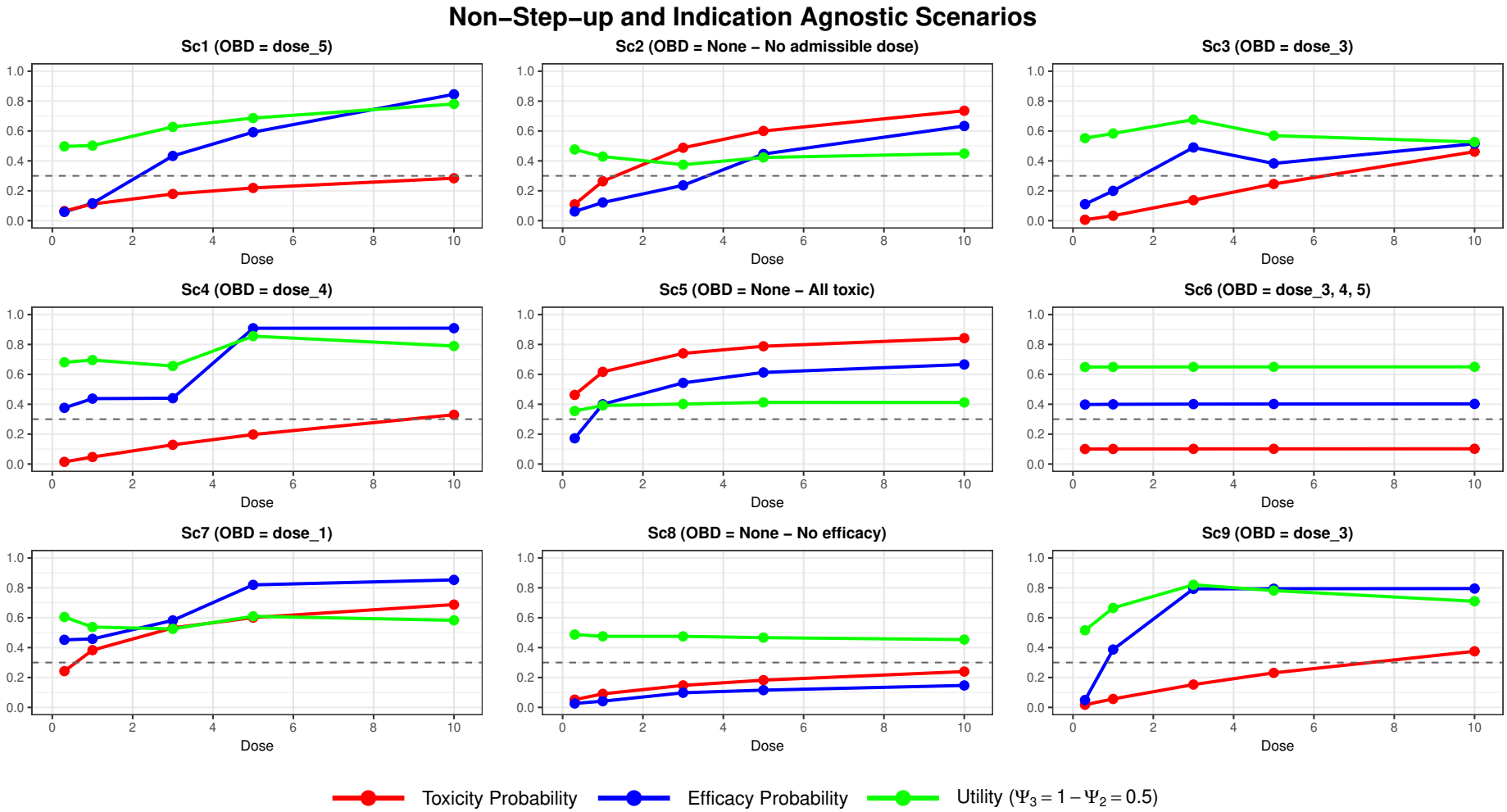
Comparison of Design Features

Feature	PREDOSE without PK	Reference Design	PEDOOP
Uses PK data	No	No	Yes
Uses PD data	No	No	derived PD
Dose Escalation	BLRM ($\frac{d_k}{\text{ref dose}}$)	mTPI-2	BLRM (AUC (d_k))
Efficacy Model	BLRM type ($\frac{d_k}{\text{ref dose}}$) with indication-specific slope	Beta-Binomial	Joint model with derived PD.
Jointly models Tox-PK + Eff-PD	No	No	Yes
Admissibility set	$\mathcal{A}$	Based on %age of toxicity and efficacy	$\mathcal{A}$
Utility framework	dose selection	—	adaptive randomization to obtain OBD
Removes redundant indication(s) before Phase 1b	Yes	No	No
Indication-specific OBD/ RP2D	Yes	No	No

Here, admissibility set $\mathcal{A} = \left\{d_k \mid \mathrm{P}(p_{Tox}(d_k) > \varphi_T) < \epsilon_T,\ \mathrm{P}(p_{Eff}(d_k) > \varphi_E) > \epsilon_E\right\}$



Indication agnostic Scenarios



Note: $Utility(d_k) = \Psi_3 \times (1 - P(Tox|d_k) + \Psi_2 \times P(Eff|d_k)$, *where,* $\Psi_3 = 1 - \Psi_2 = 0.5$.

Admissibility set $\mathcal{A} = \{d_k \mid \mathrm{P}(p_{Tox}(d_k) > 0.3|Data) < \epsilon_T,\ \mathrm{P}(p_{Eff}(d_k) > 0.3|Data) > \epsilon_E\}$

