PEX MVD

MÉTHODOLOGIE ET VALORISATION DES DONNÉES

BAYESIAN ADAPTIVE DESIGN FOR EARLY PHASE DOSE-FINDING TRIALS IN SMALL POPULATION

Olivier Imbert & Gabriel Bologna

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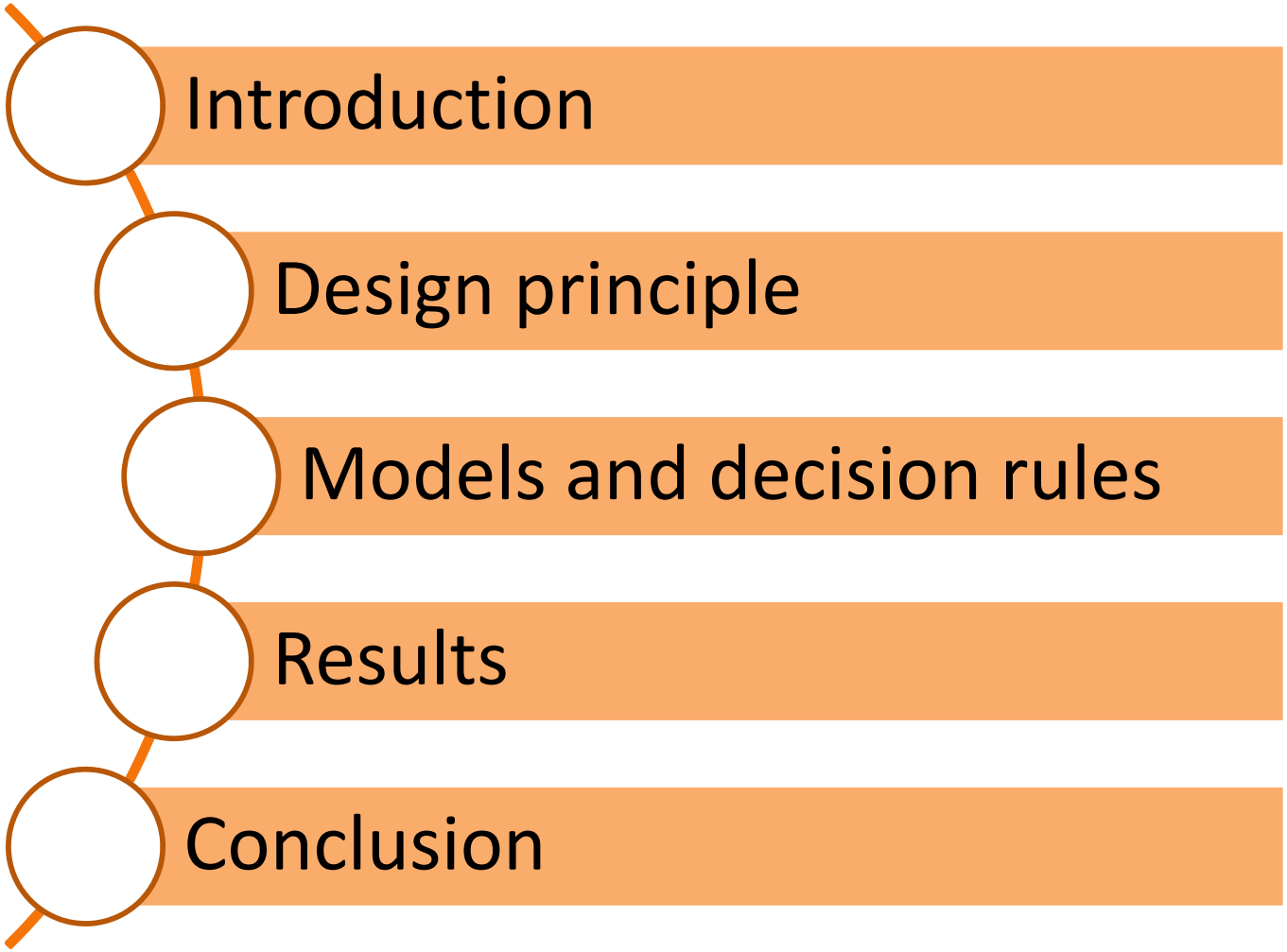

