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Isaac Newton Institute

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PODE

Speaker:

Moreno Ursino, PhD

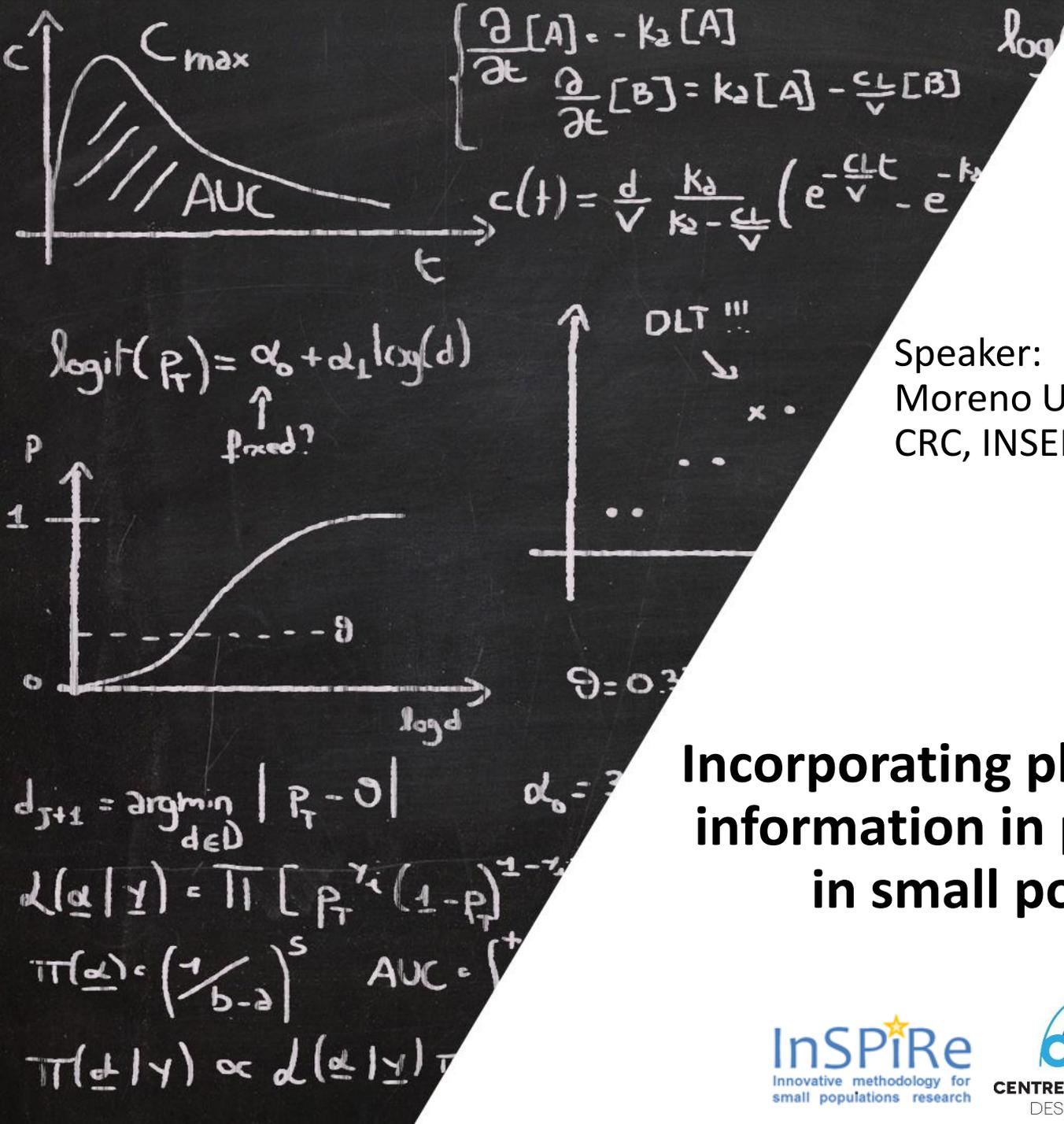
CRC, INSERM UMR 1138

Co-Authors:

Emmanuelle Comets

Sarah Zohar

Incorporating pharmacokinetic information in phase I studies in small populations



Innovative methodology for small populations research

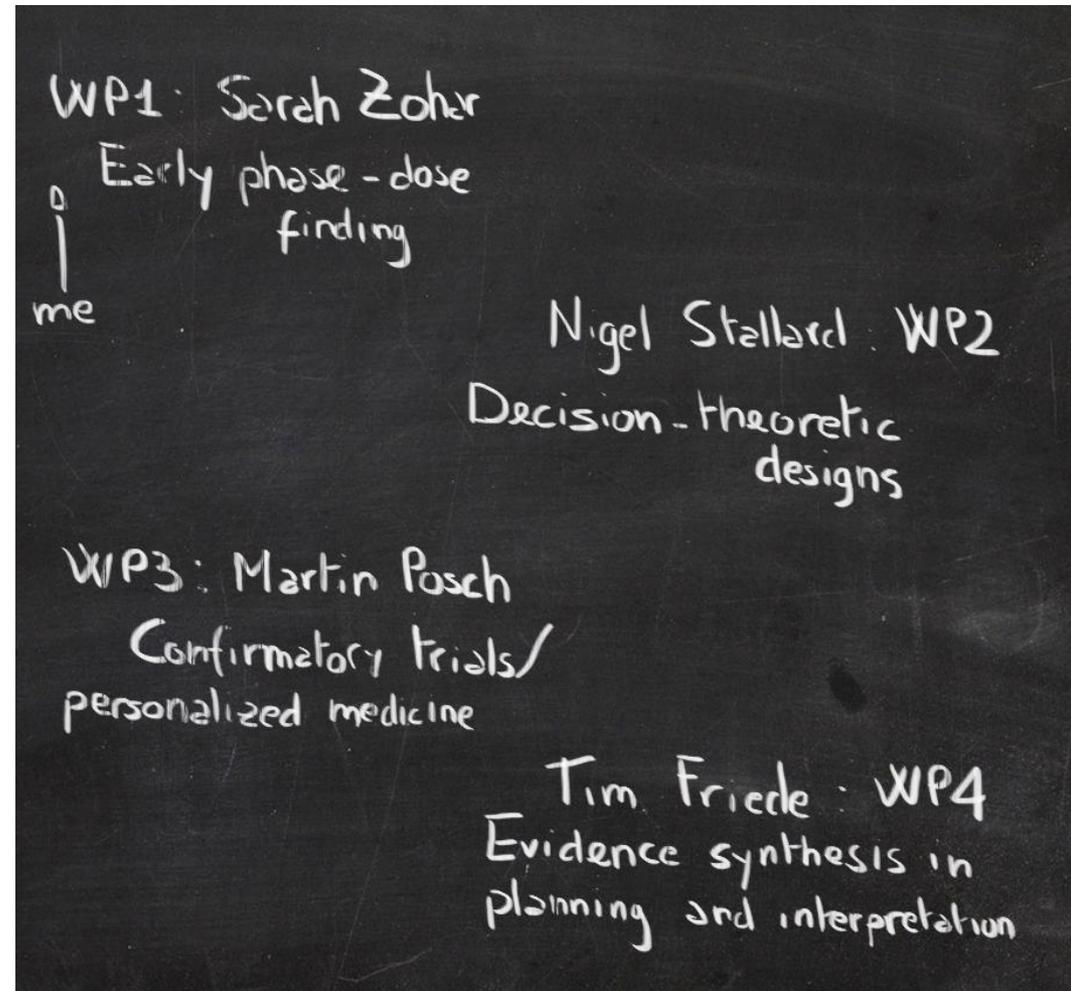
The focus is on the development of novel methods for the design and analysis of clinical trials in rare diseases or small populations defined, for example, by a rare genetic marker.