Correct Selection (%) for Indication-agnostic

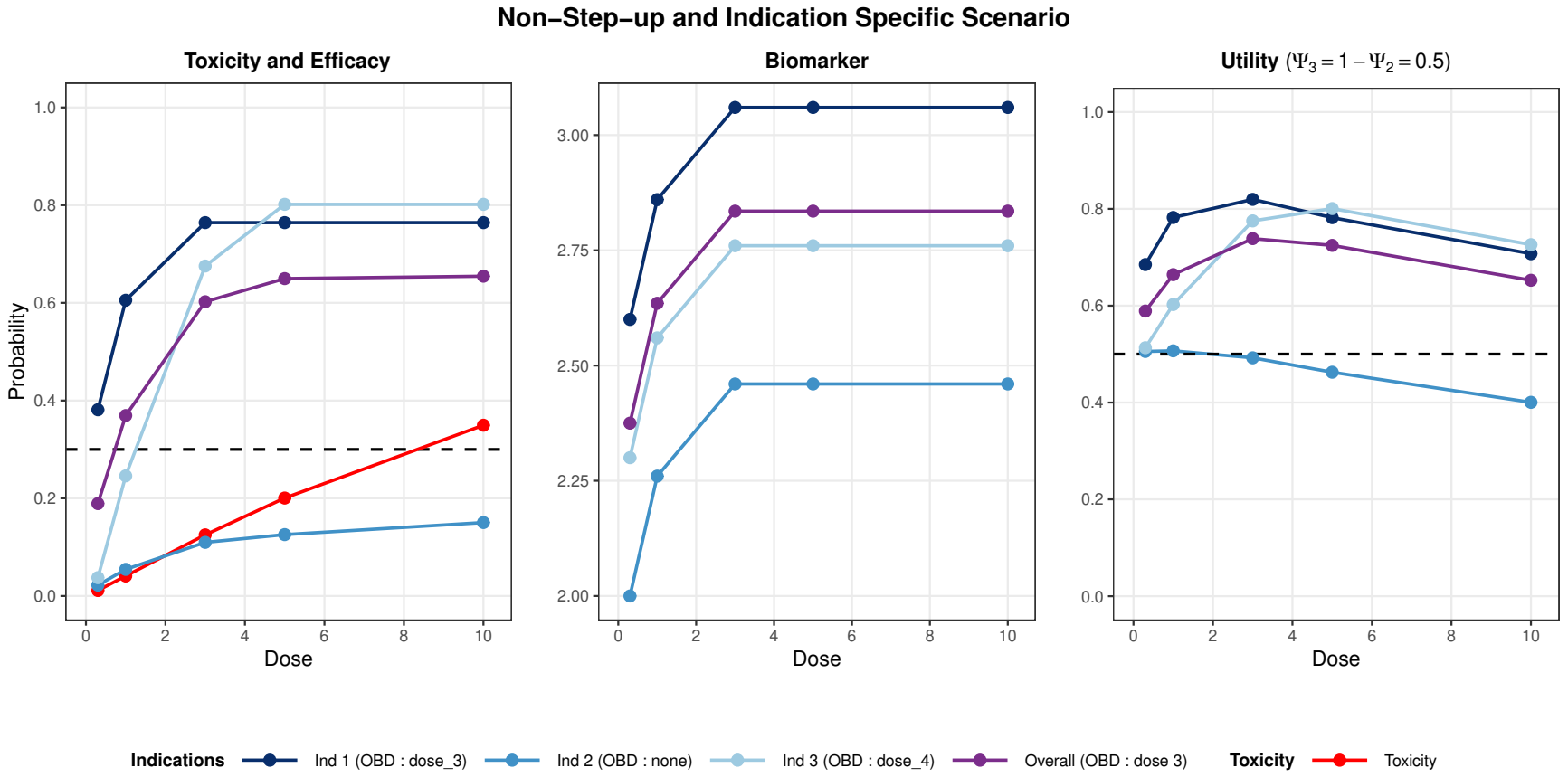
Scenario	Scenario description	True OBD	PREDOSE		Reference Design	PEDOOP
			with PK	without PK		
1	Last dose is OBD	d_5	**38.8**	33.9	22.9	27.8
2	No Admissible	None	**100.0**	**100.0**	99.9	**100.0**
3	Only one peak in Utility	d_3	**83.3**	74.0	38.7	45.8
4	Multiple local peaks in Utility	d_4	**80.1**	61.2	1.4	77.9
5	All Toxic	None	**100.0**	**100.0**	**100.0**	**100.0**
6	Utility is flat	d_3, d_4, d_5	**98.8**	97.0	98.3	82.9
7	Sensitivity	d_1	57.8	60.6	**62.9**	38.1
8	All inefficacious	None	**100.0**	**100.0**	99.8	**100.0**
9	Project Optimus	d_3	80.8	**82.0**	15.4	72.0

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

For (i) Scenario 6 (DL3, DL4 and DL5 are all OBDs), values represent %age of times **any of these doses** is selected by each design.

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

Indication specific Scenario



Note: Utility$(d_k) = \Psi_3 \times (1 - P(Tox|d_k) + \Psi_2 \times P(Eff|d_k)$, *where,* $\Psi_3 = 1 - \Psi_2 = 0.5$.

Admissibility set $\mathcal{A} = \{d_k \mid \mathrm{P}(p_{Tox}(d_k) > 0.3|Data) < \epsilon_T,\ \mathrm{P}(p_{Eff}(d_k) > 0.3|Data) > \epsilon_E\}$