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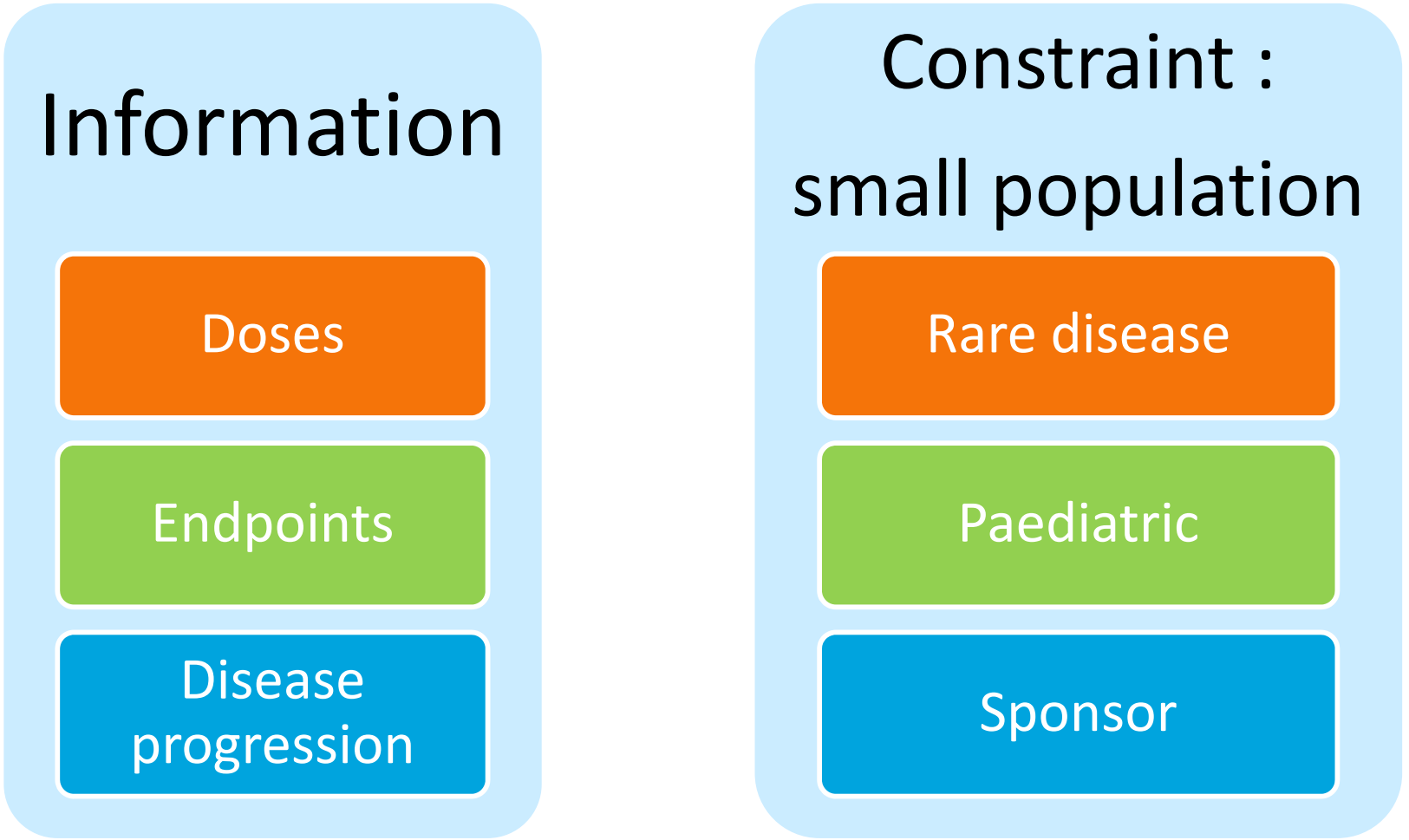
Phase IB / IIA
First on patients



Motivation

- **EMA guidelines**

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

No methods exist that are relevant to small studies that are not also applicable to large studies. However, it may be that in conditions with small and very small populations, less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results. [...]

Motivation

- **EMA guidelines**

GUIDELINE ON THE ROLE OF PHARMACOKINETICS IN THE DEVELOPMENT OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

Special consideration is often necessary when performing pharmacokinetic studies in paediatric patients and it is important that the pharmacokinetic information available is presented and used in an optimal manner. [...]

Sponsors are encouraged to explore new approaches in the development of drugs for the paediatric population. [...]

Motivation

- **EMA guidelines**

Concept paper on the revision of the guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population

[...] the need to consider both pharmacokinetic (PK) and pharmacodynamic (PD) for dose finding and dose selection must be further addressed.

[...]

Study design

- Dosage adaptation (during trial) with or without PK/PD run in leading to dosage optimisation.

