Novel integrated population PD modeling framework to inform decision making during Oncology phase I dose-scalation

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Oncology phase I dose-escalation

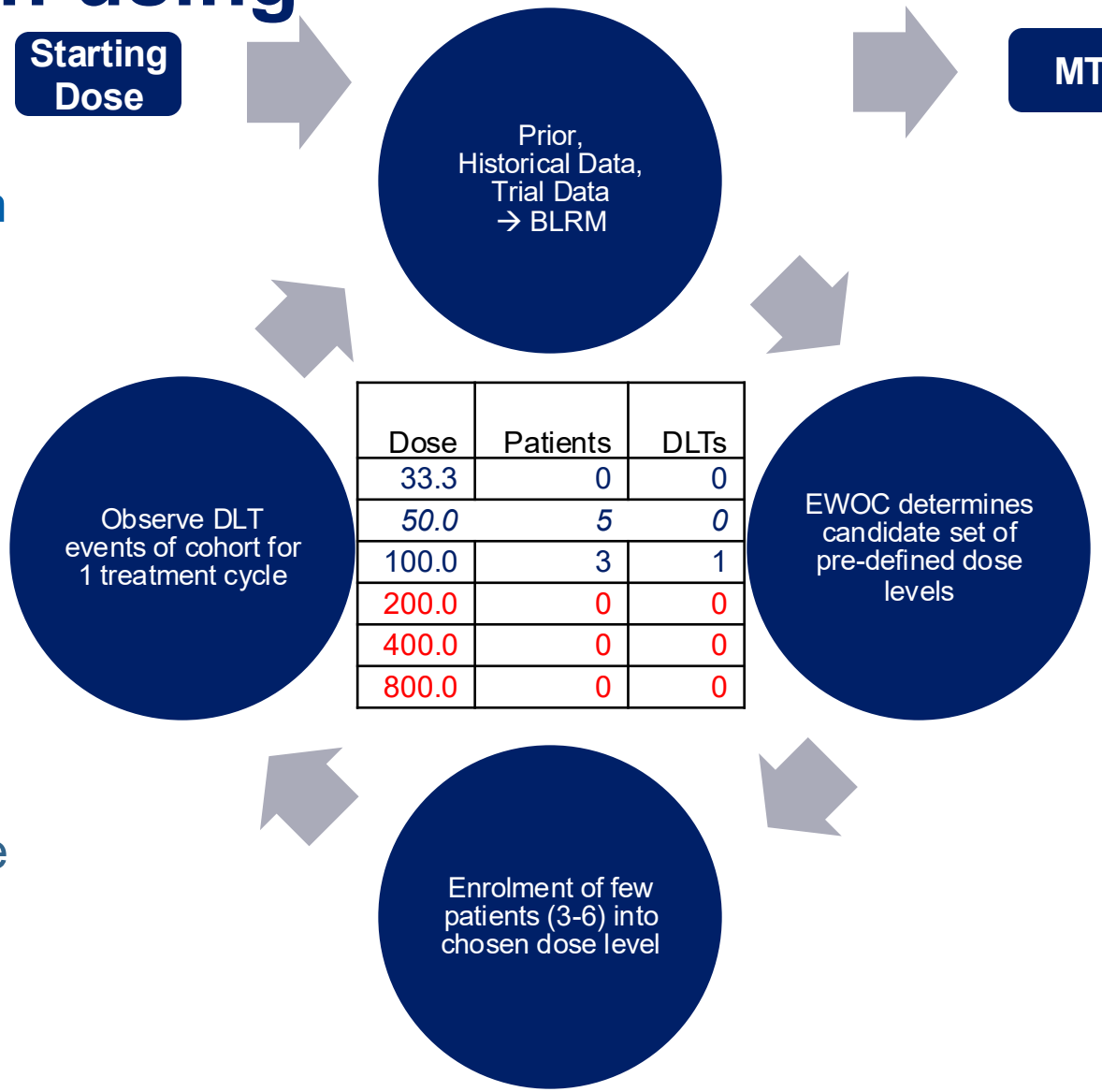
- Phase I trials in oncology ***adaptively*** escalate dose
  1. Cohorts of 3-6 patients at a time enrolled at a safe dose
  2. Monitored for primary safety follow-up of usually 1 cycle (i.e. 4 weeks)
  3. At dose escalation meeting (DEM) decision on next safe dose
     - **Which doses are safe for the next cohort?**
     - Which of these safe doses should one test next?
- With early stages data are very sparse and incomplete
  i.e., often the last cohort has safety data only, but no drug concentrations yet
- Can we make best use of the trial data to ***guide a trial at a DEM***?
  - Historical safety data from administered drug components
  - **Longitudinal models for key safety markers**
    Disease progression models sometimes available

Running a dose-escalation using the BLRM with EWOC

- **We *start* with a small sample and perform adaptive Escalation With Overdose Control (EWOC) step-by-step to warrant patient safety**
- **EWOC for dose fulfilled**

$$\Leftrightarrow \; P(\pi(d) \in \text{over dose}) < 0.25$$

  - $\pi(d)$ probability of a DLT during a cycle
  - Overdose is if $\pi(d)$ > 1/3
  - Avoids too toxic (or too uncertain) doses!
  - Equivalent to require that the 75% quantile of $P(\pi(d))$ is < 1/3