OC for Indication specific case

								Patient Allocation %				
Model	**Ind.**	**Time**	**Size**	**E.Stop%**	**Sel.%**	**No OBD%**	**C.OBD%**	d_1	d_2	d_3	d_4	d_5
Reference design	1	121.2	120.0	5.8	–	5.8	15.4	29.8	24.2	12.2	16.9	16.8
	2				–	5.8	5.8	31.8	22.7	11.5	17.1	16.9
	3				–	5.8	10.8	30.2	23.8	11.9	17.1	17.0
PREDOSE with PK	1	102.7	93.1	1.4	98.7	1.5	49.3	8.8	19.7	28.1	26.3	17.2
	2				11.6	99.4	99.4	17.0	12.6	18.4	23.5	28.5
	3				95.9	6.0	40.0	9.2	19.6	27.5	25.8	17.9
PREDOSE without PK	1	94.6	91.4	1.0	99.0	1.0	41.2	8.6	20.0	30.2	26.6	14.5
	2				17.0	99.6	99.6	17.3	12.5	20.0	24.7	25.5
	3				94.6	6.6	32.0	8.9	19.8	29.1	26.5	15.8

Note: Values based on 1,000 replications per scenario.
(i) C.OBD% = Correct OBD; Sel.% = Indication selected; E.Stop% = Early Stop; Size = Average sample size; Time = Average trial time in weeks.
(ii) For Indication 2, C.OBD% means %age of times no OBD is obtained; Sel.% not applicable for the Reference design (–).
(iii) True Indication allocation (Ind 1: 45%, Ind 2: 20%, Ind 3: 35%)
(iv) True OBD (Ind 1: d_3, Ind 2: None, Ind 3: d_4); allocation at the true OBD is coloured.

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. Removes redundant indications before trial starts Phase 1b, resulting in (i) **lower sample size** (ii) **faster completion of trial** and (iii) **better allocation of doses**.

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

Acknowledgments

I would like to sincerely thank:

- My collaborators Dr. Arunava Chakravartty and Dr. Damitri Kundu from Eli Lilly and Company,
- Prof. Yuan Ji from University of Chicago,
- KyongJu Lee from University of Pittsburgh,
- National Institute of Health and Care Research Grant [grant number: NIHR301614].