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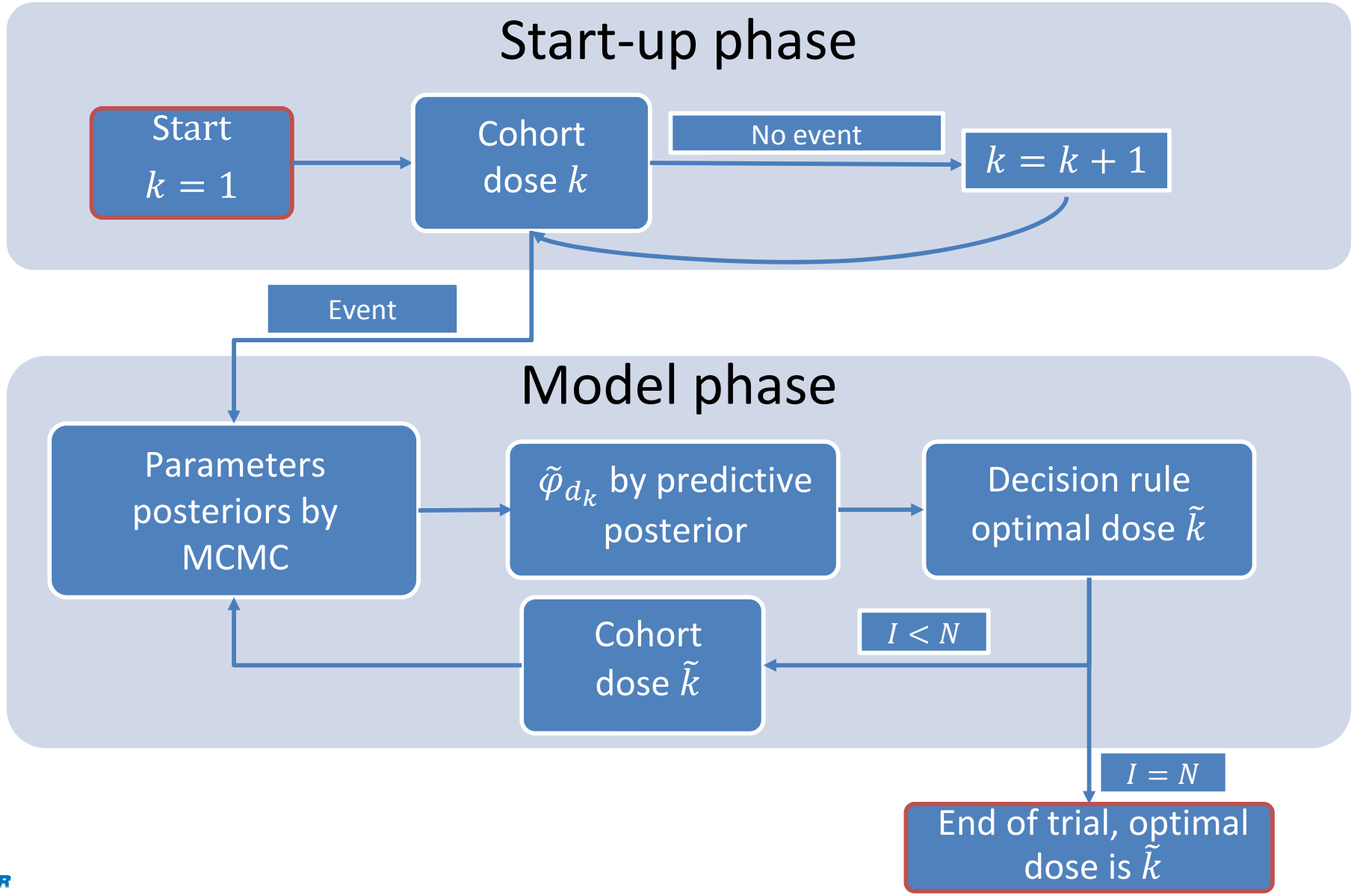
Design principle

- **Bayesian Adaptive Design**



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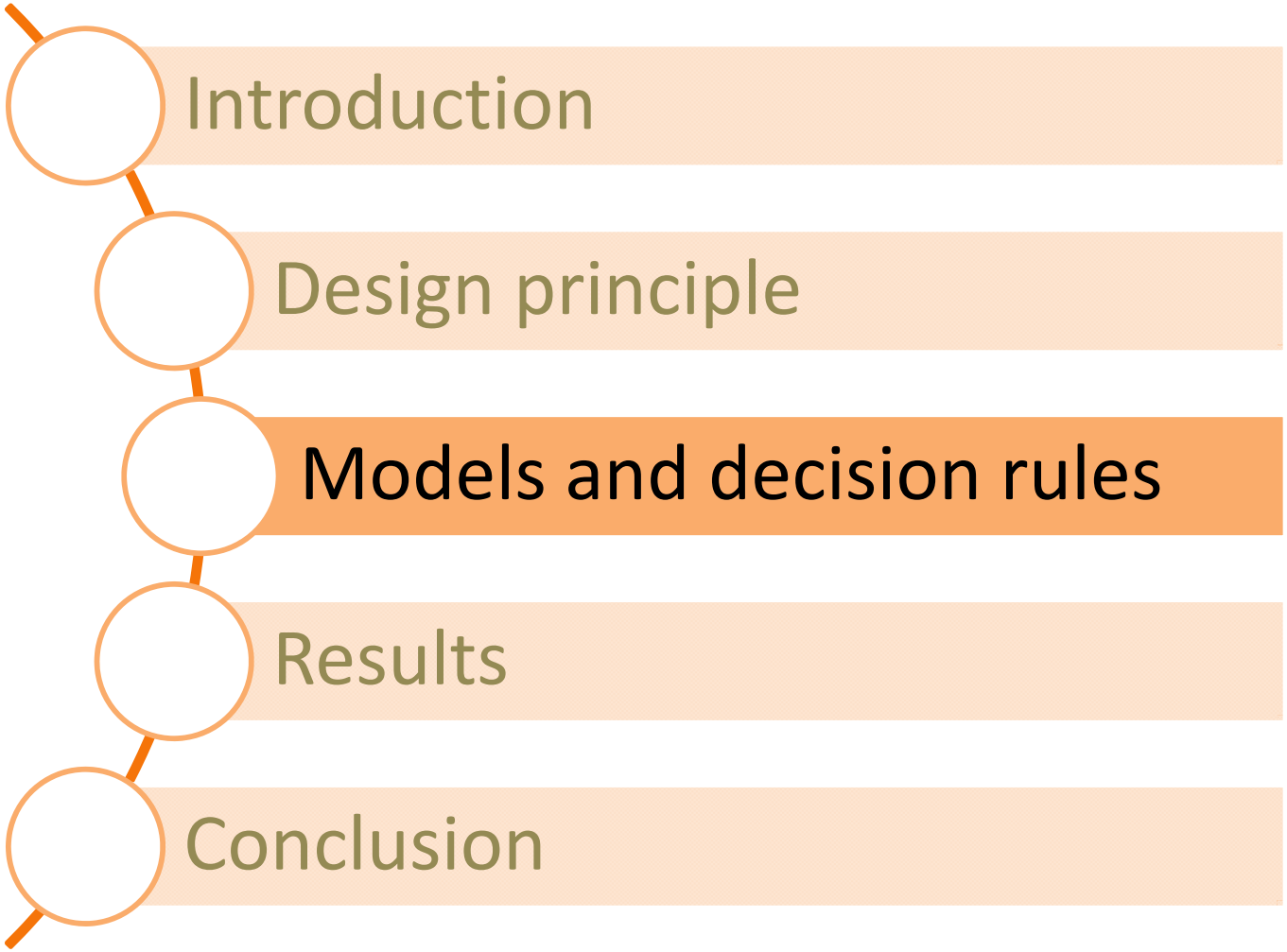


