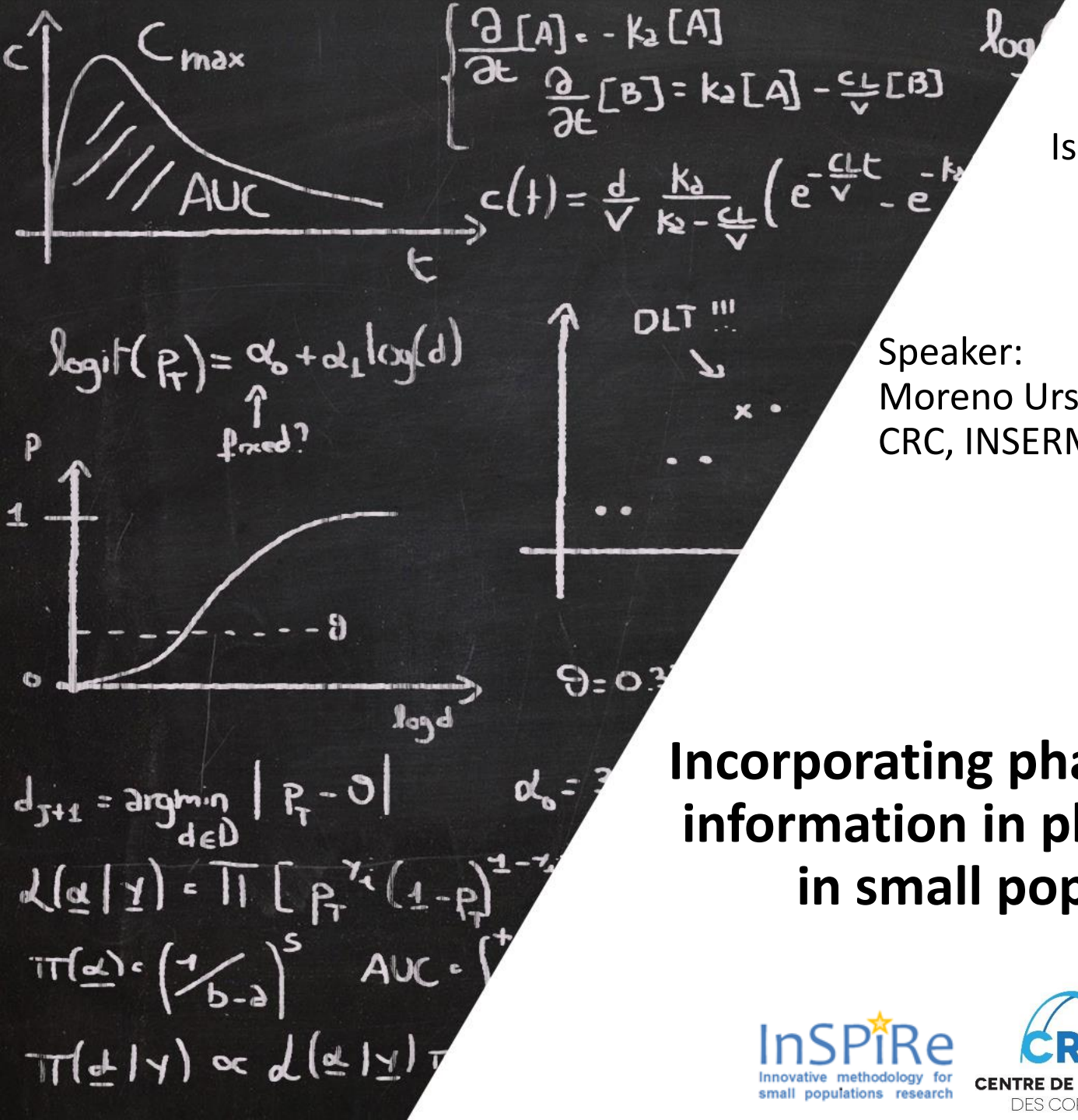


07/07/2015

Isaac Newton Institute

Cambridge

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

InSPiRe
Innovative methodology for small populations research

CRC
CENTRE DE RECHERCHE DES CORDELIERS

Inserm
Institut national de la santé et de la recherche médicale

InSPiRe project

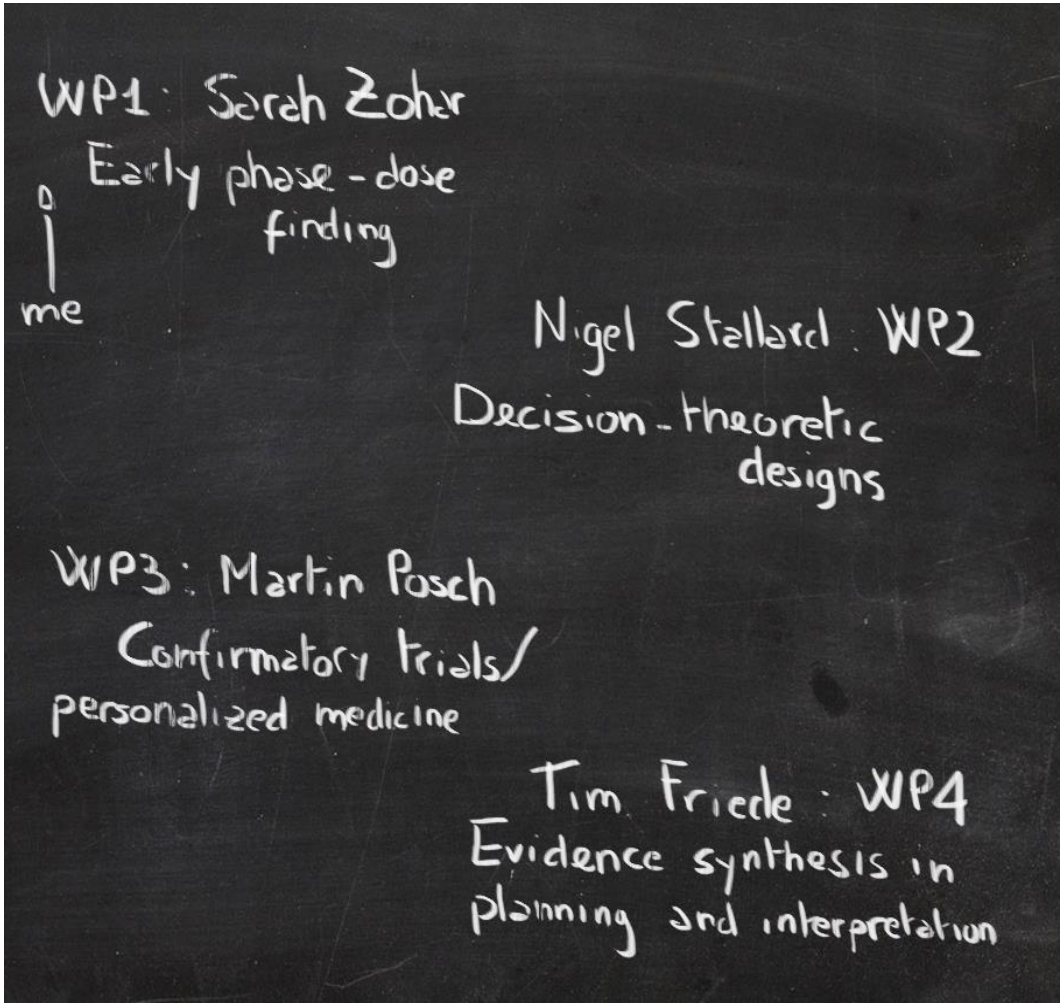
Innovative methodology for small populations research

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:

February 2014 – May 2017



WP1

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?