Project coordinator: Nigel Stallard

Project funded by:



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Members:

- Sarah Zohar
- Emmanuelle Comets
- Corinne Alberti
- Frederike Lentz
- Nigel Stallard
- Tim Friede
- Moreno Ursino

AIM

To develop novel methodology for improving **dose-finding** in early phase clinical trials by **incorporating** data on **pharmacokinetics** (PK), and **pharmacodynamics** (PD).

First year: our aim was to propose, to study and to compare methods that use PK measures in the dose-finding designs

How can we incorporate PK?

- Covariate?
- Dependent variable?

Clinical context and work done

Phase I dose-finding clinical Trials

▪ Objective:

→ estimation of the Maximum Tolerated Dose (MTD)

▪ Context:

→ discrete and fixed dose levels

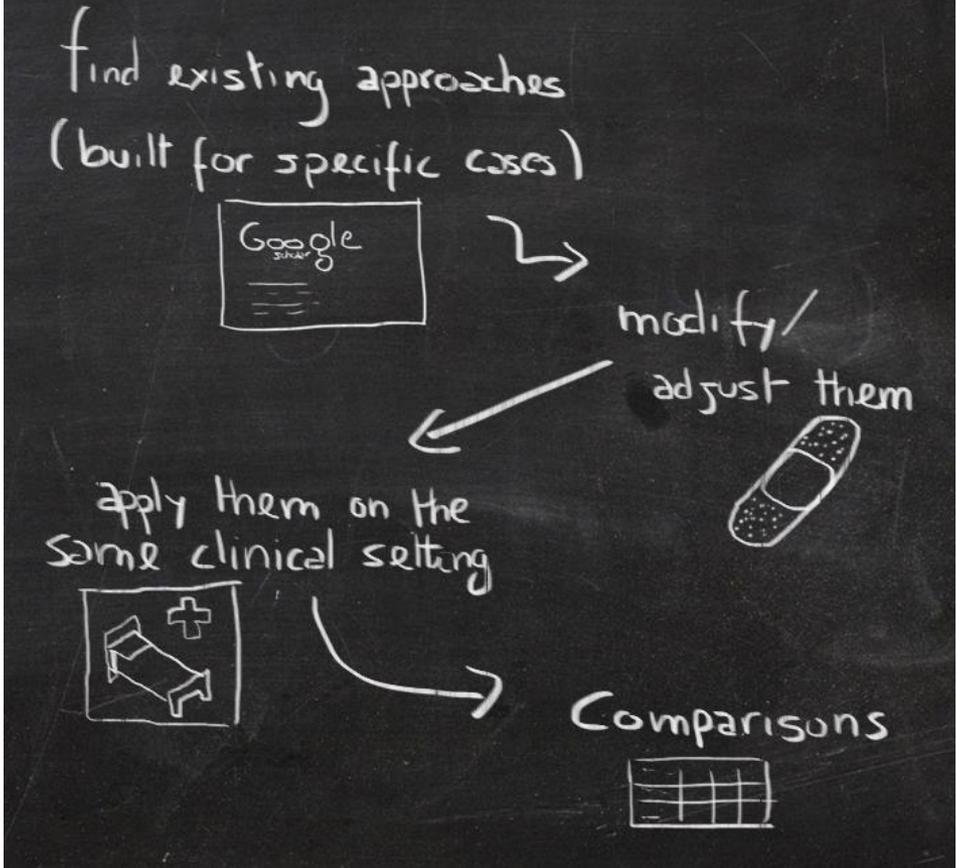
→ binary criteria

→ very small sample size

→ adaptive design

▪ Issues in small samples - rare diseases, pediatrics...

We studied and compared **dose-finding** methods that use the **PK** measure in the dose-finding design either as covariate or dependent variable in the dose-finding model.



find existing approaches
(built for specific cases)



modify/
adjust them



apply them on the
same clinical setting



Comparisons



The idea of introducing PK data in dose escalation studies is not new, but rarely used in practice:

- Collins et al. (1990): Pharmacologically guided phase I trials
- Piantadosi & Liu (1996): parametric dose-response function with a PK measure of exposure as covariate
- Patterson et al. (1999): Bayesian procedure with a nested hierarchical structure
- O'Quigley et al. (2010): dose associated with a mean PK response, based on linear regression
- Patan & Bogacka (2011 DAEW03): Dose selection incorporating PK/PD information in early phase clinical trials

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Comparisons



Models modification

Piantadosi and Liu (1996) /
PKCOV

- first paper found in literature
- extension of Continual Reassessment Method (CRM)
- parametric dose-response function with quantitative effects for both dose of drug and PK exposure (AUC – area under the curve)

$$\text{logit}(p_T) = -\beta_0 + \beta_1 d + \beta_2 \Delta_{\text{AUC}}$$

$$\text{logit}[p_T(d_k, \Delta z_{d_k}, \beta)] = -\beta_0 + \beta_1 \log d_k + \beta_2 \Delta z_{d_k}$$

Priors: $\beta_1 \sim U(\lambda_1, \mu_1)$
 $\beta_2 \sim U(\lambda_2, \mu_2)$
 β_0 fixed

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} | p_T(d_k, 0, \hat{\beta}) - \theta |$$

PK/PD driven dose-selection (1)

Patterson et al. (1999)/
PKLIM

- Bayesian procedure with nested hierarchical structure
- mixed-effect model used to analyze the PK data
- choice of the dose: highest dose satisfying constraint or D-optimal
- Cross-over study and healthy volunteers

$$\begin{aligned}z_{ij} | s_i, \theta, \nu &\sim N(\theta_1 + \theta_2 \log d_{ij} + s_i, \nu^{-1}) \\s_i | \theta, \nu &\sim N(0, \rho / (\nu(1 - \rho))) \\ \theta | \nu &\sim N_2(\mathbf{m}, (\nu \mathbf{Q})^{-1}) \\ \nu &\sim \text{GA}(\alpha, \beta)\end{aligned}$$

$$z_i | \beta, \nu \sim N(\beta_0 + \beta_1 \log d, \nu^2)$$

$$\text{Priors: } \underline{\beta} | \nu \sim N(\mathbf{m}, \nu^2 \underline{\underline{C}})$$

$$\nu \sim \text{Beta}(a, b)$$

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} | P(z_{i+1} > L | \hat{\beta}) - \vartheta |$$