Models and decision rules

- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (1/6)**

  Toxicity model

$$logit(\varphi_k) = \beta_0 + \beta_1 u_k$$

- φ_k : toxicity probability of dose k
- u_k : the « effective » dose for dose k

Models and decision rules

- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (2/6)**

  Efficacy model

$$logit(\psi_k) = \gamma_0 + \gamma_1[\nu_k \mathbb{1}(k < \tau) + \nu_\tau \mathbb{1}(k \geq \tau)]$$

- ψ_k : efficacy probability of dose k
- ν_k : the « effective » dose for dose k
- τ : plateau point, dose at which efficacy stops increasing

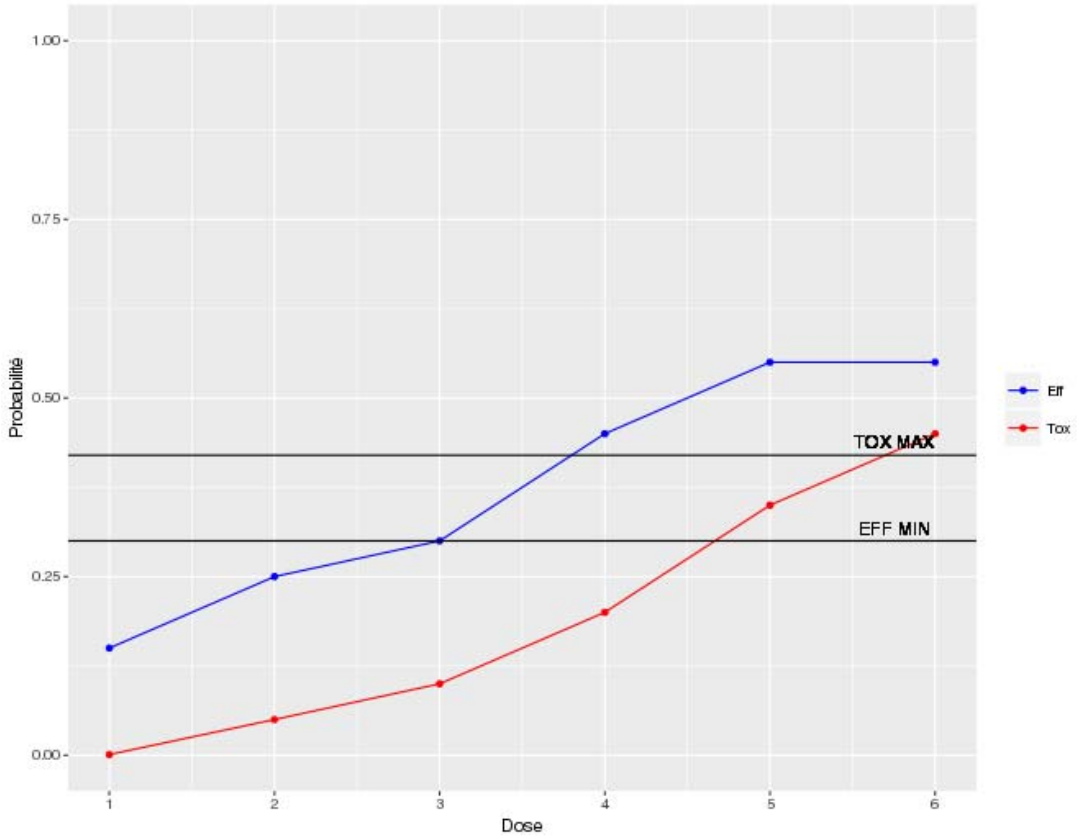
↳ Dose Selection process in two steps

Models and decision rules

- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (4/6)**

  Acceptability range

$$\mathcal{A} = \left\{k \in [\![1; K]\!] \mid \mathbb{P}(\hat{\varphi}_k > \theta) < C_T \ \& \ \mathbb{P}\left(\hat{\psi}_k > \xi\right) \geq C_{EFF}\right\}$$