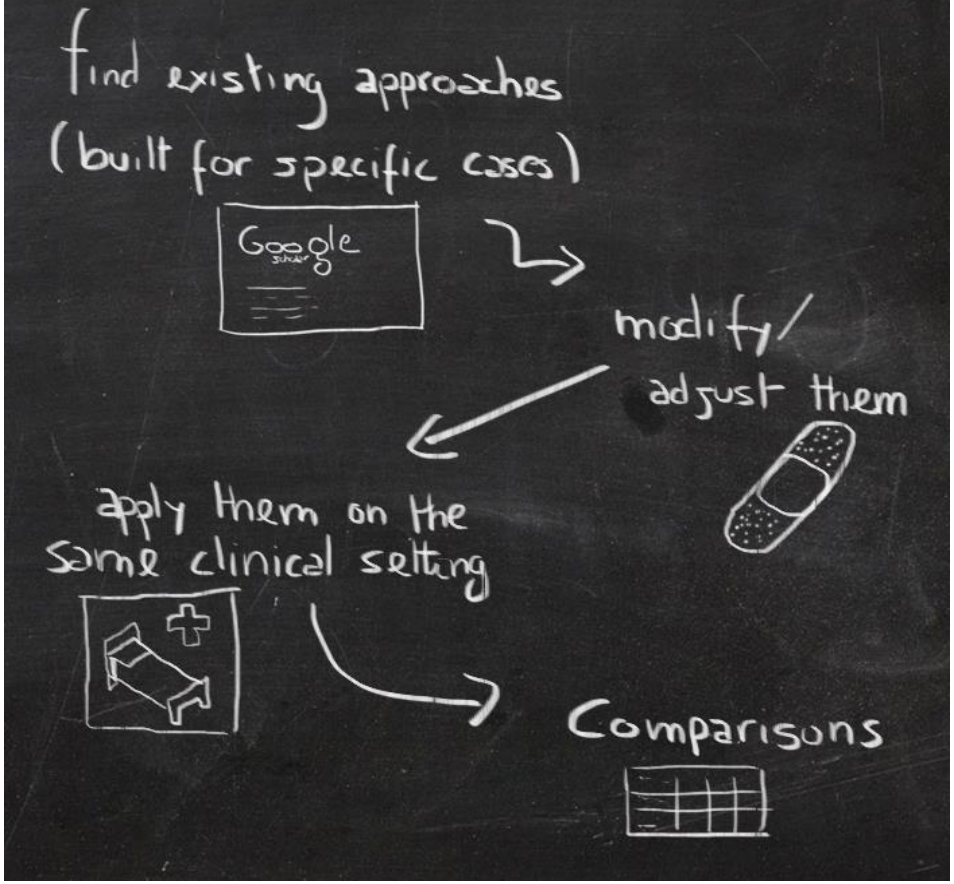
- Covariate?
- Dependent variable?

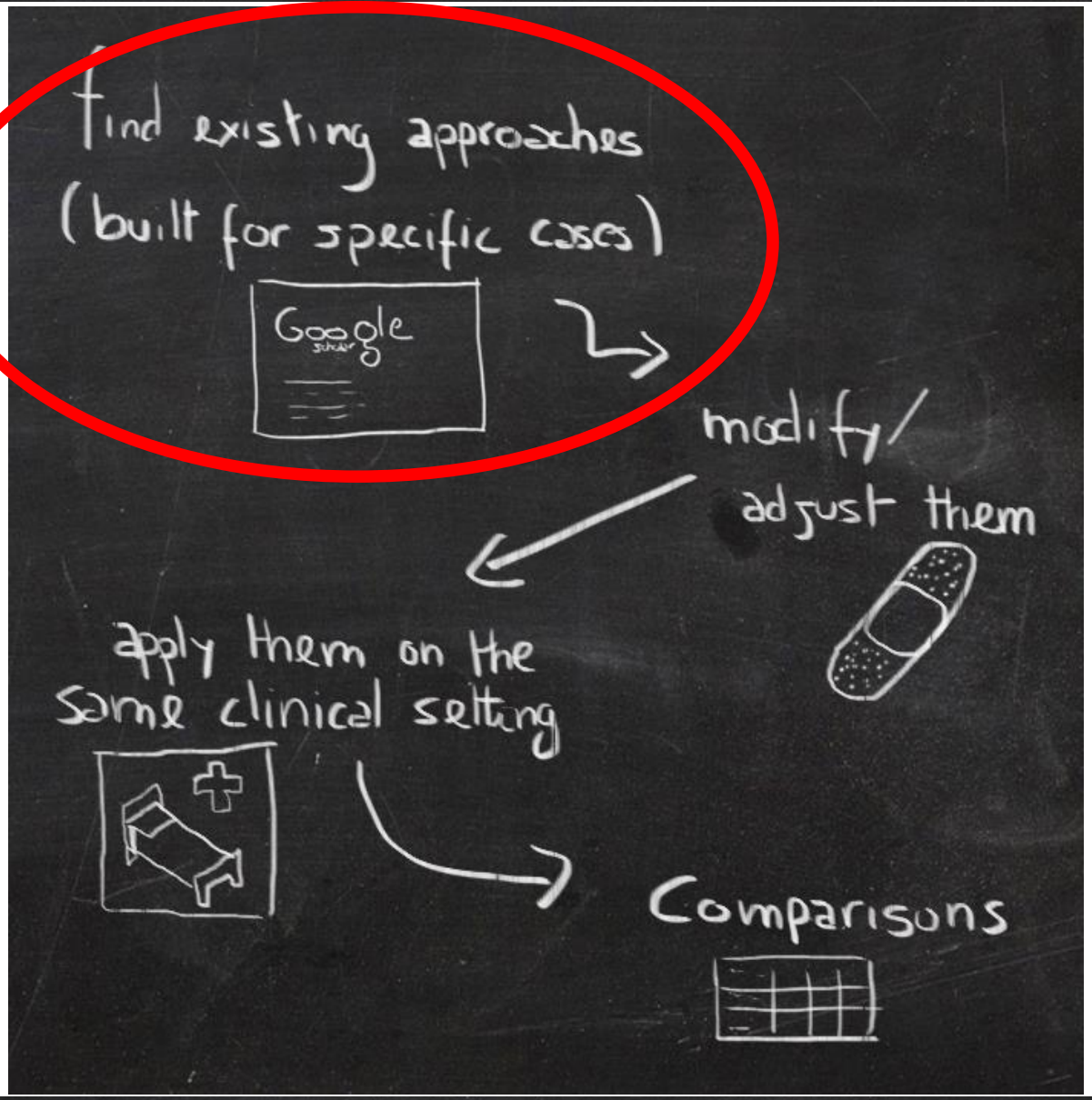
Clinical context and work done

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 <u>covariate</u> or <u>dependent variable</u> in the dose-finding model.

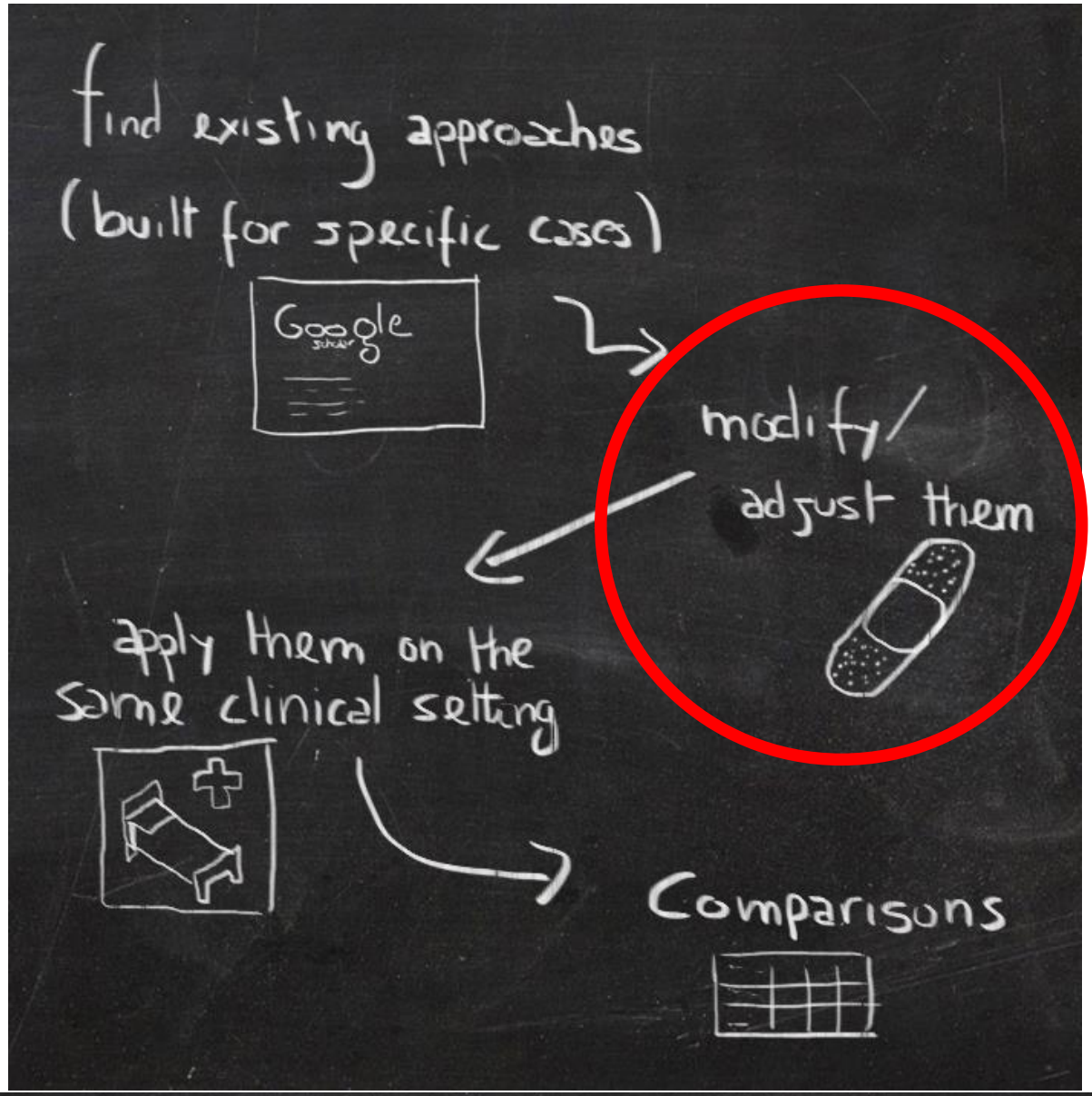



find existing approaches
(built for specific cases)
Google Scholar
modify/
adjust them
apply them on the
same clinical setting
Comparisons