L = fixed threshold parameter

PK/PD driven dose-selection (2)

Whitehead et al. (2007)/
PKLOG

- simultaneous monitoring of PK and PD responses and of the incidence of adverse events
- three models: dose-PK endpoint (a linear model), PK-PD (quadratic model), PK-toxicity (DLT, logistic model)
- Cross-over study and healthy volunteers

$$z_{ij} = \beta(\log(d_{ij} + 1)) + s_i + \epsilon_{ij}$$

$$m_{ij} = \theta_0 + \theta_1 z_{ij} + \theta_3 z_{ij}^2 + r_i + \delta_{ij}$$

$$\text{logit}(p_{T,ij}) = \lambda_1 + \lambda_2 z_{ij}$$

PKLIM

+

$$\text{logit}(p_T | z, \beta) = -\beta_3 + \beta_4 z$$

Priors: $\beta_3 \sim U(\lambda_3, \mu_3)$

$$\beta_4 \sim U(\lambda_4, \mu_4)$$

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} | P(y_{i+1} = 1 | \hat{\beta}) - \theta |$$

$$= \int \frac{1}{1 + \exp(\hat{\beta}_3 - \hat{\beta}_4 z)} g(z) dz$$

Other modifications

$$\text{CRMPK} = \text{CRM} + \text{PKLIM}$$

Dose allocation rule:

$$d_{i+1} = \min(d_{\text{CRM}}, d_{\text{PKLIM}})$$

$$\text{PKPOP} = \text{PKLOG}$$

with

Dose allocation rule:

$$d_{i+1} = \underset{d_k}{\text{argmin}} |p_T(z_k | \hat{\beta}, d_k) - \theta|$$

↓
mean value
predicted

find existing approaches
(built for specific cases)



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same clinical setting



Comparisons



Simulations studies – choosing a PK model

Defining a therapeutic window for the novel TGF- β inhibitor LY2157299 monohydrate based on a pharmacokinetic/ pharmacodynamic model

Ivelina Gueorguieva,¹ Ann L. Cleverly,¹ Anja Stauber,² N. Sada Pillay,² Jordi A. Rodon,³ Colin P. Miles,¹ Jonathan M. Yingling² & Michael M. Lahn²

Correspondence

Dr Ivelina Gueorguieva PhD, Lilly UK, Global PK/PD, Sunninghill Road, Erl Wood Manor, EMC Building, Windlesham, Surrey GU20 6PH, UK.
Tel.: +44 (0) 12 7648 3408
Fax: +44 (0) 12 7648 3588
E-mail: gueorguieva_ivelina@lilly.com

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PK/PD model, TGF- β inhibitor, therapeutic window

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- TGF- β signaling has been recognized as an important regulator of tumor growth
- Inhibiting TGF- β signaling is a novel approach
- They investigated several inhibitors and selected LY2157299

Simulation from preclinical data to predict therapeutic dose range



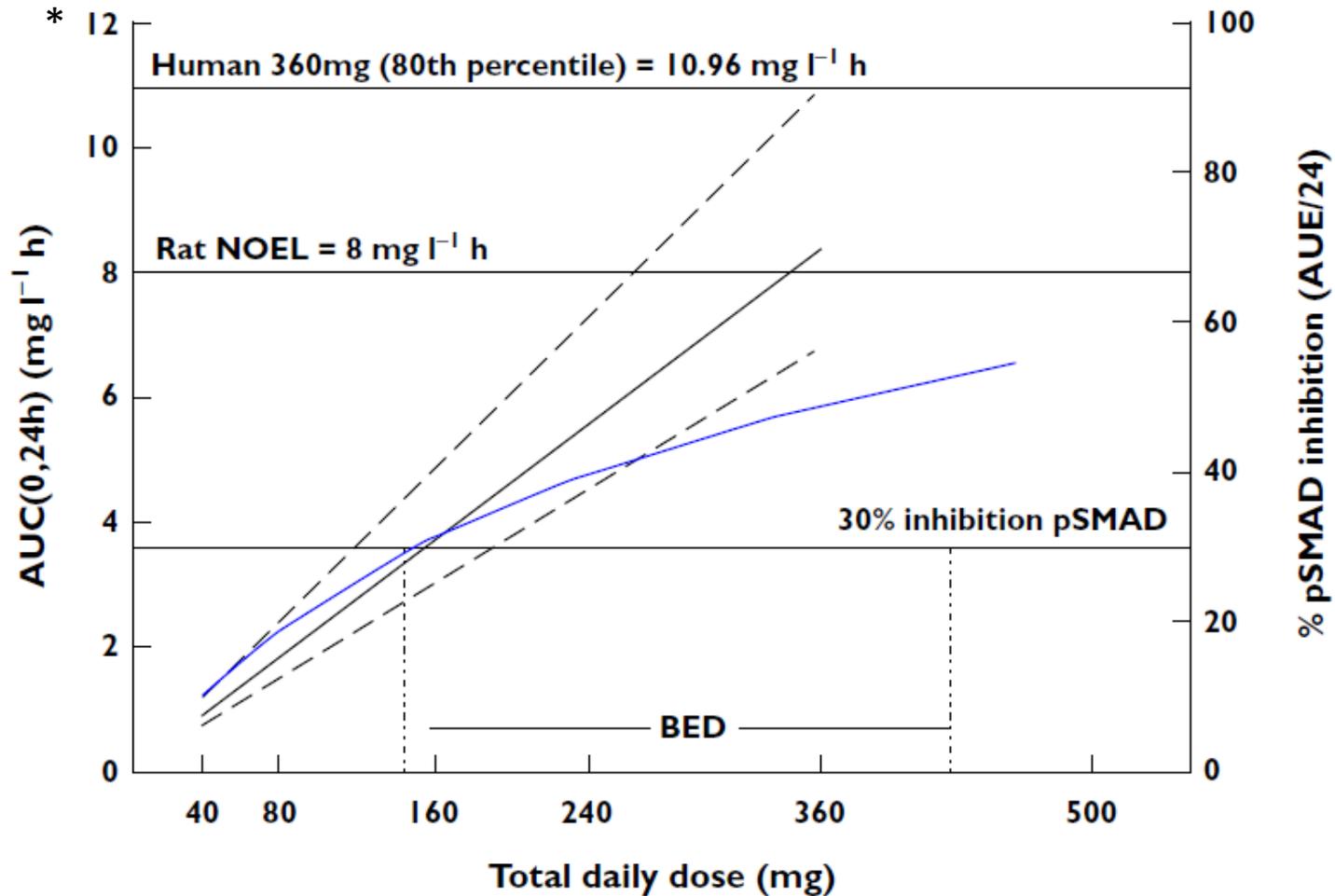
Clinical trial design depending also on preclinical late toxicity