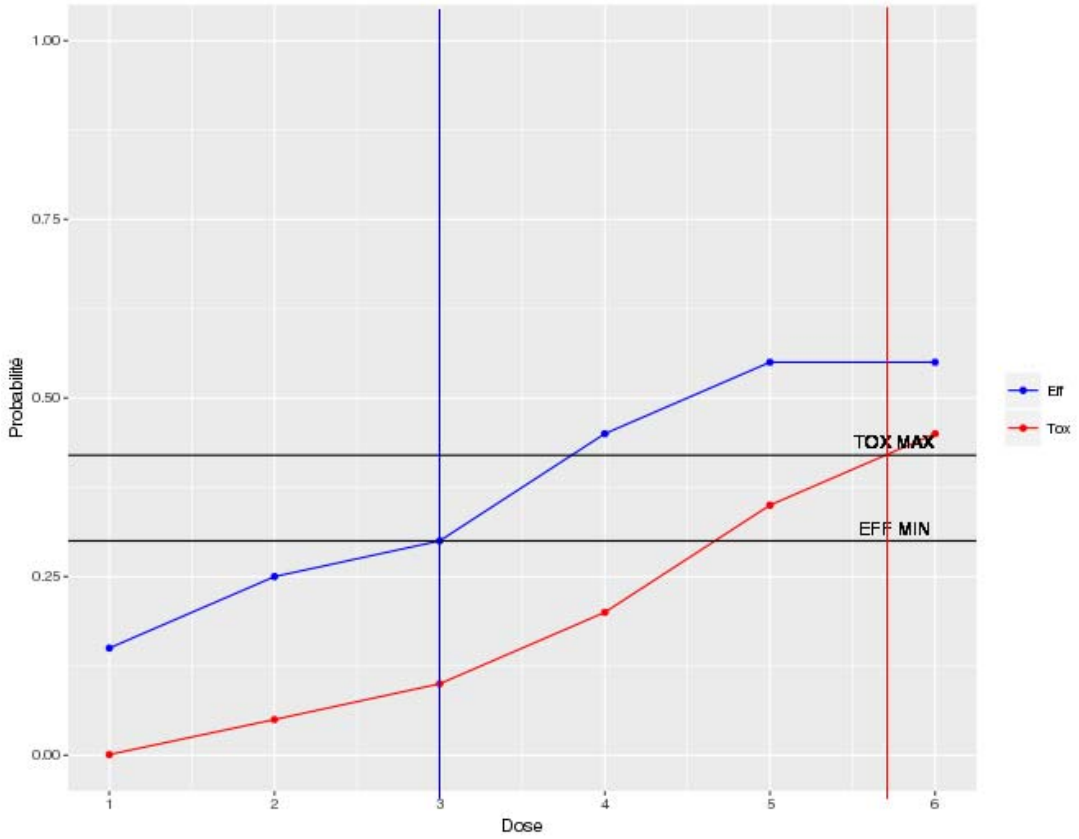


Models and decision rules

- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (4/6)**

  Acceptability range

$$\mathcal{A} = \left\{k \in [\![1; K]\!] \mid \mathbb{P}(\hat{\varphi}_k > \theta) < C_T \ \& \ \mathbb{P}\left(\hat{\psi}_k > \xi\right) \geq C_{EFF}\right\}$$