Dose	Patients	DLTs
33.3	0	0
50.0	*5*	*0*
100.0	3	1
200.0	0	0
400.0	0	0
800.0	0	0

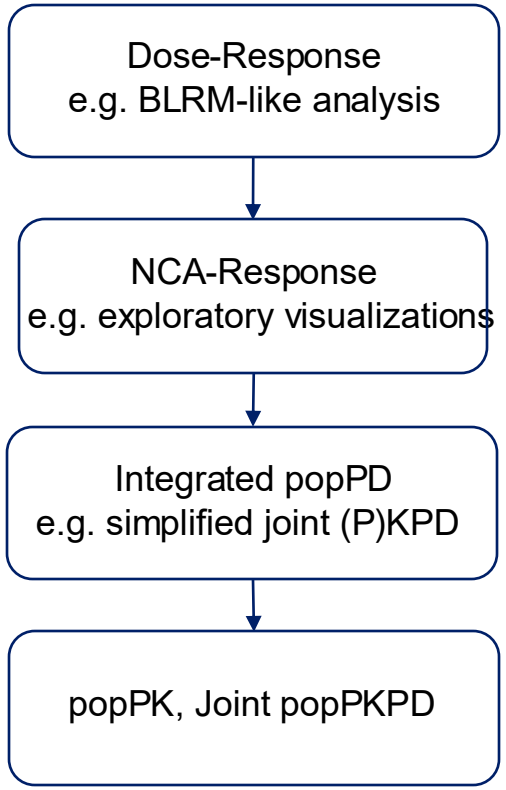
Integrated popPD approach for Phase 1 dose-escalation Oncology studies

Proposal: Integrated popPD modeling

- **Focus on modelling PD** - including data of patients with missing PK data
- Longitudinal population models **leveraging prior knowledge** (e.g. model structure and/or parameters from literature or pre-clinical)
- **Time-varying exposure** based on dosing history and/or simplified PK
- **Assess benefit & risk for future patients** using simulations

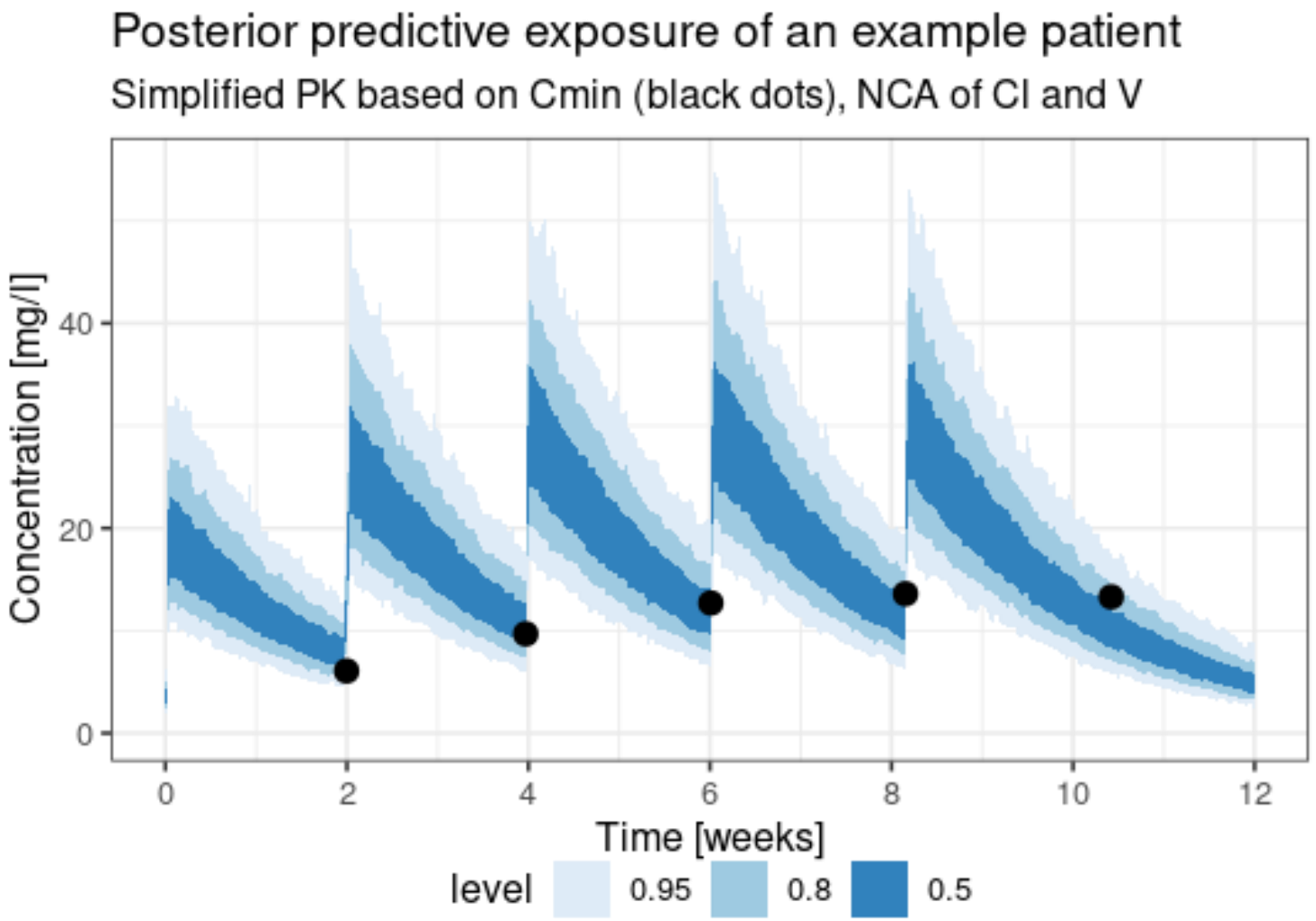
When to use: Early stages of dose escalation