PK/PD estimation in humans:

- First order absorption linear two compartment model
- Indirect model to relate plasma concentrations of LY2157299 and pSMAD data

Simulations studies – choosing a PK model (2)

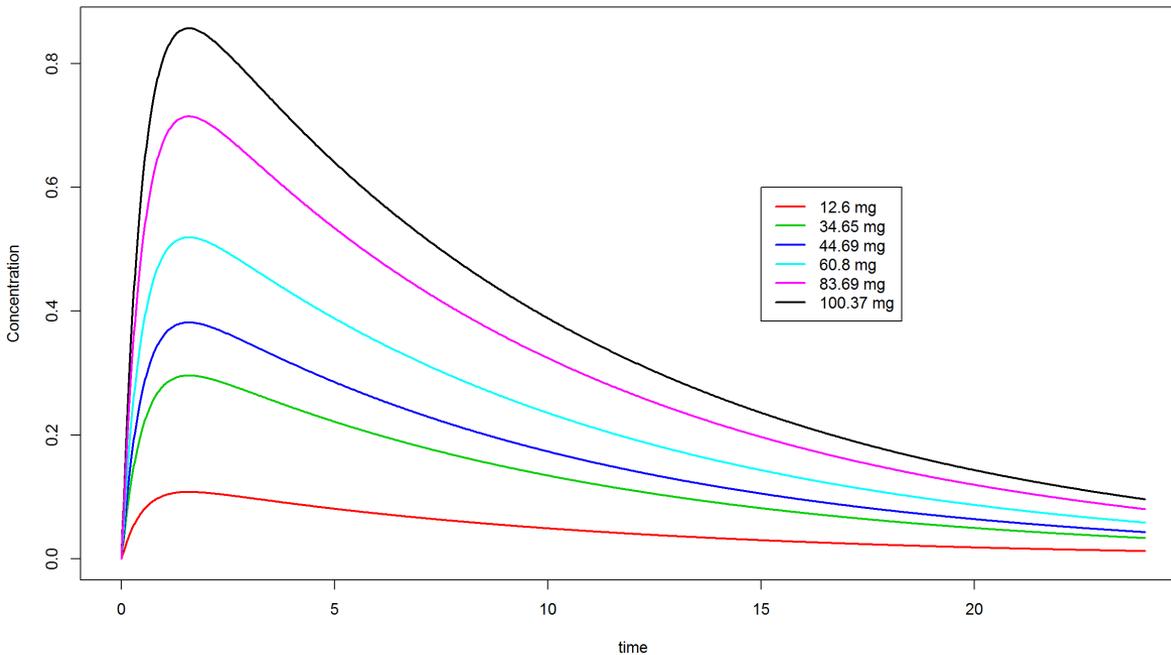


Simulations studies – choosing a PK model (3)

Modifications: only PK

$$c(t) = \frac{d_k}{V} \frac{k_a}{k_a - CL/V} \left(e^{-(CL/V)t} - e^{-k_a t} \right)$$

Pharmacokinetic



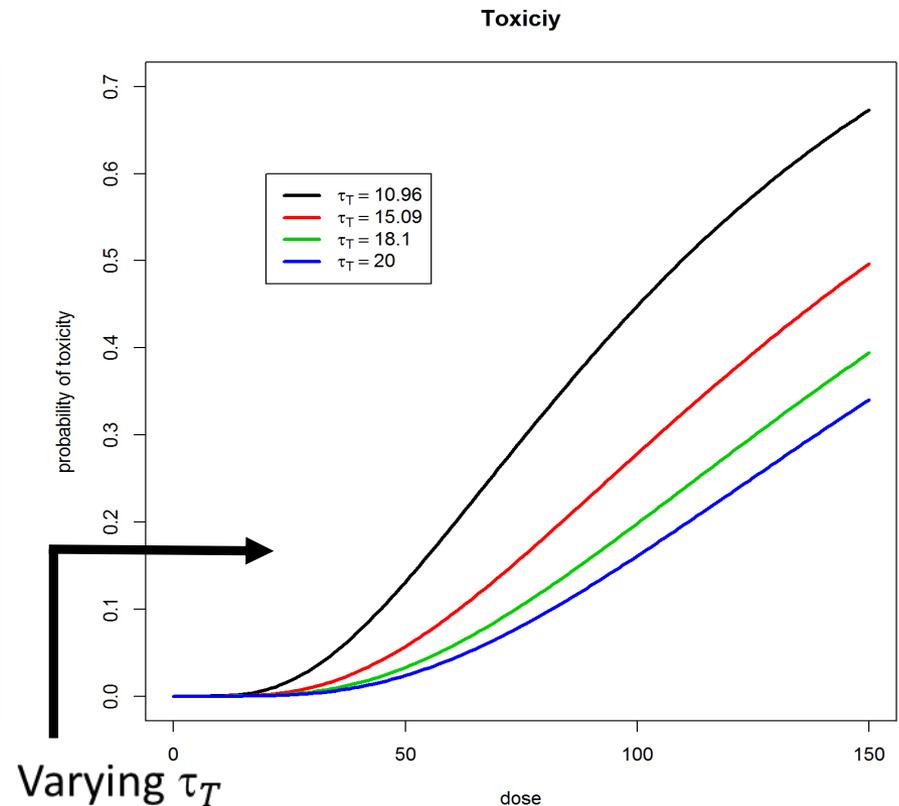
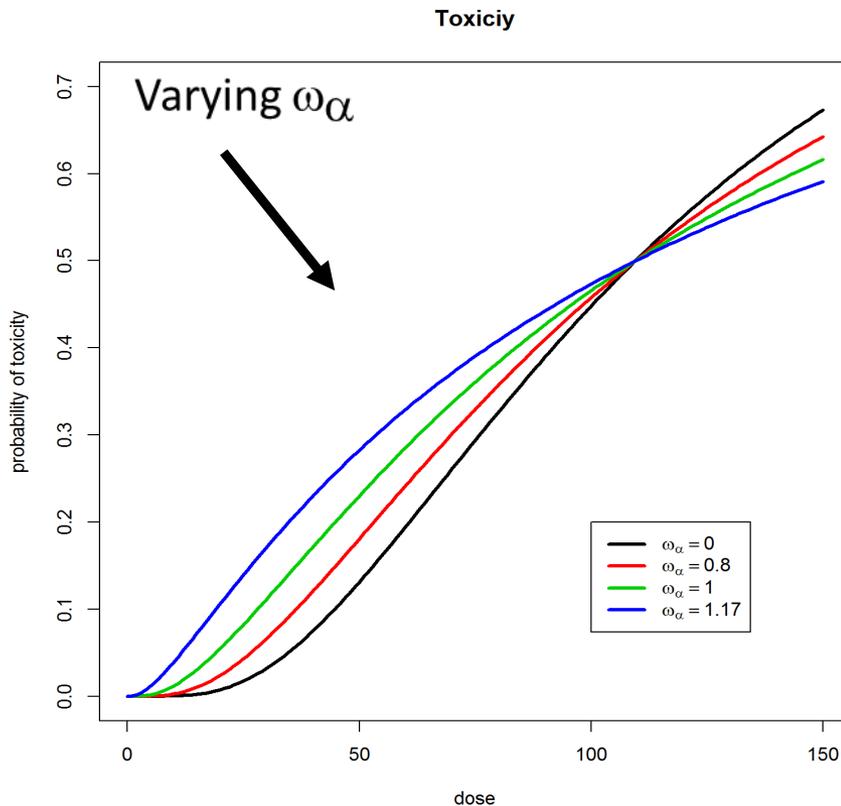
Parameter	Mean value	IIV
k_a	2	0
CL	10	ω_{CL}
V	100	ω_V