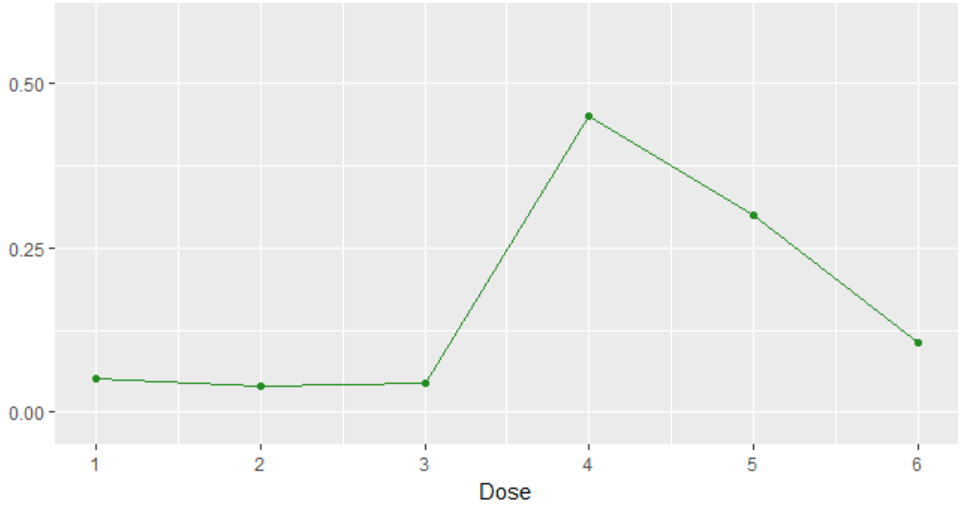
Models and decision rules

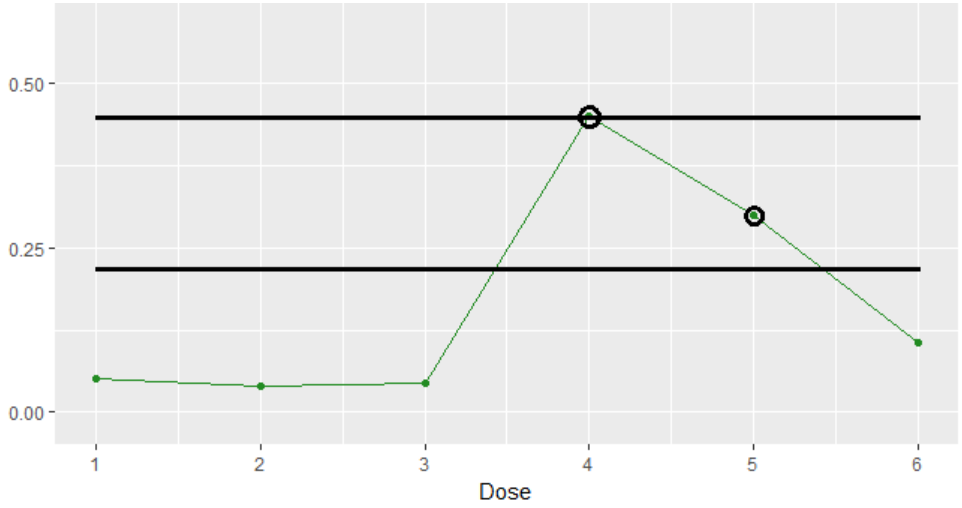
- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (5/6)**

Randomised dose allocation

$$\mathcal{A} = \left\{k \in [\![1;K]\!] \mid \mathbb{P}(\hat{\varphi}_k > \theta) < C_T \ \& \ \mathbb{P}\left(\hat{\psi}_k > \xi\right) \geq C_{EFF}\right\}$$

$$R = \left\{j \in [\![1;K]\!] \mid \max_{k \in [\![1;K]\!]} (\hat{\pi}_k) - \hat{\pi}_j \leq s_1\right\}$$





Models and decision rules

- **Phase I/II Dose-Finding Design for Molecularly Targeted Agent : Plateau Determination Using Adaptive Randomization : (6/6)**

  Randomised dose allocation

$$\mathbb{P}\left(d_{[I+1]} = k \mid k \in R\right) = \widehat{\pi}_k \Big/ \sum_{j \in R} \widehat{\pi}_j$$

- $\widehat{\pi}_k$: probability for dose k to be the plateau point
- s_1 : threshold on the difference of plateau probability

Models and decision rules

- **Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations : (1/3)**

  PKCOV

$$logit(\varphi_k) = -\beta_0 + \beta_1 \log(d_k) + \beta_2 \Delta z_k$$

$$\hat{\varphi}_{k,I+1} = \frac{1}{1 + e^{\beta_0 - \hat{\beta}_{1,I} \log(d_k)}}$$

$$d_{[I+1]} = arg \min_{d_k} \left| \hat{\varphi}_{k,I+1} - \theta \right|$$

- d_k : dose k
- Δz_k : difference in the logarithms of mean AUC and of individual AUC for dose k
- $d_{[I+1]}$: dose allocated to the next patient when I are enrolled

Models and decision rules

- **Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations : (2/3)**

PKLIM

$$z_i \mid \beta_0, \beta_1, \nu \sim \mathcal{N}(\beta_0 + \beta_1 \log(d_k)\ , \nu^2)$$

$$d_{[I+1],PKLIM} = arg \min_{d_k} \left| \mathbb{P}\left(z_{[I+1]} > \log(L) \mid \beta = \hat{\beta}_I\right) - \theta \right|$$

PKCRM

$$d_{[I+1],PKCRM} = \min\left(d_{[I+1],PKLIM}, d_{[I+1],CRM}\right)$$

- z_i : ith patient logarithm of AUC

Models and decision rules

- **Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations : (3/3)**

PKLIM

$$z_i \mid \beta_0, \beta_1 \sim \mathcal{N}(\beta_0 + \beta_1 \log(d_k)\ , \nu^2)$$

PKLOGIT

$$logit(\varphi) = -\beta_2 + \beta_3 z$$

$$\hat{\varphi}_{k,I+1} = \int \frac{1}{1 + e^{\hat{\beta}_{2,I} - \hat{\beta}_{3,I} z_{I+1}}} f(z_{I+1}) dz_{I+1}$$

$$d_{[I+1]} = arg \min_{d_k} \left| \hat{\varphi}_{k,I+1} - \theta \right|$$

- $f(z_{I+1})$: predictive normal density of z_{I+1} given $(\hat{\beta}_0, \hat{\beta}_1)$