Literature

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


find existing approaches
(built for specific cases)
Google Scholar
modify/
adjust them
apply them on the
same clinical setting
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)

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

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

Priors: $\beta_1 \sim U(l_1, u_1)$

$\beta_2 \sim U(l_2, u_2)$

β_0 fixed

Dose allocation rule:

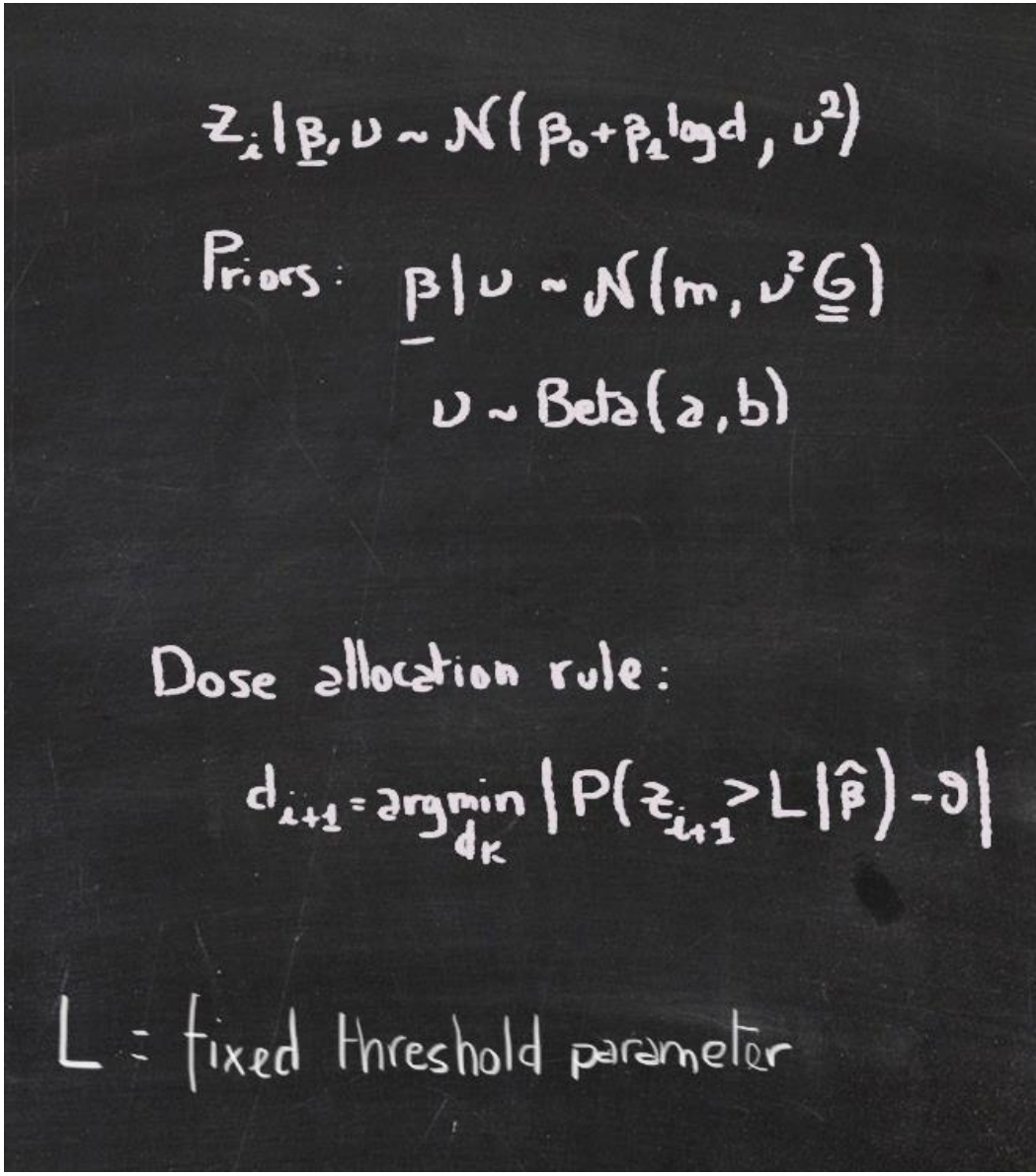
$$d_{i+1} = \underset{d_k}{\text{argmin}} \left| p_T(d_k, 0, \hat{\beta}) - \theta \right|$$

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

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



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: $\beta_3 \sim U(l_3, u_3)$

$\beta_4 \sim U(l_4, u_4)$

Dose allocation rule:

$$d_{i+1} = \underset{d_K}{\text{argmin}} \left| P(Y_{i+1} = 1 \mid \hat{\beta}) - \vartheta \right|$$

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

Other modifications

CRMPK =

CRM + PKLIM

Dose allocation rule:

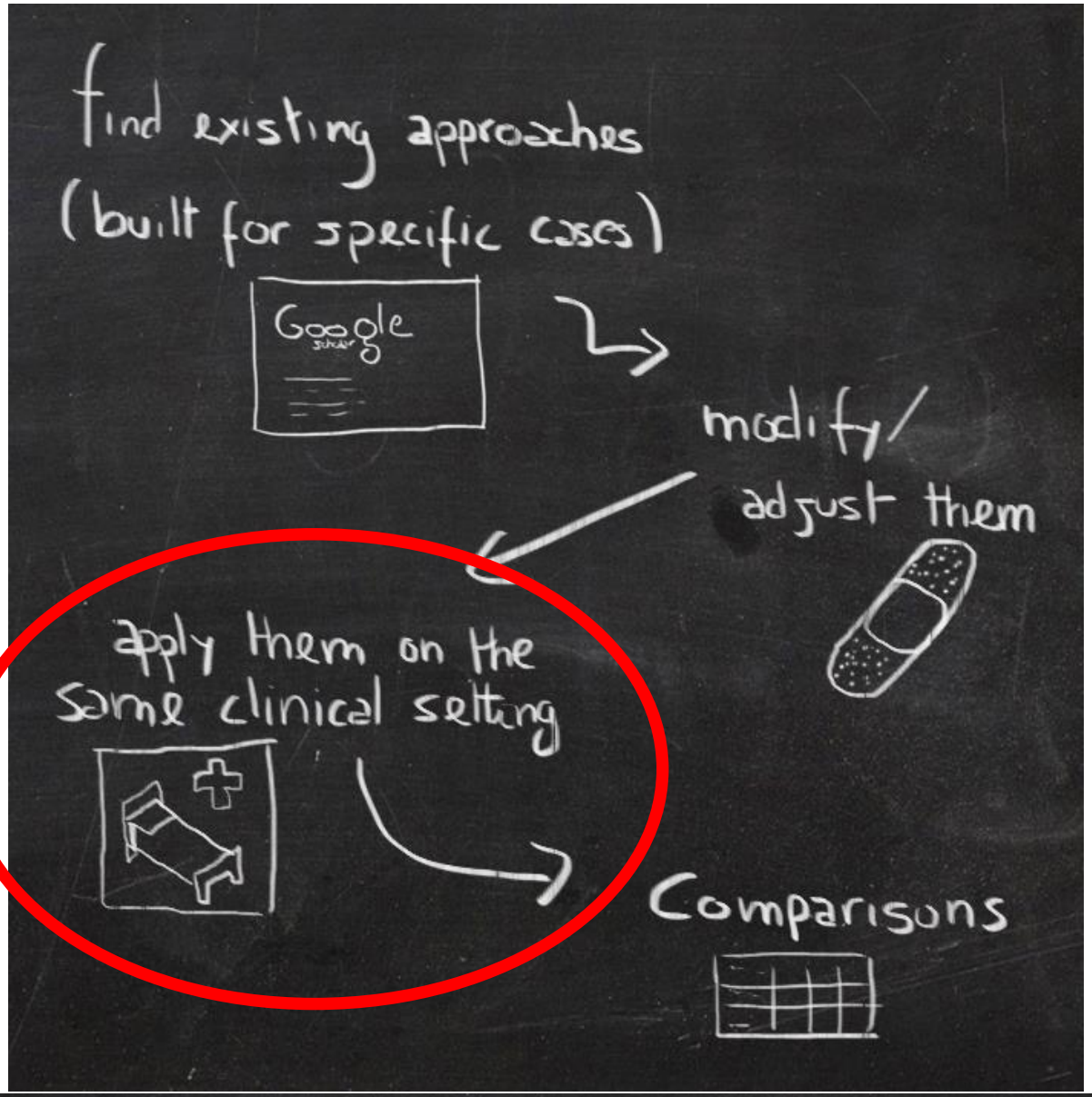
$$d_{i+1} = \min(d_{CRM}, d_{PKLIM})$$

PKPOP = PKLOG with

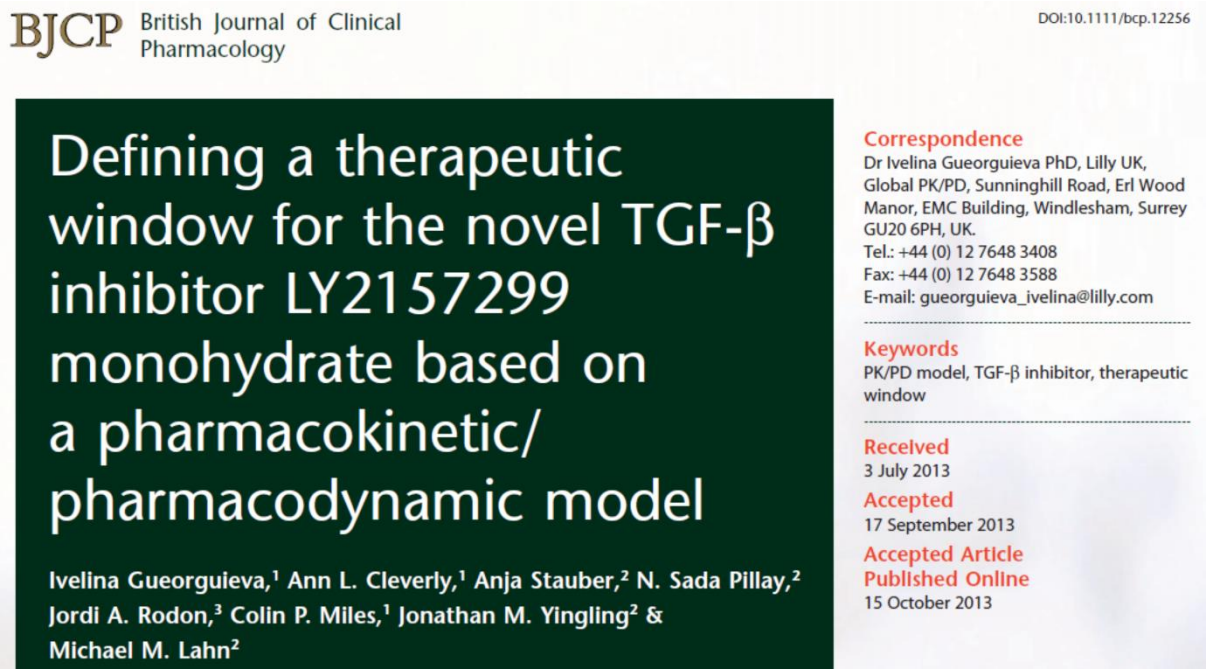
Dose allocation rule:

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

mean value predicted


find existing approaches
(built for specific cases)
Google Scholar
modify/
adjust them
apply them on the
same clinical setting
Comparisons

Simulations studies – choosing a PK model



BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12256

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. Yingling[2] & Michael M. Lahn[2]

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

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

Received
3 July 2013
Accepted
17 September 2013
Accepted Article Published Online
15 October 2013

- 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

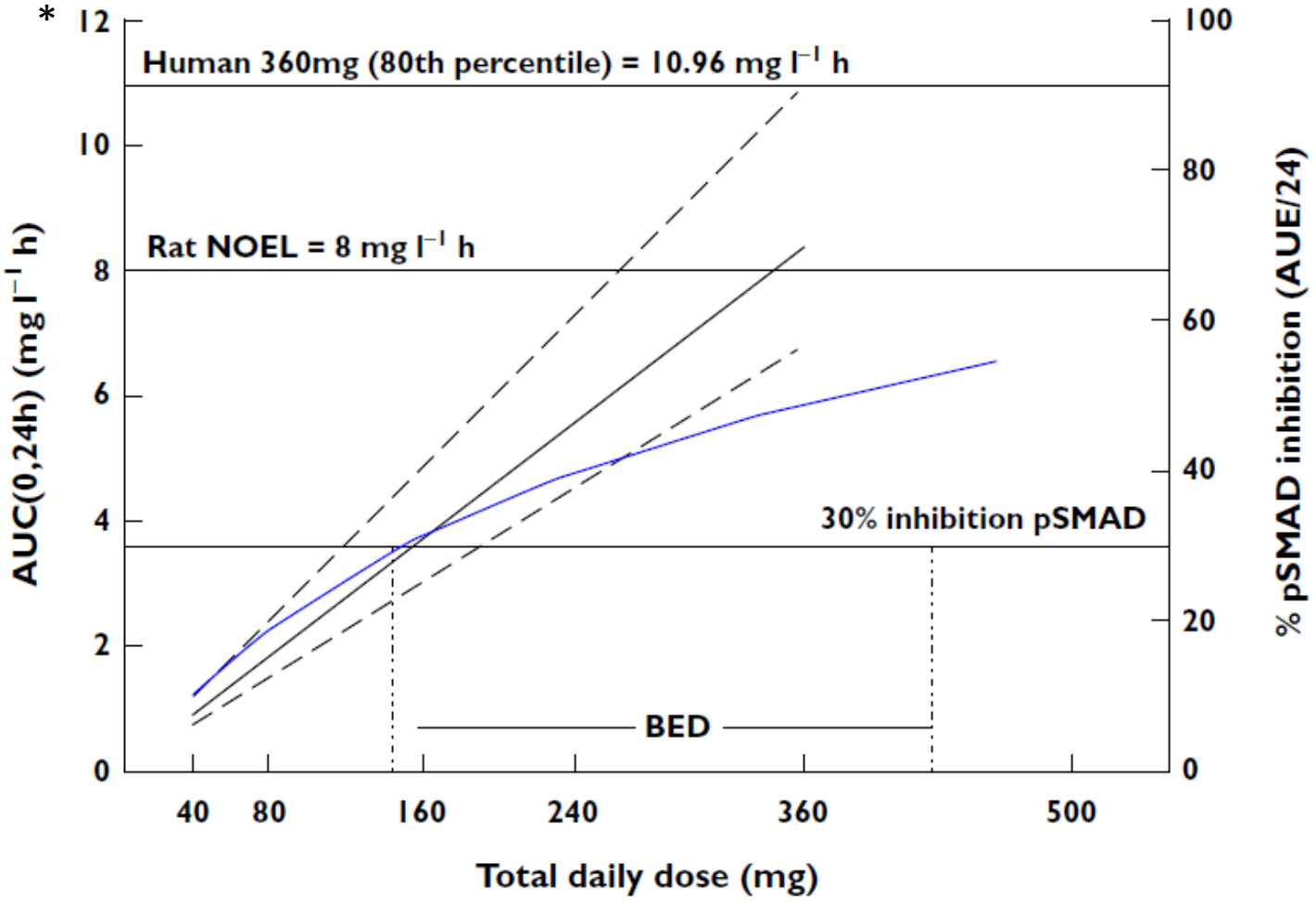
Simulation from preclinical data to predict therapeutic dose range

→ Clinical trial design depending also on preclinical late toxicity →

PK/PD estimation in humans:

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

Simulations studies – choosing a PK model (2)