- **Quick turnaround** tailored to the program needs
- To be used when **popPKPD is not yet established**
- Model assumptions for time-varying exposure must be **reasonably met given analysis goals** (in agreement with known drug pharmacology)



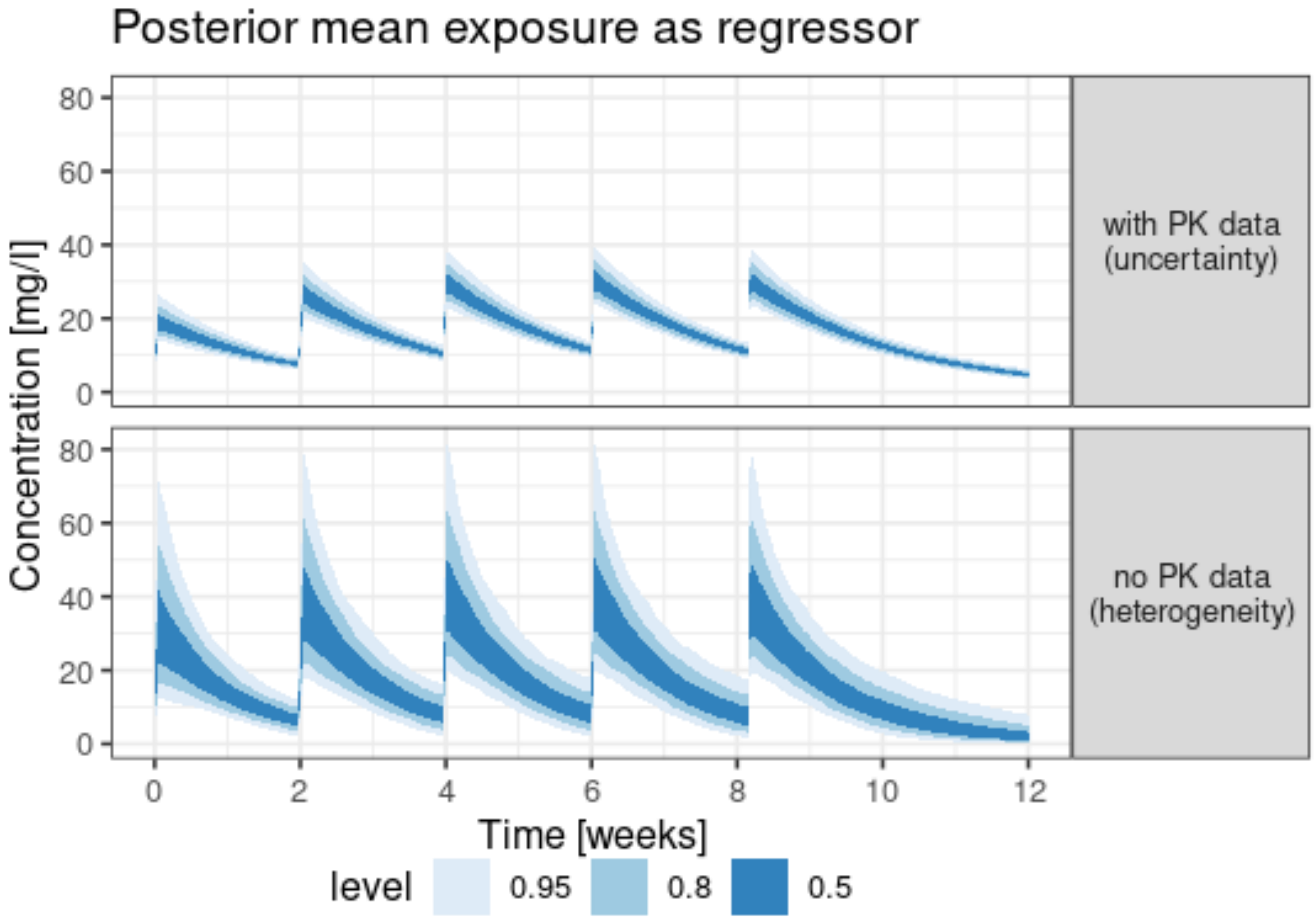
Concentration based exposure comes with significant uncertainty