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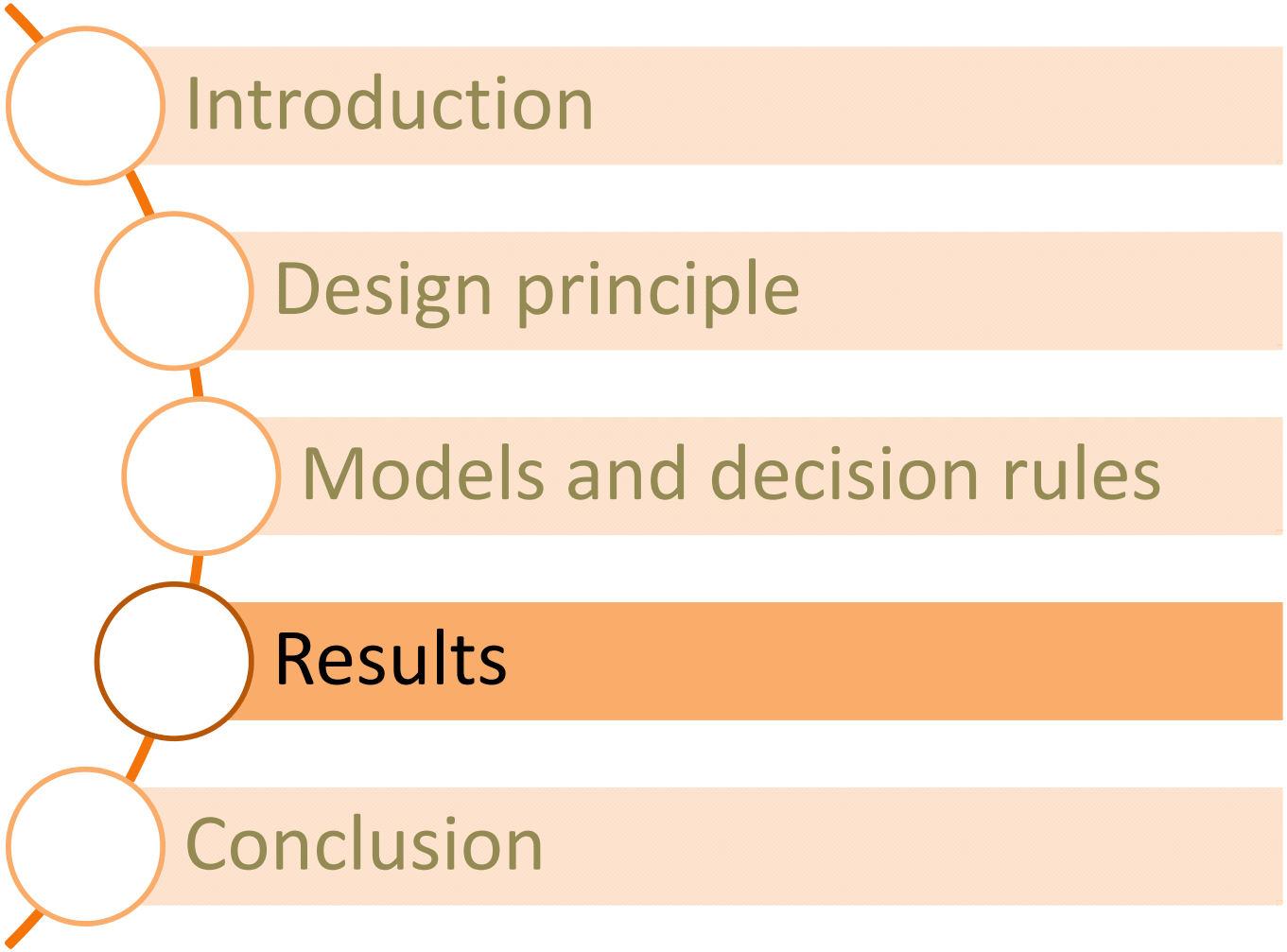