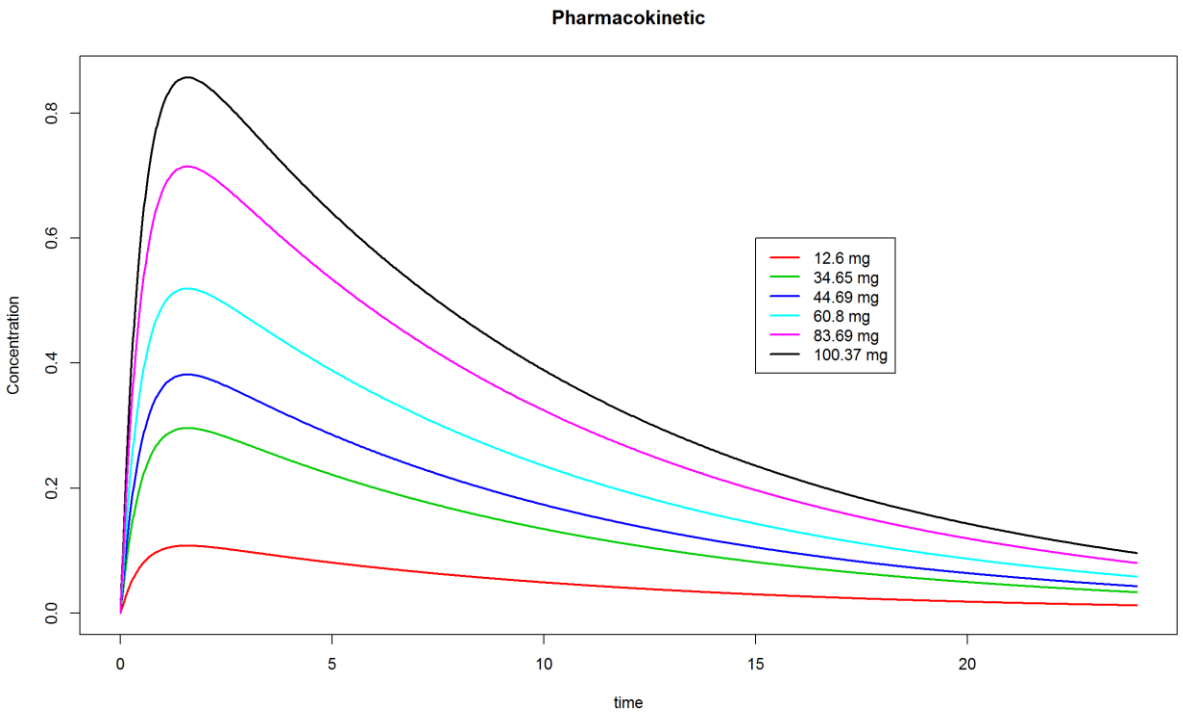


*Gueorguieva *et al.* (2014). British Journal of Clinical Pharmacology, 77: 796 - 807.

Simulations studies – choosing a PK model (3)

Modifications: only PK

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



*

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

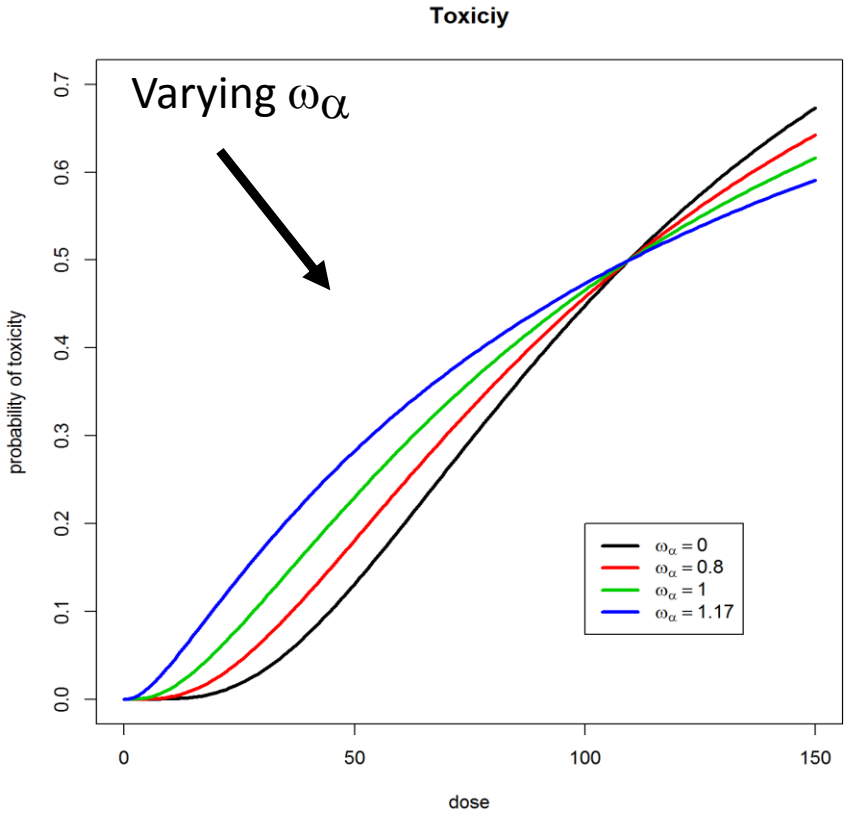
with $\omega_{CL} = \omega_V \in \{0.3, 0.7\}$

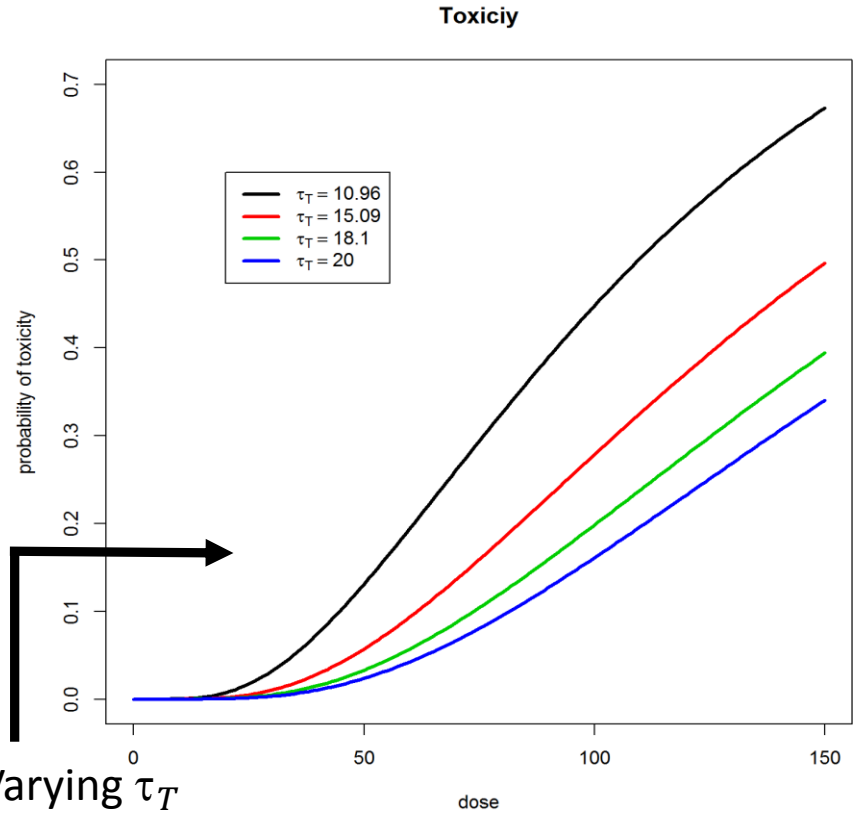
*Lestini *et al.* (2015). Pharmaceutical Research. In press.

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 $$p_T(d_k) = \Phi\left(\frac{\log d_k - \log \tau_T - \log CL}{\sqrt{\omega_{CL}^2 + \omega_\alpha^2}}\right)$$