- Estimation uncertainty
- (Residual error)

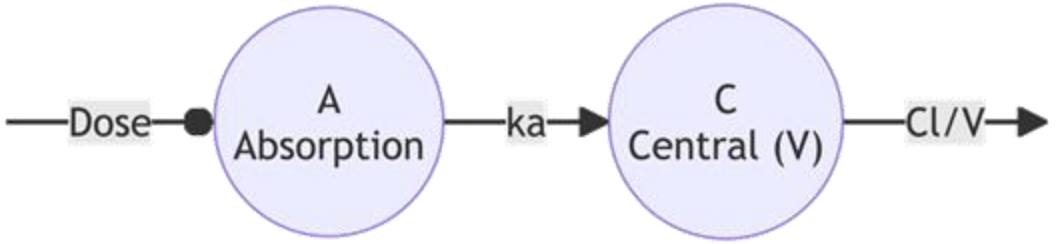


Lack of PK data leads to substantial uncertainty due to heterogeneity

- Available PK data leads to relatively precise exposure metric
- Lack of PK data leads to substantial uncertainty due to between-patient heterogeneity
  - Regression of PD data of patients in **absence of PK data**
  - Used for simulation of future patients outcomes as **needed for dosing recommendations**
- **=> Integrated modeling approach (avoids shrinkage issues)**



Time-varying exposure as latent concentration or simplified PK model



Goal: To describe exposure longitudinally over time with focus on steady state kinetics including reaching and leaving steady-state (characterize dosing regimens/drug holidays/non-compliance)

Data: Actual dosing history and readily available data such as NCA estimates for clearance, volume, and observed C_{min} & C_{max}

Out of scope: Highly accurate modeling of drug pharmacology. E.g. short-term absorption process often complex and not needed for modeling longer term PD. Desirable to have a not too wrong C_{max}, but given less priority for the sake of simplicity.

PK model: First order absorption one-compartment linear elimination model based on dosing history only or if with PK data then a fully generative such that the model extends with uncertainty to new unseen patients

Integrated popPD approach

Example endpoints

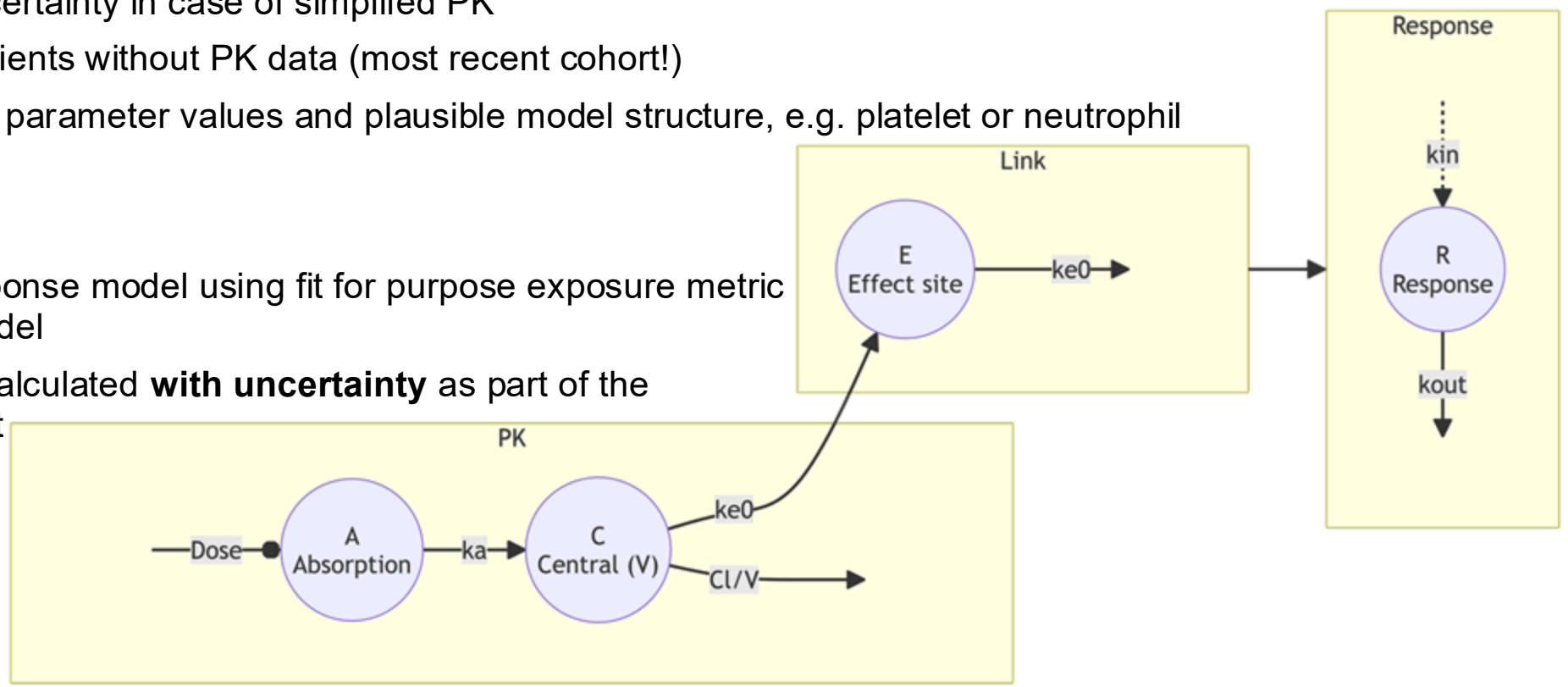
- Events
  Hazard proportional to exposure
- Continuous Turn-Over Model