with $\omega_{CL} = \omega_V \in \{0.3, 0.7\}$

Simulations studies – link between PK and toxicity

We assumed that the i -th patient shows toxicity if $s(AUC_i) = \alpha_i AUC_i \geq \tau_T$.

With $\log \alpha_i \sim N(0, \omega_\alpha)$ we obtain
$$p_T(d_k) = \Phi \left(\frac{\log d_k - \log \tau_T - \log CL}{\sqrt{\omega_{CL}^2 + \omega_\alpha^2}} \right)$$



Scenarios and simulated trials settings

	τ_T	ω_α	IIV (CL,V)
Scenario 1	10.96	0	0.7
Scenario 2	15.08	0	0.7
Scenario 3	18.1	0	0.7
Scenario 4	10.96	1.17	0.7
Scenario 5	10.96	0.8	0.7
Scenario 6	10.96	0	0.3
Scenario 7	10.96	1	0.3

Trials settings:

- 30 patients per trial
PK, tox at each dose level
- cohorts of 1.
- 1000 simulations per scenario
- "no skipping rule"
- methods applied after first toxicity
- 10 sampling points for AUC estimation

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Comparisons

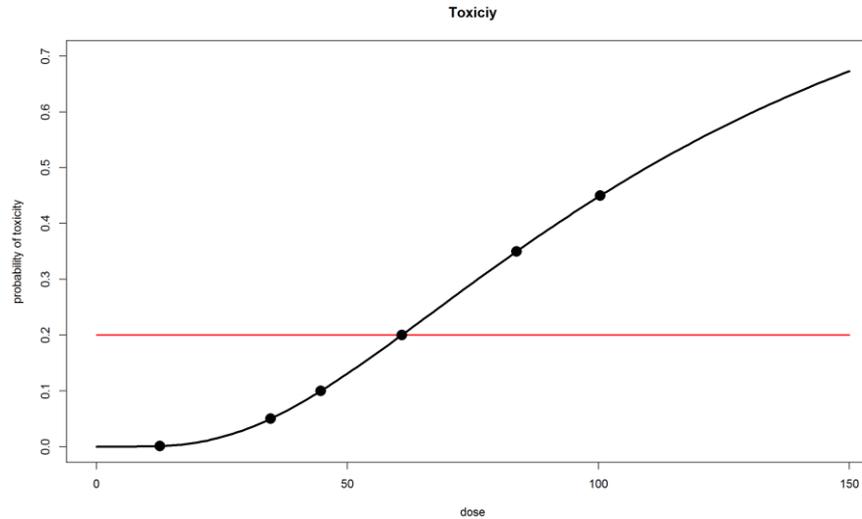


Scenario 1

$$\tau_T = 10.96$$

$$\omega_\alpha = 0$$

$$IIV = 0.7$$

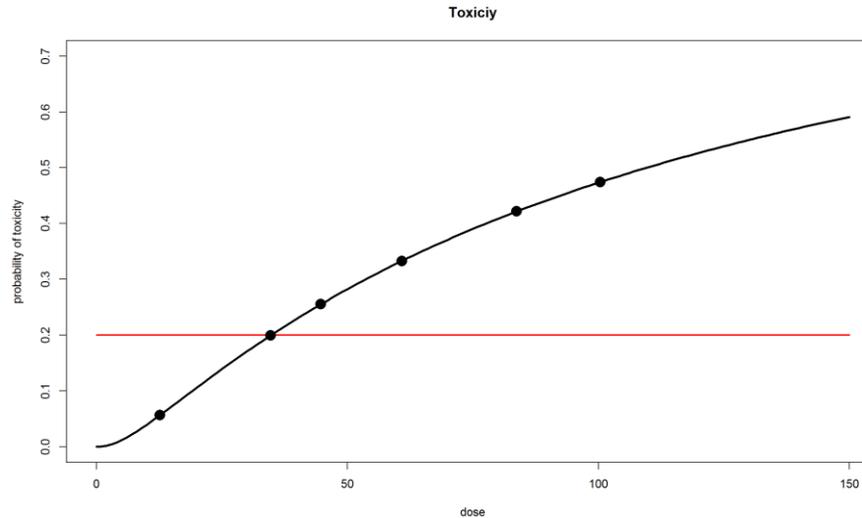


MTD:
dose level 4

Method	% dose selection						number of DLTs		
	1	2	3	4	5	6	median (n)	min - max	
PKCOV	0.054	0.015	0.177	0.550	0.163	0.041	6	1	11
PKLOG	0.054	0.048	0.331	0.485	0.074	0.008	5	1	10
PKPOP	0.049	0.024	0.216	0.550	0.142	0.019	6	1	11
CRMPK _{L=7.05}	0.104	0.381	0.475	0.040	0	0	3	1	9
CRMPK _{L=10.96}	0.055	0.017	0.259	0.583	0.083	0.003	5	1	11
CRMPK _{L=15.09}	0.030	0.013	0.202	0.591	0.157	0.007	6	1	11
CRMPK _{L=18.1}	0.020	0.014	0.196	0.600	0.161	0.009	6	1	11