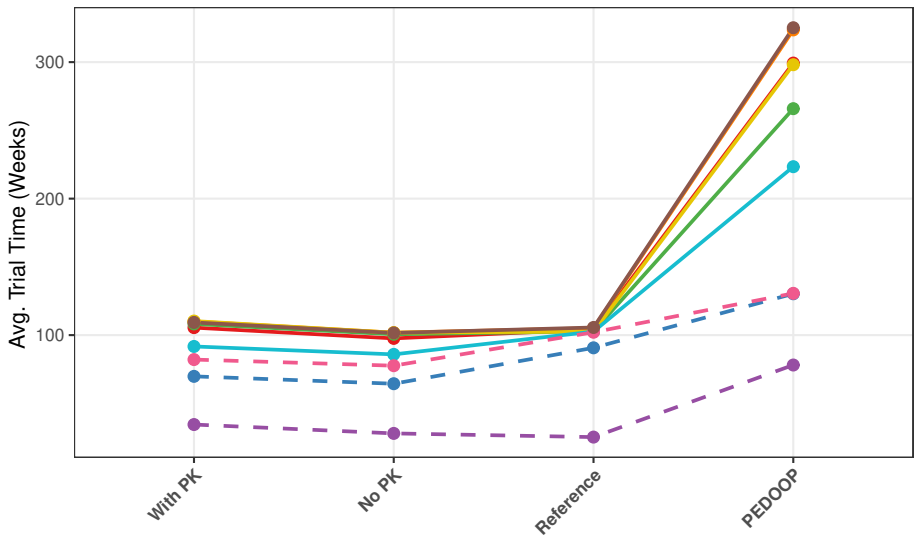
THANK YOU

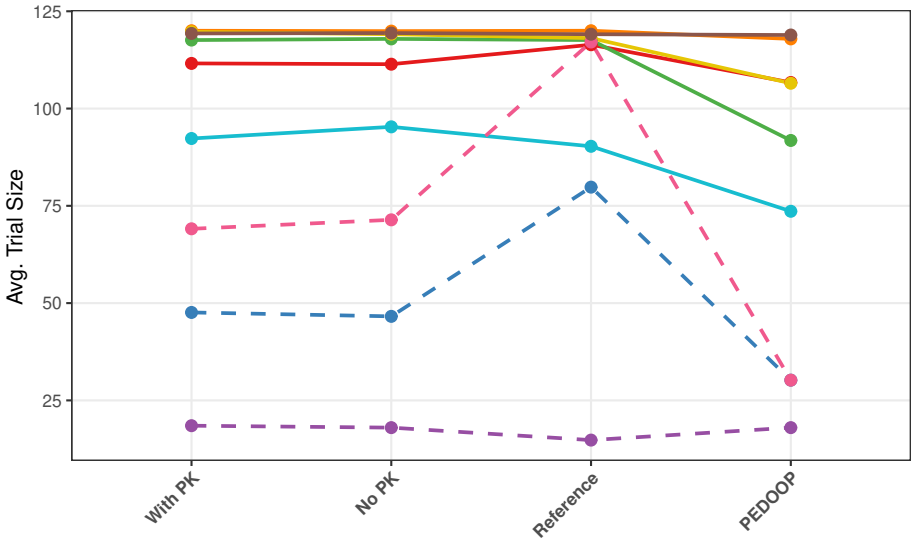
No. of times OBD Selected by Model and Indication

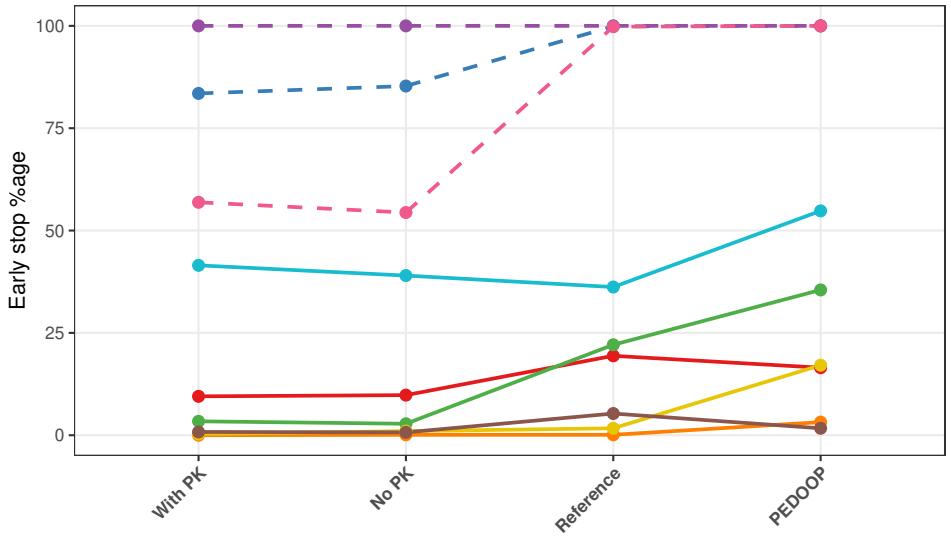
			No. of Times OBD Selected					
Model	**Ind.**	**OBD**	d_1	d_2	d_3	d_4	d_5	**No OBD**
Reference design	1	d_3	22	635	154	108	23	58
	2	None	22	635	154	108	23	58
	3	d_4	22	635	154	108	23	58
PREDOSE with PK	1	d_3	31	279	493	170	12	15
	2	None	0	0	0	6	0	994
	3	d_4	0	32	400	488	20	60
PREDOSE without PK	1	d_3	60	465	412	52	1	10
	2	None	0	0	1	3	0	996
	3	d_4	0	59	320	536	19	66

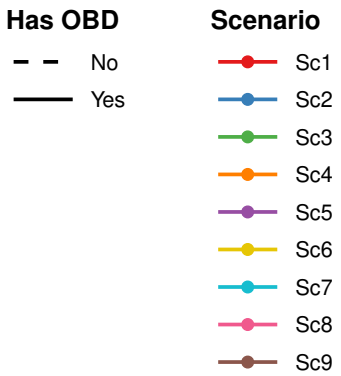
Ind 1 OBD: d_3 Ind 2 OBD: None Ind 3 OBD: d_4

Trial time, size and early stopping %









Note: PREDOSE with and without PK are represented as "With PK" and "No PK" respectively.