Goal: Analyze with the time-varying exposure model (latent concentration or simplified PK model) as a building block for different endpoints

- Account for parameter uncertainty in case of simplifed PK
- Inclusion of PD data of patients without PK data (most recent cohort!)
- Use of prior knowledge on parameter values and plausible model structure, e.g. platelet or neutrophil counts

Approach:

- Semi-mechanistic PD response model using fit for purpose exposure metric derived from exposure model
- Derived exposure metric calculated **with uncertainty** as part of the integrated popPD model fit



Methodology summary

Time-varying exposure using a simplified PK model

- Stable model fit
- Considerable uncertainty in estimates with small sample sizes expected
- Informed from readily available data

Benefits of simplified PK model

- Without PK data the simplified PK model can be reduced to a latent concentration
- Includes extensive visualizations of latent model structure

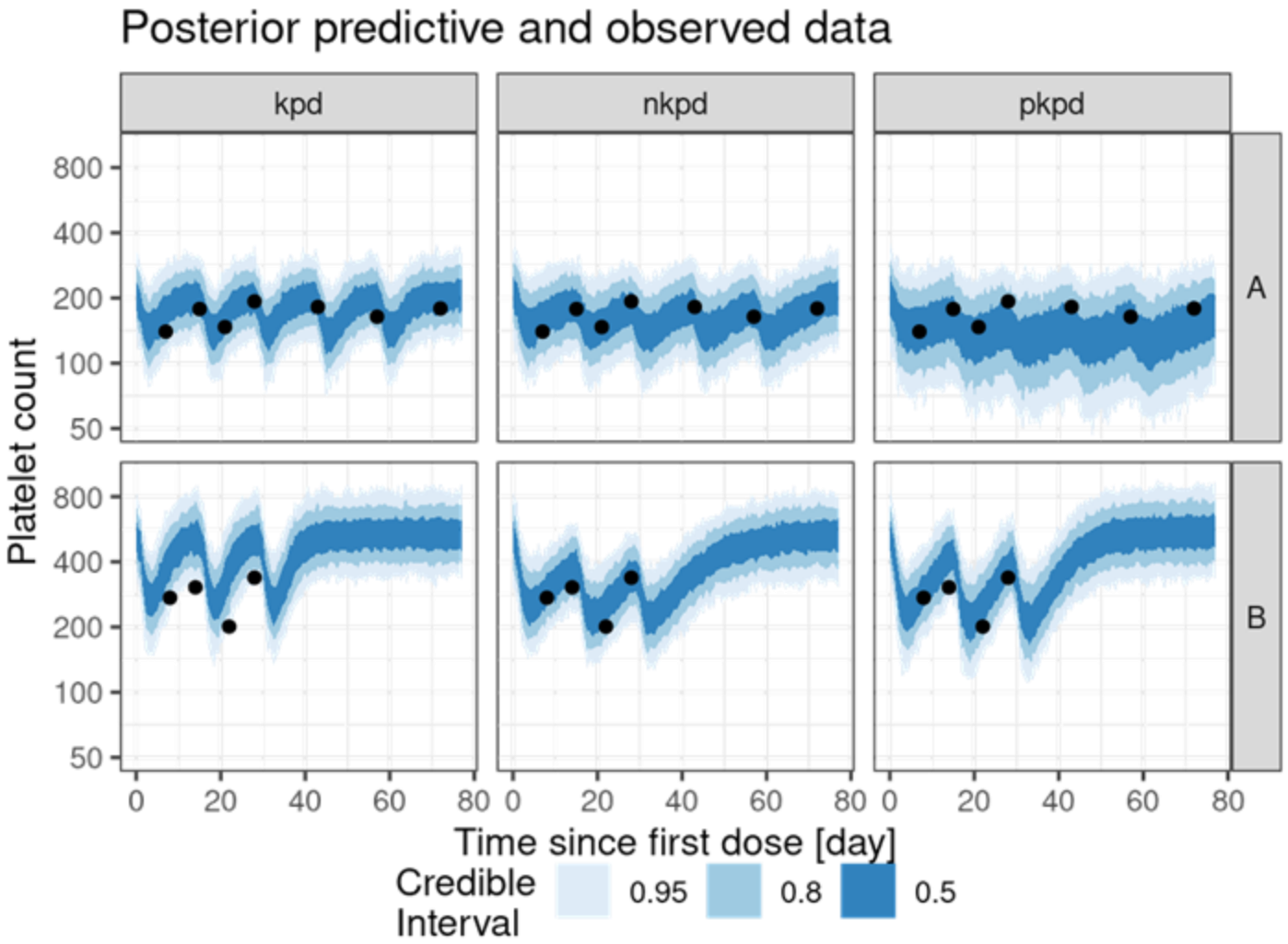
For integrated popPD model we use an approximation of the simplified PK model posterior