Scenario 4

$\tau_T = 10.96$
 $\omega_\alpha = 1.17$
 $\text{IIV} = 0.7$

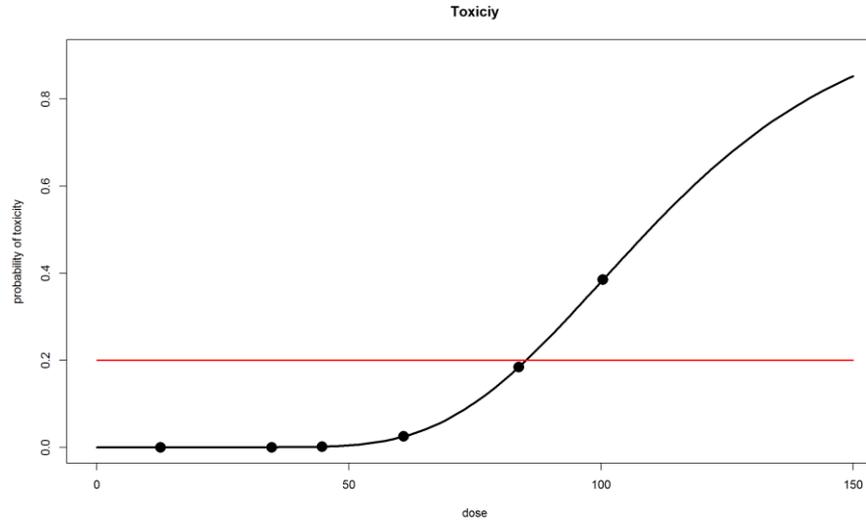


MTD:
 dose level 2

Method	% dose selection						number of DLTs		
	1	2	3	4	5	6	median (n)	min - max	
PKCOV	0.315	0.223	0.299	0.134	0.024	0.005	7	1	14
PKLOG	0.268	0.407	0.220	0.080	0.014	0.011	6	1	13
PKPOP	0.258	0.291	0.302	0.122	0.020	0.007	7	1	13
CRMPK _{L=7.05}	0.211	0.536	0.246	0.007	0	0	6	1	11
CRMPK _{L=10.96}	0.121	0.439	0.324	0.112	0.004	0	7	1	12
CRMPK _{L=15.09}	0.104	0.433	0.332	0.113	0.017	0.001	7	1	13
CRMPK _{L=18.1}	0.099	0.430	0.337	0.115	0.016	0.003	7	1	13

Scenario 6

$\tau_T = 10.96$
 $\omega_\alpha = 0$
 $\text{IIV} = 0.3$

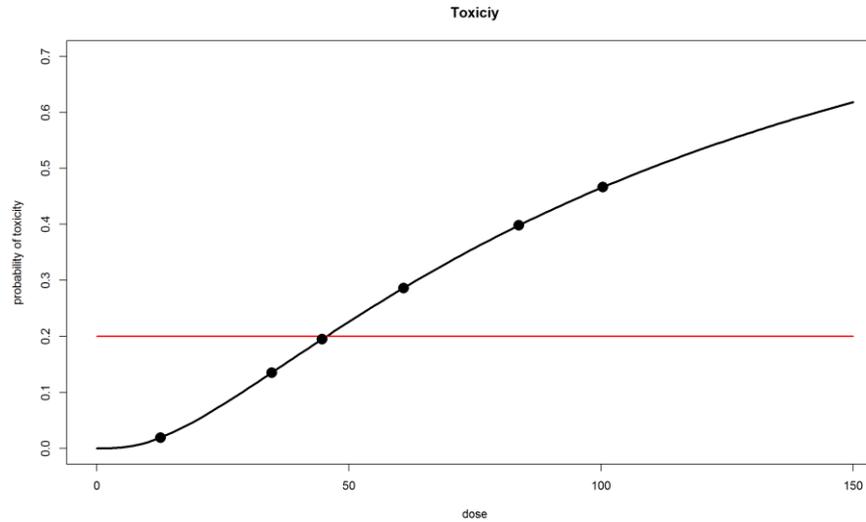


MTD:
 dose level 5

Method	% dose selection						number of DLTs	
	1	2	3	4	5	6	median (n)	min - max
PKCOV	0	0	0	0.080	0.672	0.248	6	2 - 10
PKLOG	0	0	0	0.176	0.704	0.120	5	2 - 9
PKPOP	0	0	0	0.157	0.667	0.176	6	2 - 9
CRMPK _{L=7.05}	0	0.001	0.518	0.481	0	0	1	1 - 4
CRMPK _{L=10.96}	0	0	0	0.129	0.820	0.051	5	1 - 8
CRMPK _{L=15.09}	0	0	0	0.093	0.763	0.144	5	2 - 9
CRMPK _{L=18.1}	0	0	0	0.093	0.762	0.145	5	2 - 9

Scenario 7

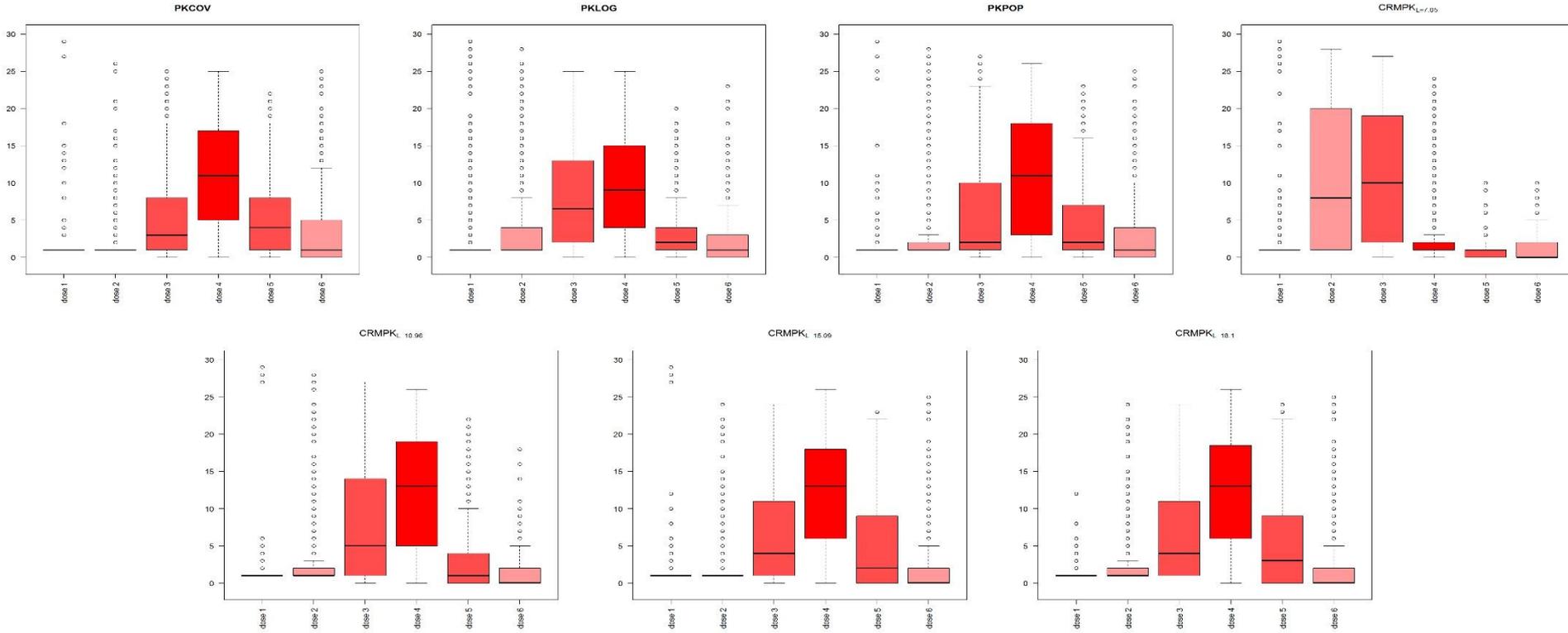
$\tau_T = 10.96$
 $\omega_\alpha = 1$
 $\text{IIV} = 0.3$