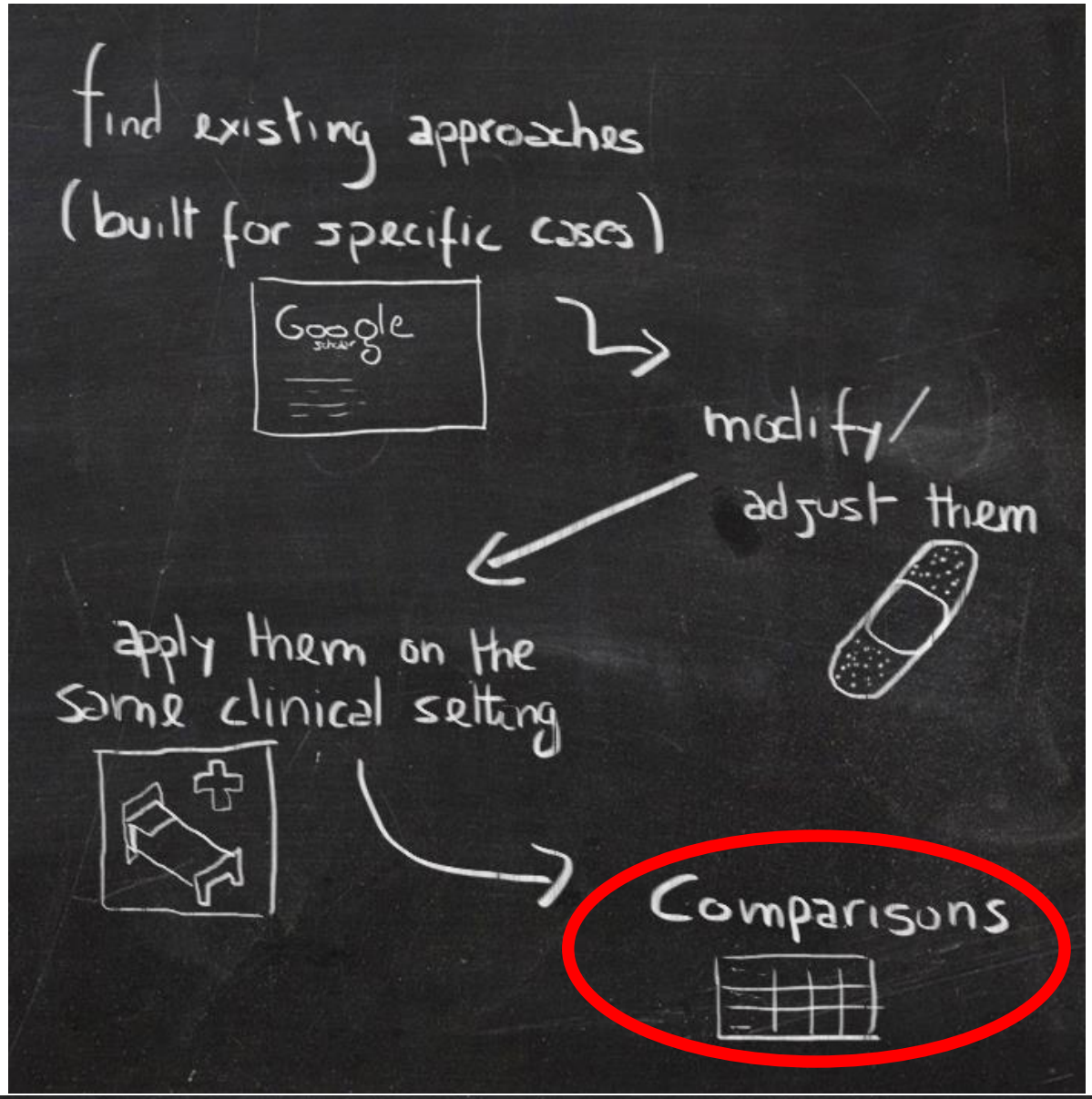
Varying τ_T

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

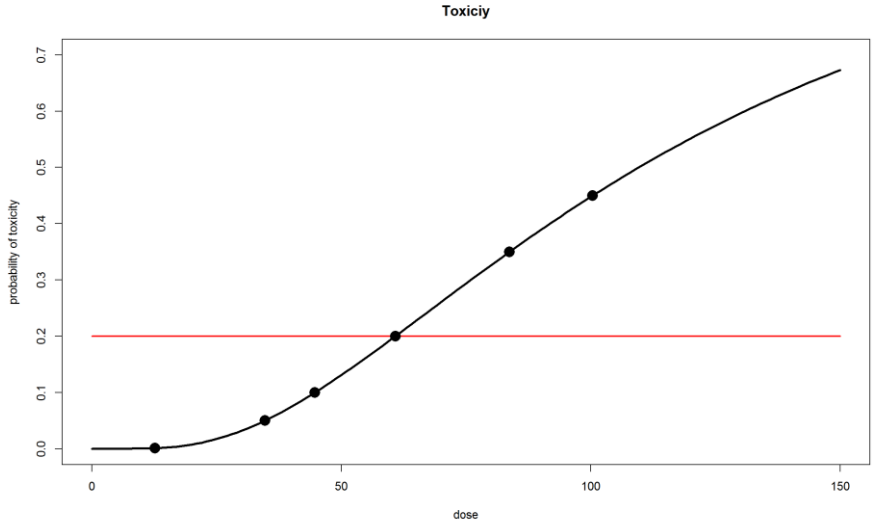
Trials settings:

- 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


find existing approaches
(built for specific cases)
Google Scholar
modify/
adjust them
apply them on the
same clinical setting
Comparisons