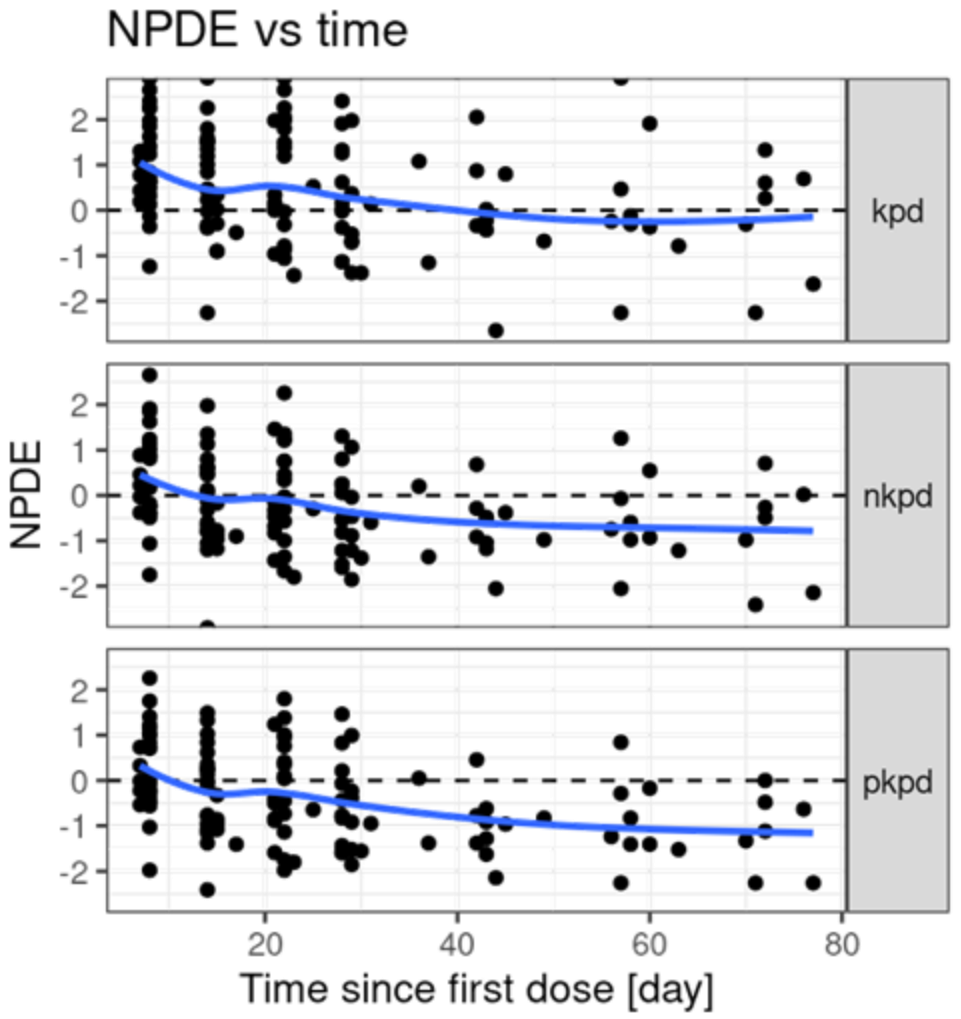
- Omits PK data in the context of a popPD fit
- **Accounting for uncertainty** in PK parameter estimates (including individual random effects)
- **Generative** – simplified PK model extends to unseen patients by population model

Case example for continuous endpoint platelet counts

- Data from trial NCT02375958 studying PCA062 given as infusion (in mg/kg) every 2 weeks (q2w) to patients with pCAD+ tumors
- DEM data was **emulated** for each DEM with PK data of the last two patients enrolled in each cohort set to missing
- Platelet counts were closely monitored as part of regular safety assessment
- A simplified structural model of platelet counts and priors are aligned with models published prior to the trial in a related class of drugs
- Models evaluated & data used for exposure model
  - K-PD: Actual dosing history, average PK parameters CL & V for all patients
  - NK-PD: adds non-compartmental analysis (NCA) estimates of CL & V per patient
  - PK-PD: adds Cmin measurements