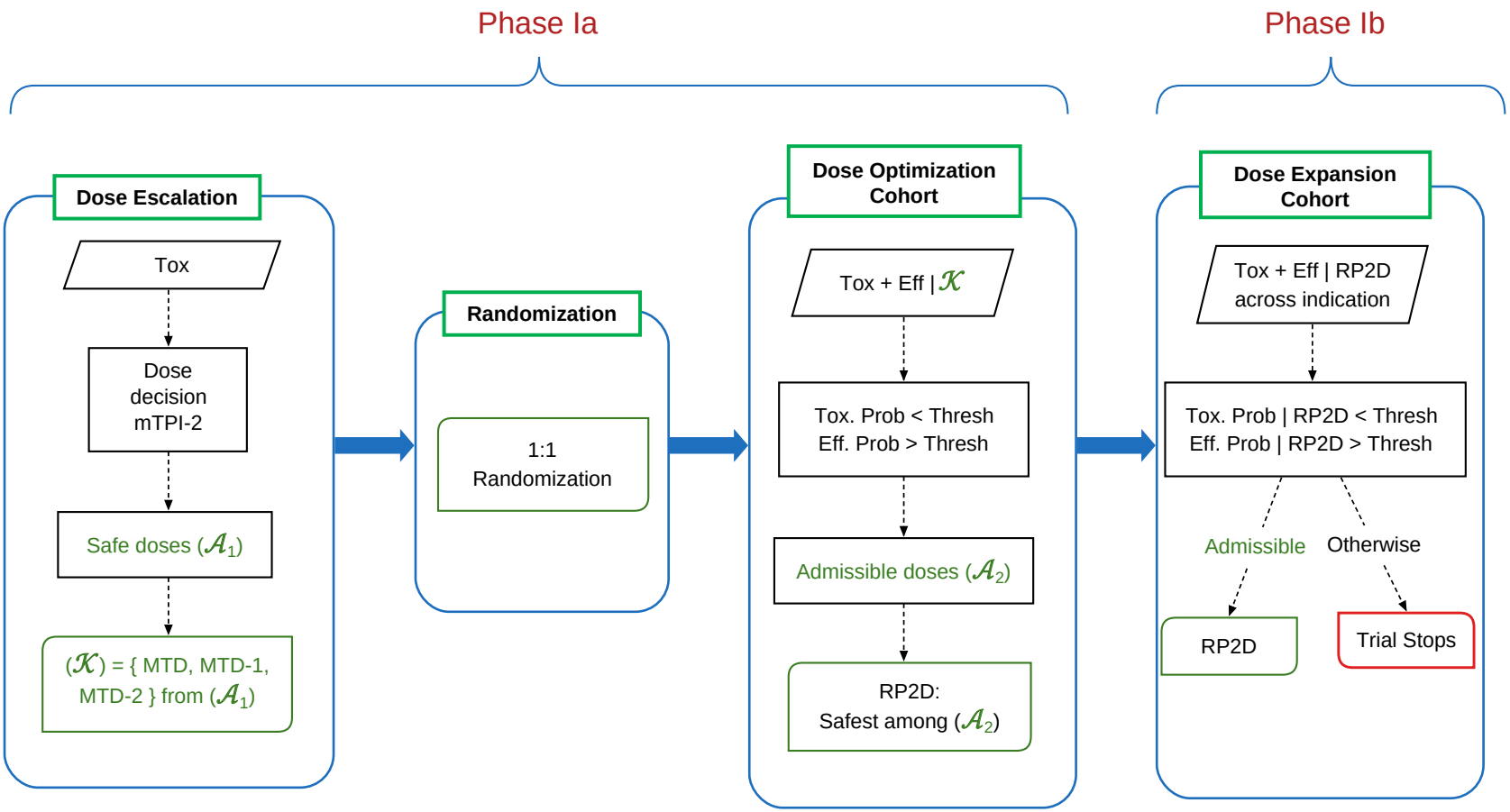
OC for Indication agnostic case

Sc(OBD)	Model	Time	Size	E.Stop	No OBD	C.OBD	Patient Allocation %				
							d_1	d_2	d_3	d_4	d_5
	Reference Design	104.2	116.4	19.4	19.4	22.9	31.9	21.1	14.3	13.2	19.6
Sc1	PEDOOP	299.3	**106.7**	16.5	18.4	27.8	5.3	9.3	26.3	28.7	**30.5**
(d_5)	PREDOSE with PK	105.5	111.6	9.5	**12.6**	**38.8**	9.0	13.4	31.6	24.8	21.2
	PREDOSE without PK	**97.6**	111.4	9.8	13.5	33.9	8.6	14.5	32.4	25.0	19.5
	Reference Design	102.8	117.6	22.1	22.1	38.7	30.9	24.9	14.9	20.0	9.3
Sc3	PEDOOP	265.9	**91.8**	35.5	38.0	45.8	4.6	6.1	37.2	36.9	15.2
(d_3)	PREDOSE with PK	108.2	117.6	3.4	**7.6**	**83.3**	10.4	17.0	**38.9**	24.9	8.8
	PREDOSE without PK	**100.6**	117.9	2.8	10.8	74.0	12.0	17.2	37.9	25.2	7.7
	Reference Design	105.1	120.0	0.1	0.1	1.4	31.4	23.2	12.3	14.8	18.2
Sc4	PEDOOP	323.6	**117.9**	3.2	3.4	77.9	6.9	12.6	12.6	**48.3**	19.6
(d_4)	PREDOSE with PK	110.0	120.0	0.0	**0.0**	**80.1**	16.0	18.8	18.0	27.6	19.6