Scenario 1

τ_T = 10.96
ω_α= 0
IIV = 0.7

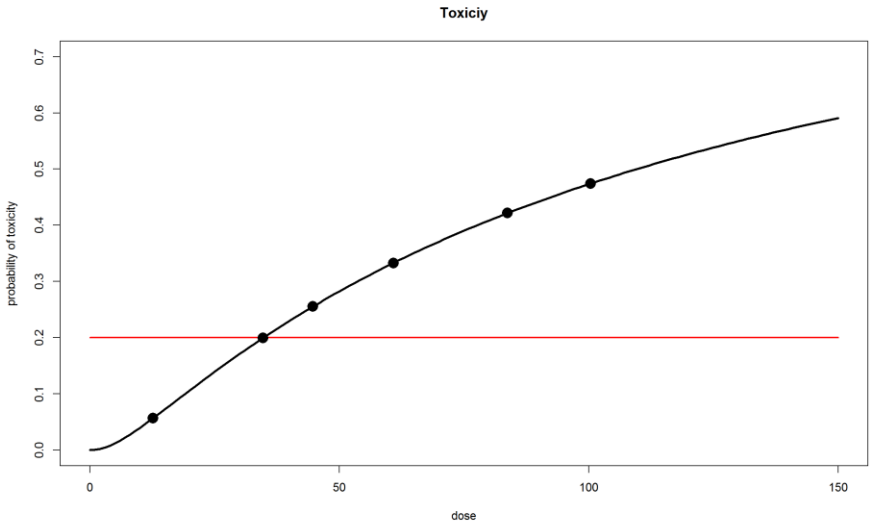


MTD:
dose level 4

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

τ_T = 10.96
ω_α= 1.17
IIV = 0.7

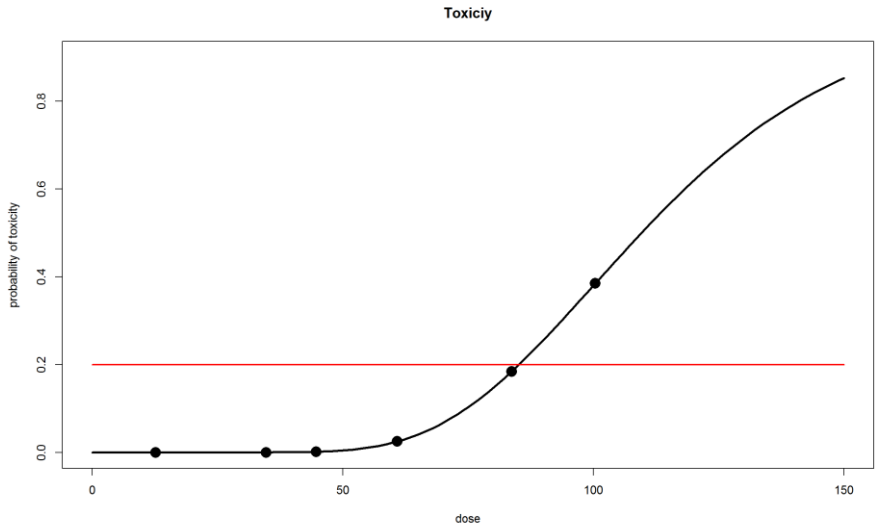


MTD:
dose level 2

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

τ_T = 10.96
ω_α= 0
IIV = 0.3

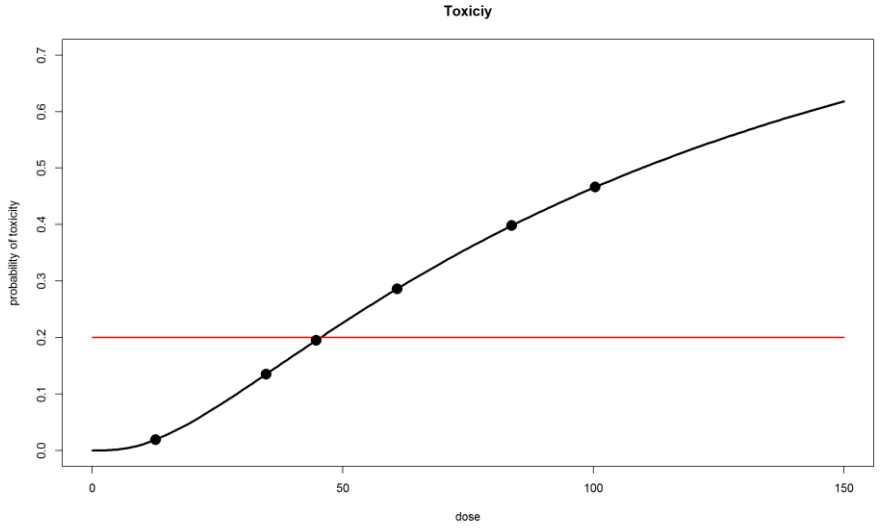


MTD:
dose level 5

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

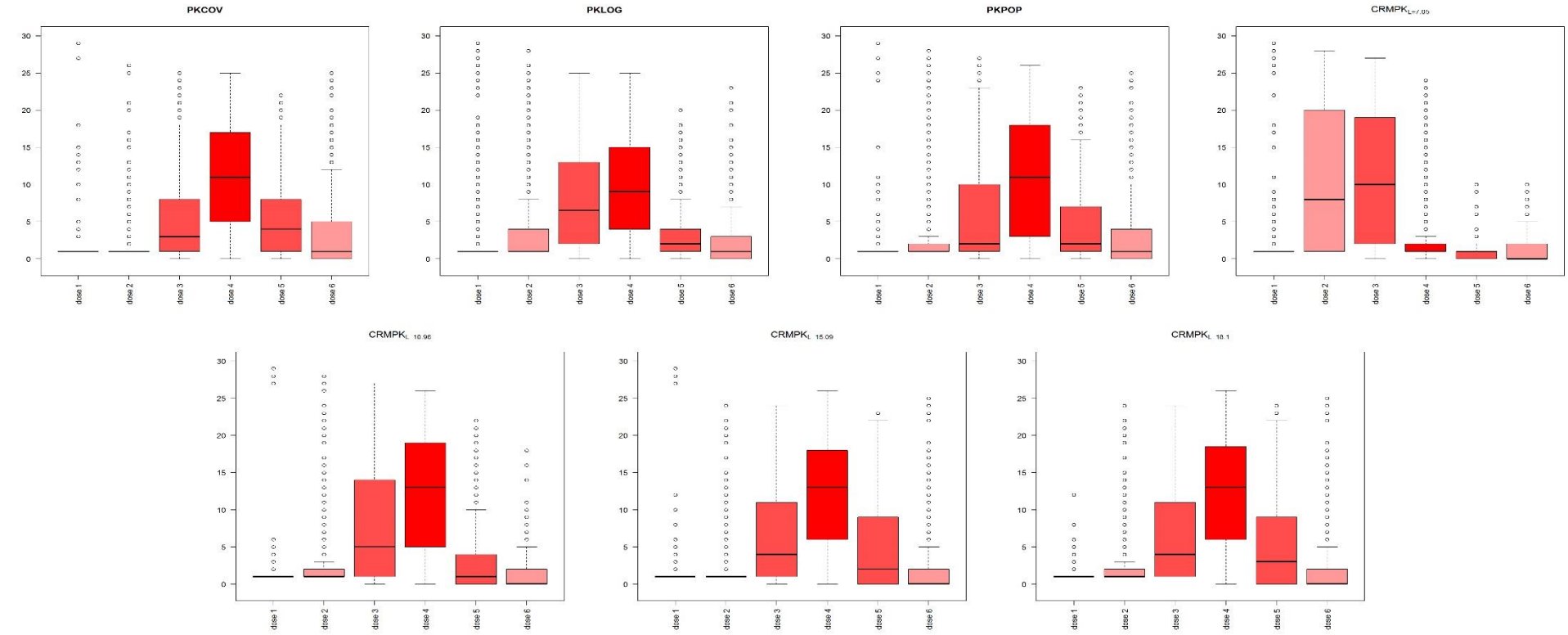
τ_T = 10.96
ω_α= 1
IIV = 0.3



MTD:
dose level 2

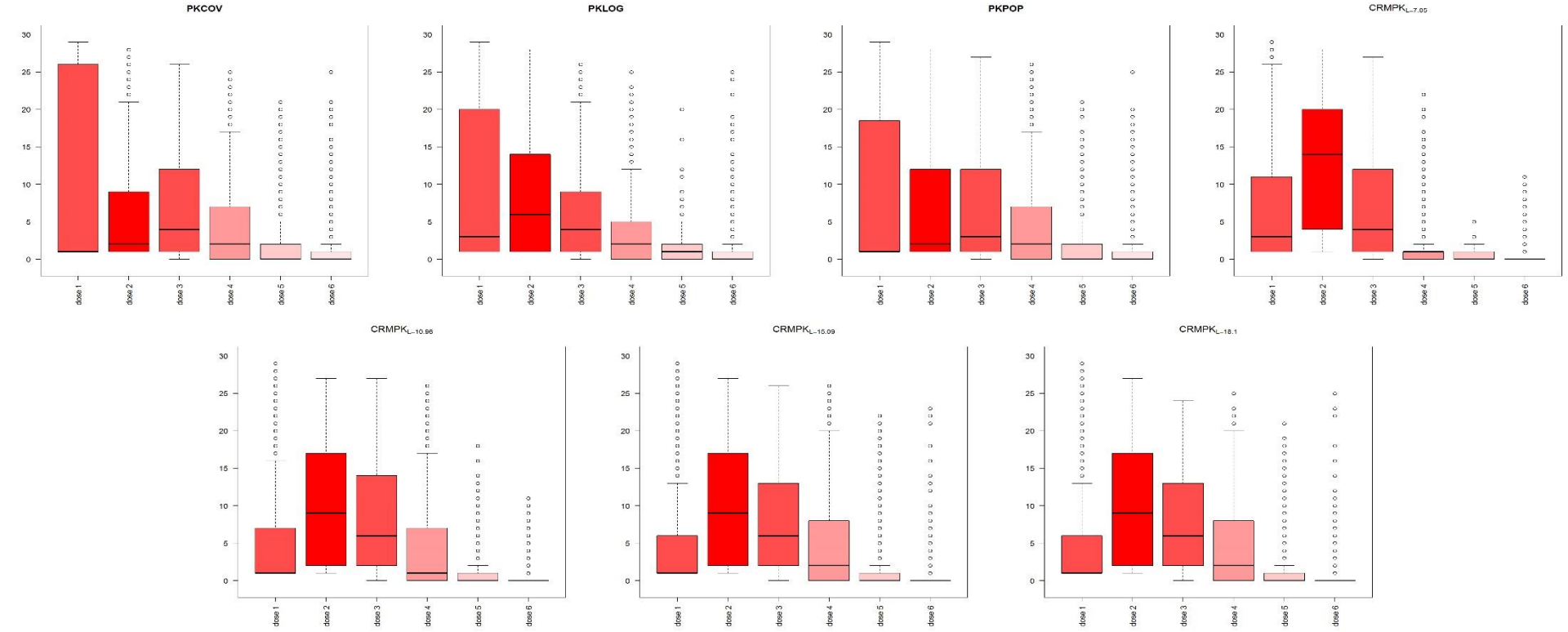
Method	% dose selection						number of DLTs		
	1	2	3	4	5	6	median (n)	min	max
PKCOV	0.185	0.114	**0.342**	0.306	0.050	0.003	6	1	13
PKLOG	0.114	0.234	**0.372**	0.232	0.042	0.006	6	1	12
PKPOP	0.131	0.182	**0.361**	0.286	0.035	0.005	6	1	12
$\text{CRMPK}_{L=7.05}$	0.015	0.249	**0.583**	0.153	0	0	6	1	11
$\text{CRMPK}_{L=10.96}$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