Model evaluation



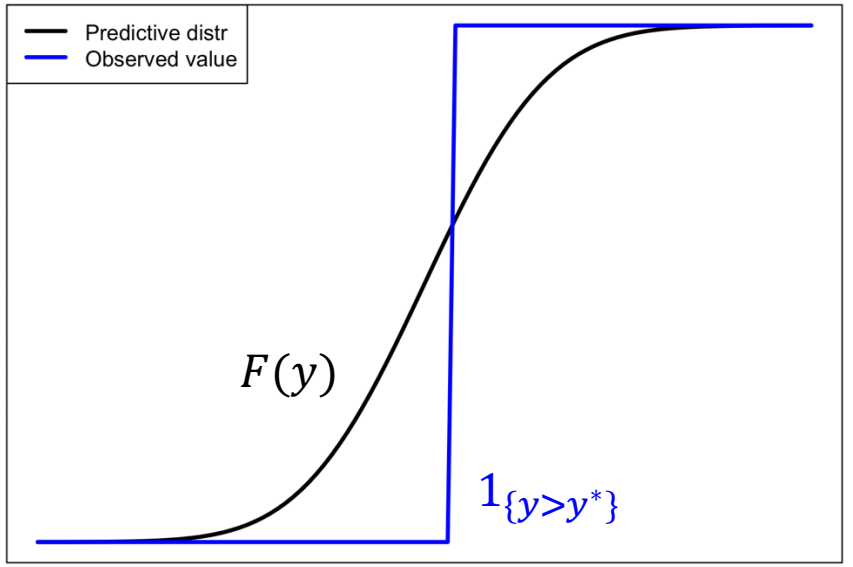


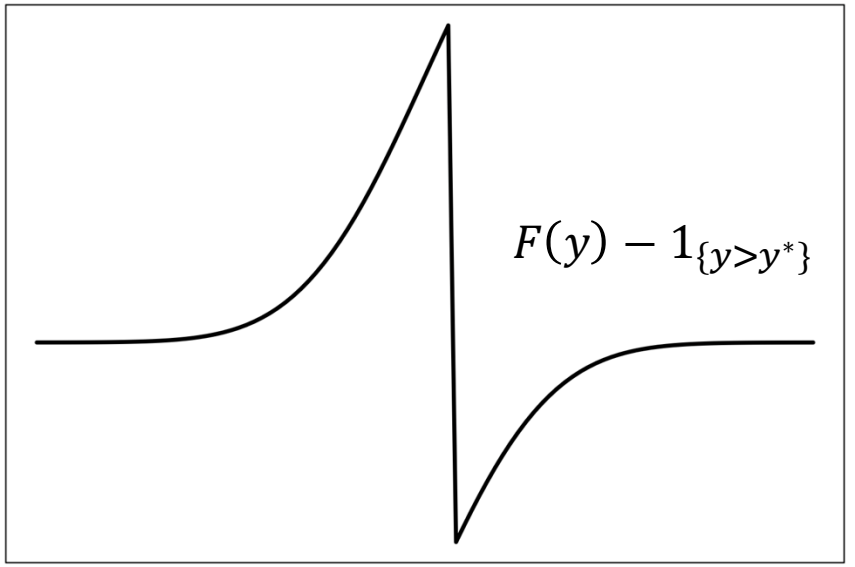
Model performance assessment: Continuous ranked probability score

- Scoring rules assess a predictive distribution vs an observed value
- The continuous ranked probability score (CRPS, Gneiting et al 2007) is given by

$$CRPS(F, y^*) = -\int_{-\infty}^{\infty} \left(F(y) - 1_{\{y>y^*\}}\right)^2 dy$$