	PREDOSE without PK	**101.8**	119.9	0.1	0.4	61.2	16.7	18.6	20.4	27.0	17.2
	Reference Design	102.6	90.3	36.2	**36.2**	**62.9**	**81.2**	13.2	4.2	1.2	0.3
Sc7	PEDOOP	223.4	**73.6**	54.8	61.1	38.1	69.6	26.0	3.5	0.8	0.1
(d_1)	PREDOSE with PK	91.7	92.3	41.5	41.8	57.7	78.4	18.8	2.2	0.4	0.1
	PREDOSE without PK	**85.9**	95.3	39.0	39.0	60.6	77.5	19.3	2.6	0.5	0.1
	Reference Design	105.6	119.1	5.3	5.3	15.4	30.5	25.0	13.8	16.7	14.0
Sc9	PEDOOP	325.2	**118.9**	1.7	2.1	72.0	3.0	12.7	**43.4**	28.3	12.7
(d_3)	PREDOSE with PK	109.3	119.3	0.8	**0.8**	80.8	4.8	21.6	33.5	26.5	13.6
	PREDOSE without PK	**101.6**	119.4	0.7	**0.8**	**82.0**	4.3	23.0	34.9	25.6	12.1

Note: Values based on 1,000 replications per scenario. True OBD shown under each scenario.
(i) C.OBD = Correct OBD; E.Stop = Early Stop; Time = Average trial time in weeks; Size = Average sample size.
(ii) Bold: lowest Time, Size and No OBD, highest C.OBD, and highest allocation at the true OBD within each scenario.