MTD:
 dose level 2

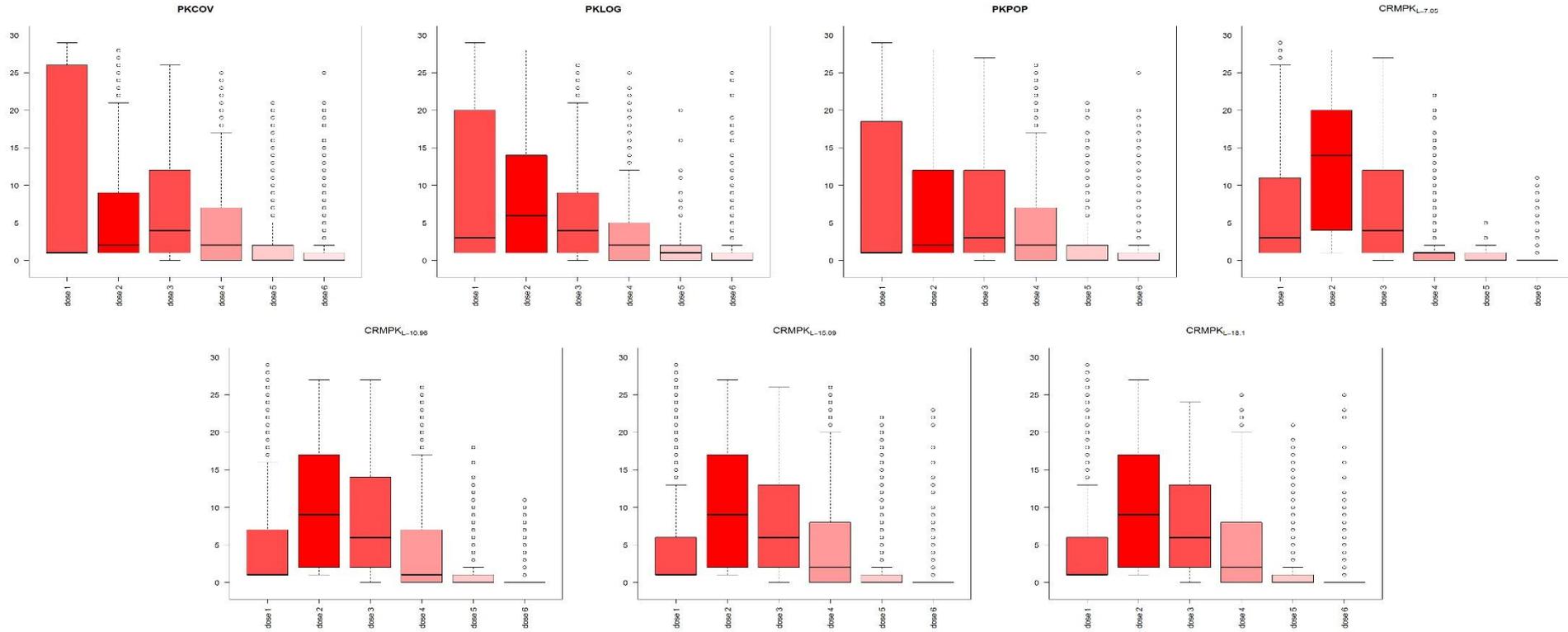
Method	% dose selection						number of DLTs		
	1	2	3	4	5	6	median (n)	min - max	
PKCOV	0.185	0.114	0.342	0.306	0.050	0.003	6	1	13
PKLOG	0.114	0.234	0.372	0.232	0.042	0.006	6	1	12
PKPOP	0.131	0.182	0.361	0.286	0.035	0.005	6	1	12
CRMPK _{L=7.05}	0.015	0.249	0.583	0.153	0	0	6	1	11
CRMPK _{L=10.96}	0.009	0.241	0.426	0.286	0.038	0	6	1	11
CRMPK _{L=15.09}	0.008	0.238	0.434	0.280	0.038	0.002	6	1	12
CRMPK _{L=18.1}	0.007	0.238	0.434	0.282	0.037	0.002	6	2	12