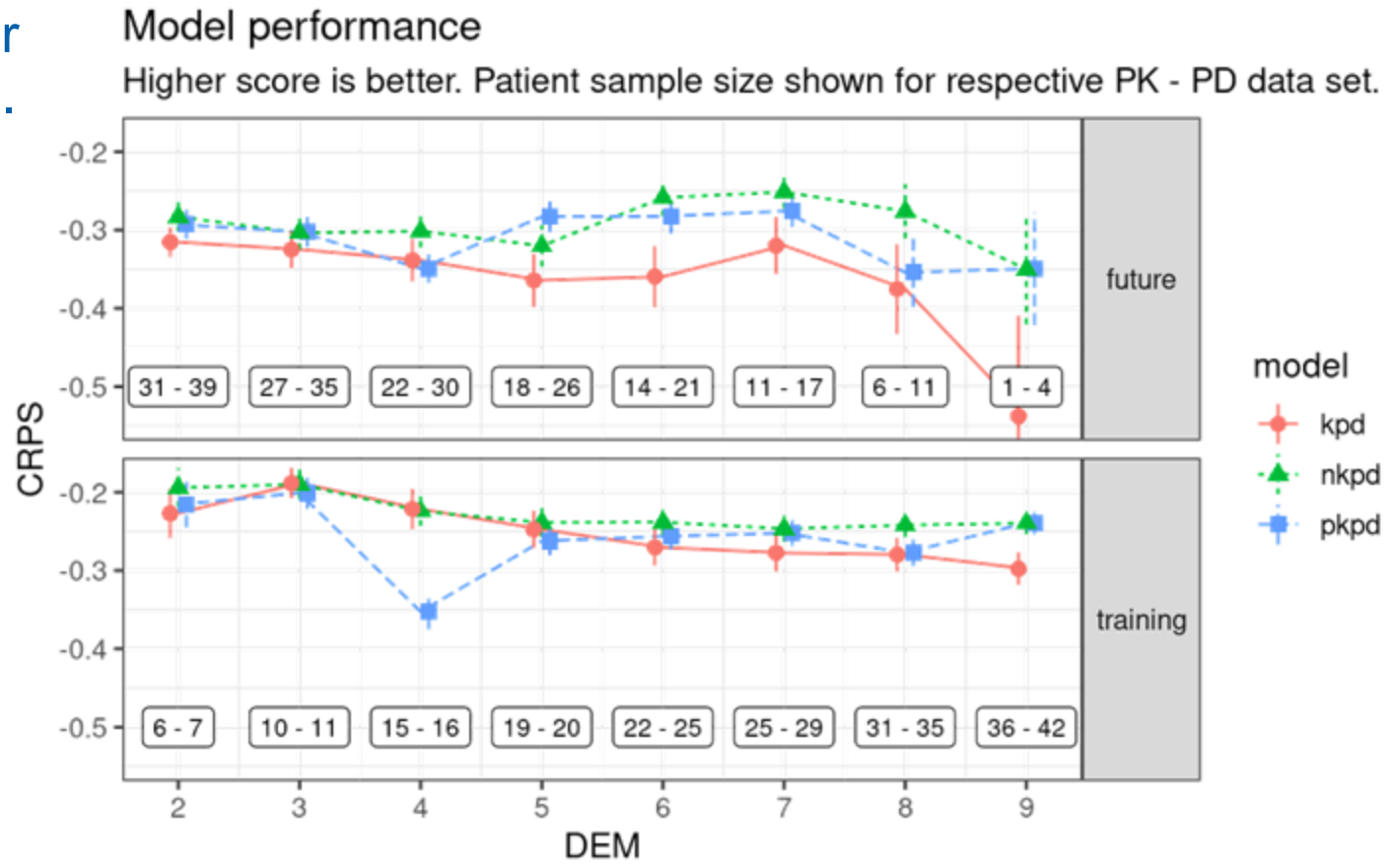
  - $F(y)$ cdf of the predictive distribution of each model
  - y^* longitudinal data of each patient
  - No need for predictive density makes an evaluation simple with MCMC samples of predictive
- Higher CRPS → better scores by predictions with
  - Low bias
  - High precision





Model performance comparison

- The CRPS has a higher score for lower bias and for lower variance predictions.
- The **training** row shows the scores for each model per DEM cut-off.
  -> Which model we would take at a given DEM
- The **future** row shows the scores on the complementary data set of the respective future.
  -> How good would have been the decision at that time point?
- The NK-PD model appears best overall.



Summary

- Dose escalation meeting decisions:
  Which doses are safe for the next cohort? & Which of these should one test?
  - Cross-sectional safety models currently common
  - Population PK “popPK” models / non-compartmental analysis (NCA) often used as a surrogate for safety & efficacy
- Proposal to routinely build population PD ”popPD” models
  - Must account for incomplete data
    Latest cohort safety PD data available while PK data is not ready in time
  - Must be simple enough for stable estimation in sparse data settings
  - Should propagate uncertainty in longitudinal exposure metric
  - Practical approach is a 2-step “with uncertainty” fitting approach
- Case study benchmarks K-PD, “NK-PD” vs PK-PD models
  “NK-PD” accounts for patient specific expose through NCA estimate of CL & V, which appears to be sufficient for good modeling of platelet counts

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Thank you

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Model priors

Parameter	Units	Definition	Distribution	Prior 95% CrI	Note
Cl	L/hr	Clearance of central compartment	Log-normal	0.0006, 0.16	
ω_{CL}	None	Patient random effect standard deviation log(Cl)	Log-normal	0.04, 1.05	0 for K-PD
V	L	Volume of central compartment	Log-normal	0.64, 156.71	5L for K-PD
ω_{V}	None	Patient random effect standard deviation log(V)	Log-normal	0.12, 0.32	0 for K-PD
$\mathrm{k_a}$	1/hr	Absorption rate	Constant	log(2)/(1/6)	
$\mathrm{F_r}$	None	overall scaling factor (applied to dose)	Log-normal	0.62, 1.62	1 for K-PD & NK-PD
$\omega_{\mathrm{F_r}}$	None	Patient random effect standard deviation log($\mathrm{F_r}$)	Log-normal	0.04, 1.05	0 for K-PD & NK-PD
κ	None	Transfer rate to effect compartment relative to Cl/V	Log-normal	0.14, 7.10	
ω_{κ}	None	Patient random effect standard deviation log(κ)	Half-Normal	0.02, 1.12	
ω_{Rs}	None	Measurement error of observed log(Rs)	Half-normal	0.003, 0.22	
k_{out}^{-1}	hr	first order elimination time-scale of response	Log-normal	15.1, 79.3	
Imax	None	Maximal inhibition proportion	Uniform	0.025, 0.975	
ω_{Imax}	None	Patient random effect standard deviation logit(Imax)	Half-Normal	0.02, 1.12	
E_{50}	mg/L	Half effect concentration in effect compartment	Log-normal	0.13, 31.3	