Reference design

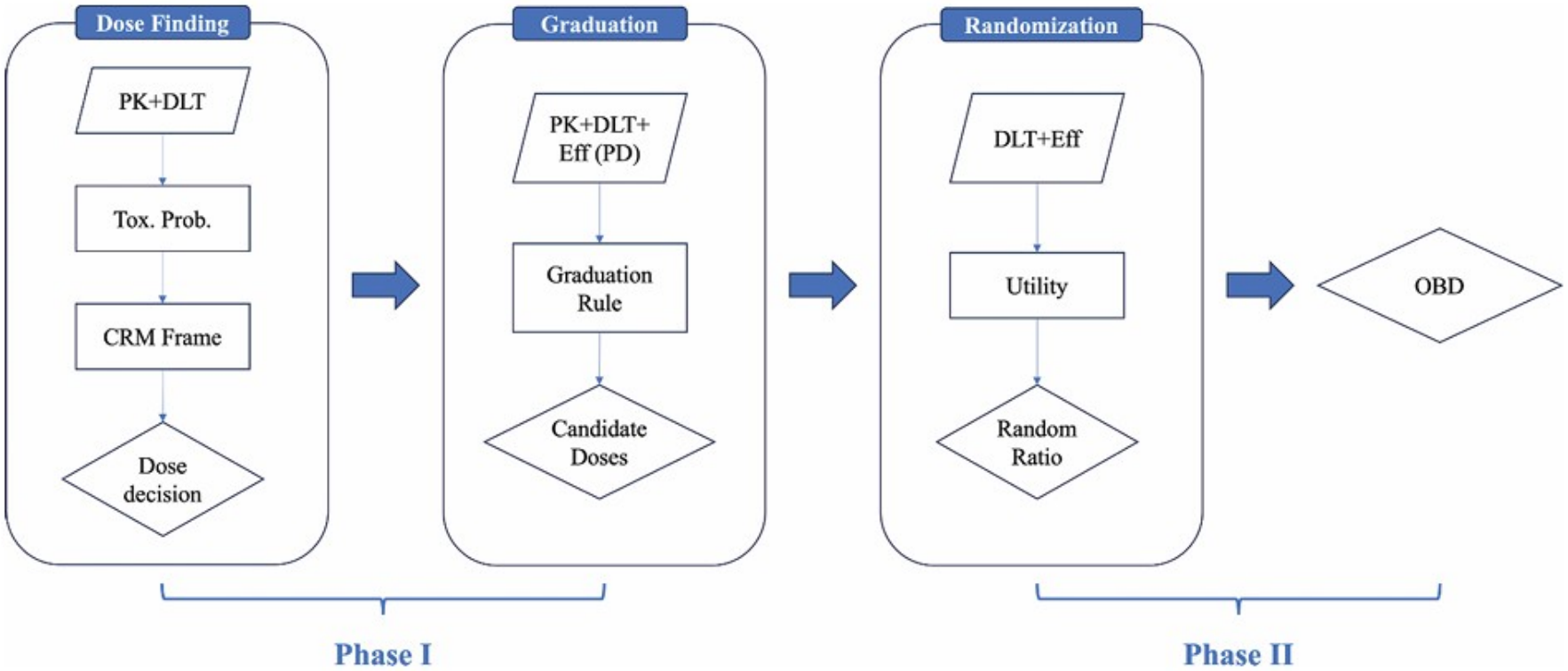


Abbreviations: Eff: Efficacy, **Prob**: Probability, **Tox**: Toxicity, **Thresh**: Threshold, **mTPI-2**: Modified Toxicity Probability Interval-2, **MTD**: Maximum Tolerated Dose, **RP2D**: Recommended Phase II Dose.

Symbols: $\mathcal{A}_1$: Safe set of doses in dose escalation, $\mathcal{K}$: Selected Phase Ia doses, $\mathcal{A}_2$: Admissible set of doses in dose optimization cohort.

In Reference 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. .