Distribution of doses – Scenario 1



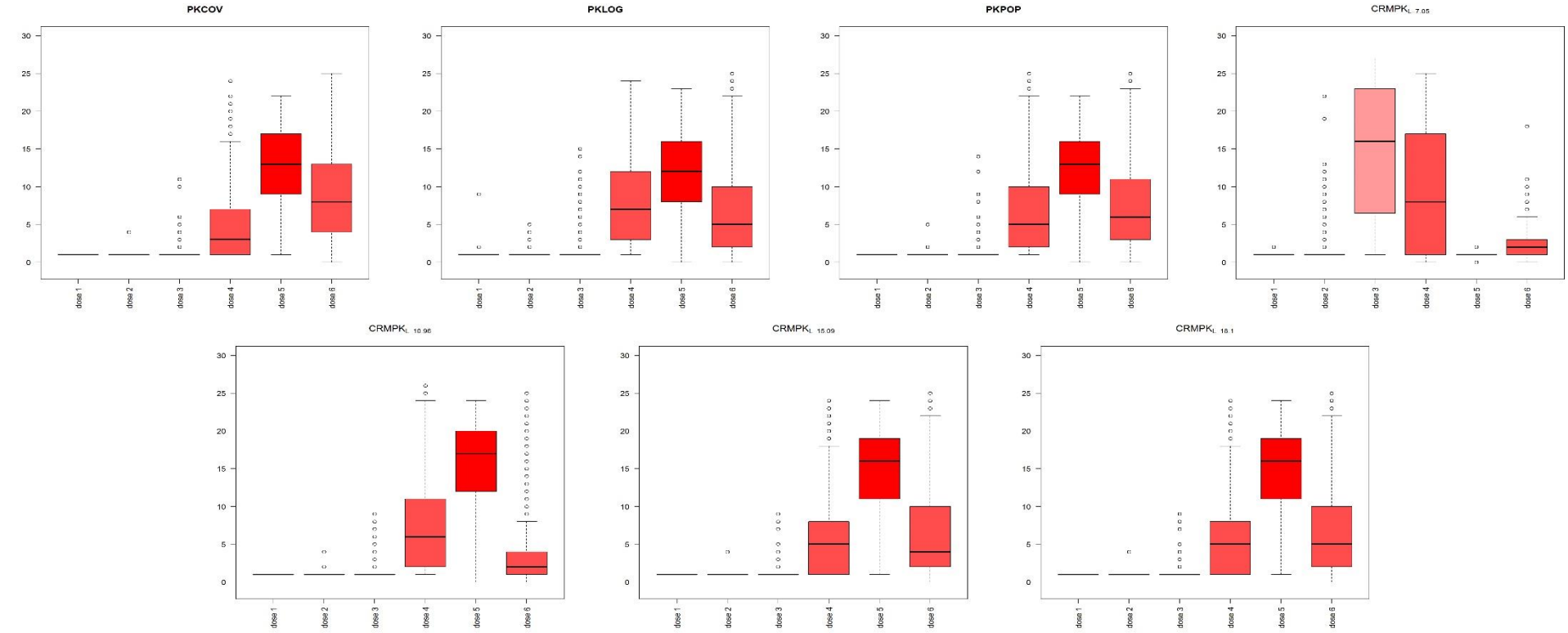
	k_a		V		CL		ω_V		ω_{CL}	
	bias	rmse	bias	rmse	bias	rmse	bias	rmse	bias	rmse
PKCOV	-0.04338	0.24841	-0.57601	13.16734	0.07992	1.27871	-0.02159	0.09691	-0.02088	0.10122
PKLOG	-0.03711	0.23920	-0.43232	13.20554	0.07397	1.26668	-0.02040	0.09543	-0.01981	0.10165
PKPOP	-0.04569	0.24757	-0.55612	13.29356	0.08368	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		ω_V		ω_{CL}	
	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 logit(p) vs log(dose) …and also PKPOP…

PKLOG

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

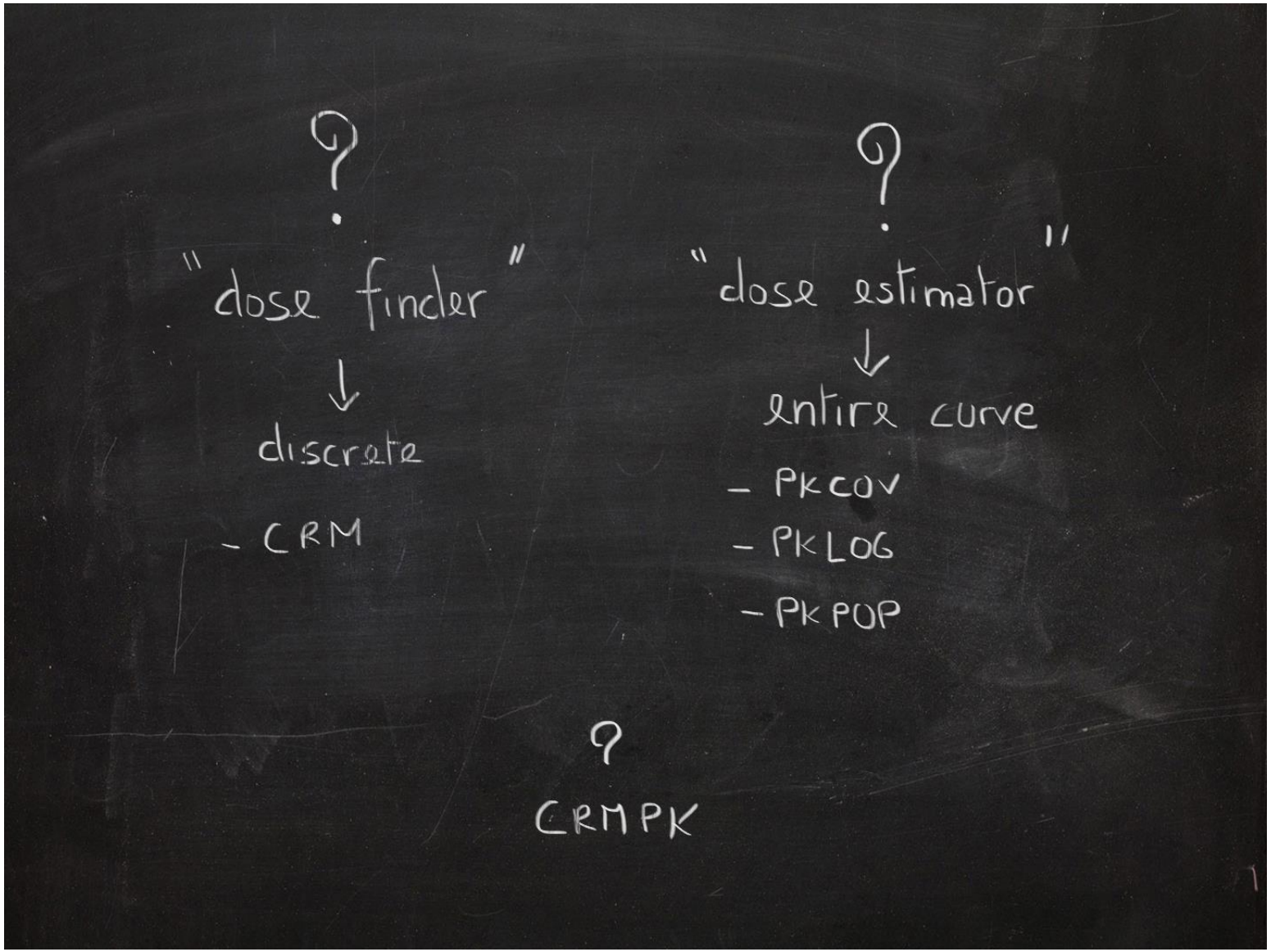
- Issue in the estimation when the relationship between tox and AUC is an Heaviside function

CRMPK

$$CRMPK = CRM + PKLIM$$

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

Discussion (2)



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

Aknowledgment

InSPiRe
Innovative methodology for small populations research

Sarah Zohar
Emmanuelle Comets
Frederike Lents
Corinne Alberti
Nigel Stallard
Tim Friede

Drug Disease Model Resources
ddmore

Giulia Lestini
France Mentré

IDeAl
Integrated DEsign and AnaLysis of small population group trials

Ivelina Gueorguieva

Bibliography

J.M. Collins *et al.* .Pharmacologically guided phase I clinical trials based upon preclinical drug development. *Journal of the National Cancer Institute*, *82*(16), 1321-1326, 1990.

I. Gueorguieva *et al.*. Defining a therapeutic window for the novel TGF-β inhibitor LY2157299 monohydrate based on a pharmacokinetic/pharmacodynamic model. British journal of clinical pharmacology, 77(5), 796-807, 2014.

J. O'Quigley *et al.*. Dynamic calibration of pharmacokinetic parameters in dose-finding studies. *Biostatistics*, kxq002, 2010

S. Piantadosi and G. Liu. Improved designs for dose escalation studies using pharmacokinetic measurements. Statistics in Medicine, 15(15): 1605 - 1618, 1996.

S. Patterson *et al.*. A novel Bayesian decision procedure for early-phase dosending studies. Journal of biopharmaceutical statistics, 9(4): 583 - 597, 1999.

J. Whitehead *et al.*. A Bayesian approach for dose-escalation in a phase I clinical trial incorporating pharmacodynamic endpoints. Journal of biopharmaceutical statistics, 17(6): 1117 - 1129, 2007.

G. Lestini *et al.*. Influence of the Size of Cohorts in Adaptive Design for Nonlinear Mixed Effects Models: an Evaluation by Simulation for a Pharmacokinetic and Pharmacodynamic Model in Oncology. Pharmaceutical Research. In press - 2015.