Distribution of doses – Scenario 1



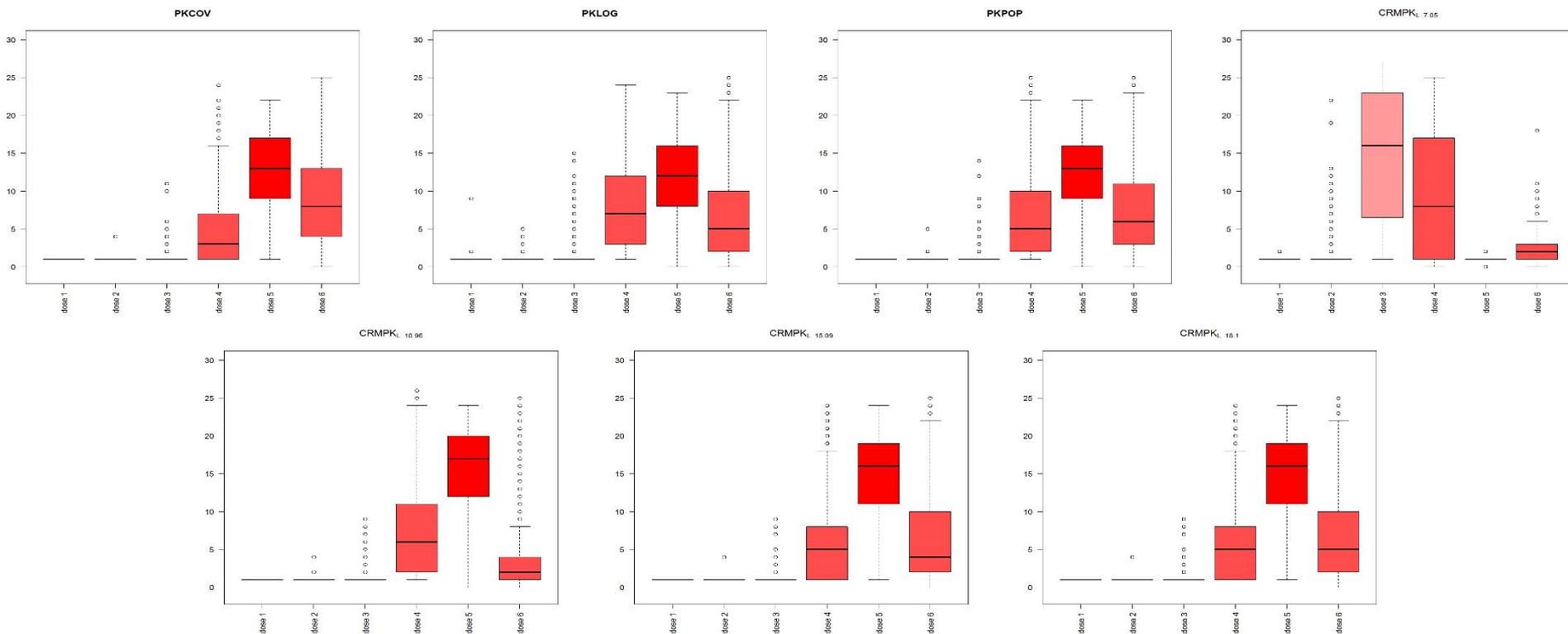
	k_a		V		CL		ωV		ωCL	
	bias	rmse	bias	rmse	bias	rmse	bias	rmse	bias	rmse
PKCOV	-0.04338	0.24841	-0.57601	13.16734	0.07992	1.27871	-0.02159	0.09691	-0.02088	0.10122
PKLOG	-0.03711	0.23920	-0.43232	13.20554	0.07397	1.26668	-0.02040	0.09543	-0.01981	0.10165
PKPOP	-0.04569	0.24757	-0.55612	13.29356	0.08368	1.27599	-0.02107	0.09574	-0.02143	0.10045
CRMPK _{L=7.05}	-0.04399	0.23963	-0.60811	13.25571	0.06264	1.26120	-0.02058	0.09576	-0.01950	0.10118
CRMPK _{L=10.96}	-0.04077	0.23565	-0.52555	13.11899	0.07308	1.27228	-0.02095	0.09677	-0.02067	0.10038
CRMPK _{L=15.09}	-0.04751	0.24078	-0.65523	13.24643	0.06966	1.27365	-0.02140	0.09660	-0.02058	0.10081
CRMPK _{L=18.1}	-0.05013	0.24057	-0.68737	13.16026	0.07562	1.27391	-0.02109	0.09614	-0.02162	0.10029

Distribution of doses – Scenario 4



	k_a		V		CL		ωV		ωCL	
	bias	rmse	bias	rmse	bias	rmse	bias	rmse	bias	rmse
PKCOV	-0.03957	0.23738	-0.45921	13.28512	0.07042	1.27644	-0.02136	0.09575	-0.02034	0.10080
PKLOG	-0.04369	0.24221	-0.44800	13.23955	0.06481	1.26391	-0.02100	0.09508	-0.01884	0.10108
PKPOP	-0.04102	0.23811	-0.46679	13.09446	0.06246	1.27940	-0.02140	0.09504	-0.01955	0.10130
CRMPK $_L=7.05$	-0.04669	0.23083	-0.45773	13.19937	0.06544	1.26127	-0.02105	0.09537	-0.01889	0.10010
CRMPK $_L=10.96$	-0.05820	0.24559	-0.65773	13.37577	0.05804	1.26469	-0.02085	0.09662	-0.01969	0.10096
CRMPK $_L=15.09$	-0.05487	0.24647	-0.65210	13.24059	0.05610	1.26733	-0.02059	0.09567	-0.01957	0.10069
CRMPK $_L=18.1$	-0.04408	0.23058	-0.40387	13.12355	0.06171	1.26518	-0.02061	0.09567	-0.01869	0.10100

Distribution of doses – Scenario 6



	k_a		V		CL		ω_V		ω_{CL}	
	bias	rmse	bias	rmse	bias	rmse	bias	rmse	bias	rmse
PKCOV	0.01065	0.17329	-0.02975	6.04274	0.02386	0.55869	-0.41069	0.41306	-0.40827	0.41058
PKLOG	0.00072	0.17134	-0.14214	5.97800	0.01751	0.56380	-0.41080	0.41309	-0.40854	0.41087
PKPOP	0.00852	0.17466	-0.05070	6.09459	0.01665	0.56114	-0.41047	0.41281	-0.40875	0.41107
CRMPK _{L=7.05}	0.00684	0.17349	-0.07623	6.02613	0.01697	0.56081	-0.41072	0.41313	-0.40847	0.41082
CRMPK _{L=10.96}	0.00181	0.17304	-0.16768	6.02040	0.02123	0.56096	-0.41115	0.41350	-0.40799	0.41026
CRMPK _{L=15.09}	0.00315	0.16687	-0.10216	5.95436	0.02229	0.56322	-0.41039	0.41271	-0.40811	0.41046
CRMPK _{L=18.1}	0.00572	0.16737	-0.04470	5.95808	0.02372	0.56346	-0.41057	0.41289	-0.40804	0.41039

Conclusions

We compared methods, that include PK measure of exposure (AUC), on different scenarios in case of small population.

We looked at:

Percentage of MTD selection



- CRMPK, with the right L, has the best performance
- the best trade-off is CRMPK with larger L

Estimation of PK parameters



- despite different distributions of dose allocation, no big difference in estimation

Discussion

Including only PK measure of exposure, as the AUC, in dose-finding does not increase the percentage of right MTD selection

PKCOV

$$\text{logit}[p_T(d_k, \Delta z_{d_k}, \beta)] = -\beta_0 + \beta_1 \log d_k + \beta_2 \Delta z_{d_k}$$

- It depends also on the right β_0
- It is similar to $\text{logit}(p)$ vs $\log(\text{dose})$...and also PKPOP...

PKLOG

$$\text{PKLIM} + \text{logit}(p_T(z, \beta)) = -\beta_3 + \beta_4 z$$

- Issue in the estimation when the relationship between tox and AUC is an Heaviside function

CRMPK

$$\text{CRMPK} = \text{CRM} + \text{PKLIM}$$

- Dependence on the threshold L
- It tends to CRM alone while L increases

Discussion (2)

?

"dose finder"

↓
discrete

- CRM

?

"dose estimator"

↓
entire curve

- PKCOV

- PKLOG

- PKPOP

?

CRMPK

Future work

- Moving to Phase I/II including efficacy
 - binary
 - continuous
- Including PK/PD estimation during the escalation
 - full-model based
- Working of priors distributions
 - combining data from different sources

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France Mentré



Integrated DEsign and AnaLysis
of small population group trials

Ivelina Gueorguieva

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