Results

- **Performance criteria**

Percentage of final selection

Final estimations

Percentage of attribution

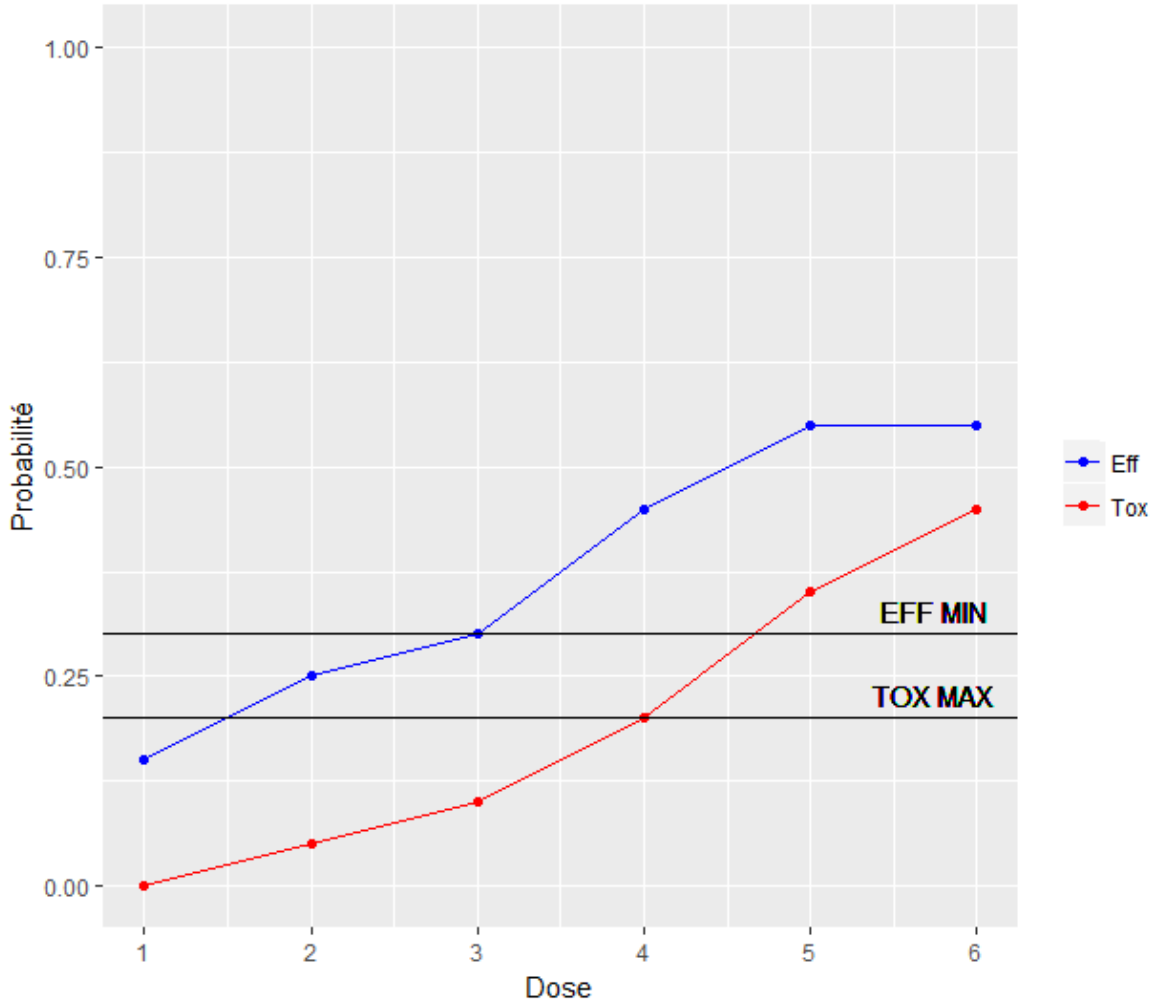
Evolution of selection

Evolution of estimations

Simulations results : Relation 1

↳ Relations from articles

↳ Allow to test complete biologic reaction



- **Simulations results : Relation 1**

Percentage of selection

		Stop	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
1 pat	PKCOV	0.000	0.000	0.000	0.002	0.976	0.022	0.000
(N=100)	PKLOGIT	0.000	0.000	0.000	0.002	0.998	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.002	0.998	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	MTA	0.358	0.000	0.018	0.170	0.346	0.076	0.032
	CRM		0.000	0.000	0.000	1.000	0.000	0.000
3 pat	PKCOV	0.000	0.000	0.000	0.000	0.992	0.008	0.000
(N=99)	PKLOGIT	0.000	0.000	0.000	0.162	0.838	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	MTA	0.192	0.004	0.042	0.108	0.460	0.174	0.020
	CRM		0.000	0.000	0.000	1.000	0.000	0.000

- **Simulations results : Relation 1**

Percentage of selection

		Stop	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
1 pat	PKCOV	0.000	0.000	0.000	0.002	0.976	0.022	0.000
(N=100)	PKLOGIT	0.000	0.000	0.000	0.002	0.998	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.002	0.998	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	MTA	**0.358**	0.000	0.018	0.170	**0.346**	0.076	0.032
	CRM		0.000	0.000	0.000	1.000	0.000	0.000
3 pat	PKCOV	0.000	0.000	0.000	0.000	0.992	0.008	0.000
(N=99)	PKLOGIT	0.000	0.000	0.000	0.162	0.838	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	1.000	0.000	0.000
	MTA	0.192	0.004	0.042	0.108	0.460	0.174	0.020
	CRM		0.000	0.000	0.000	1.000	0.000	0.000

Results

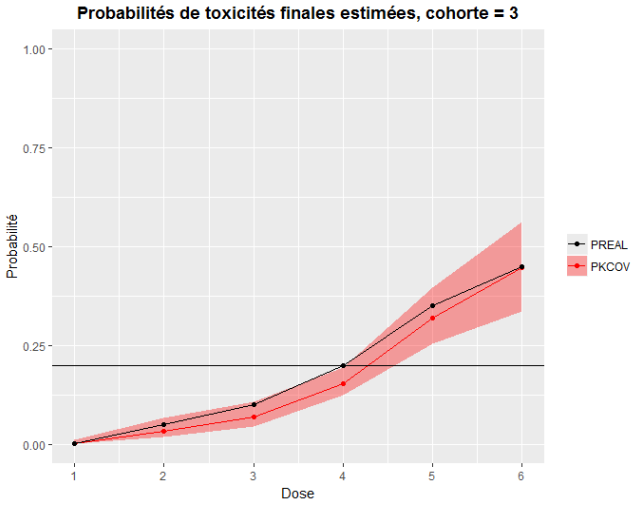
- **Simulations results : Relation 1**

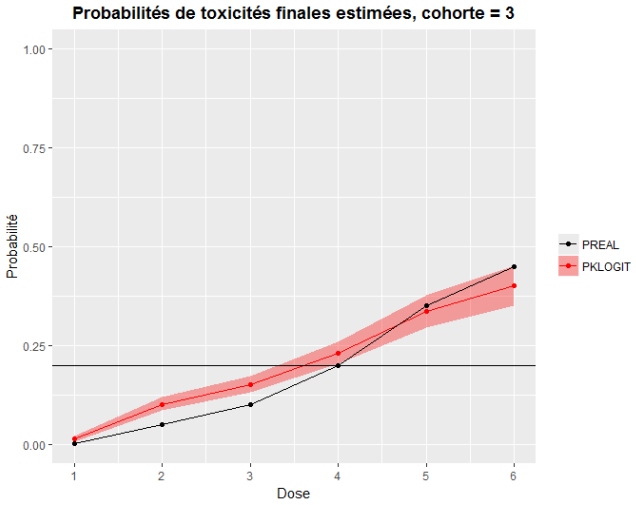
Percentage of selection

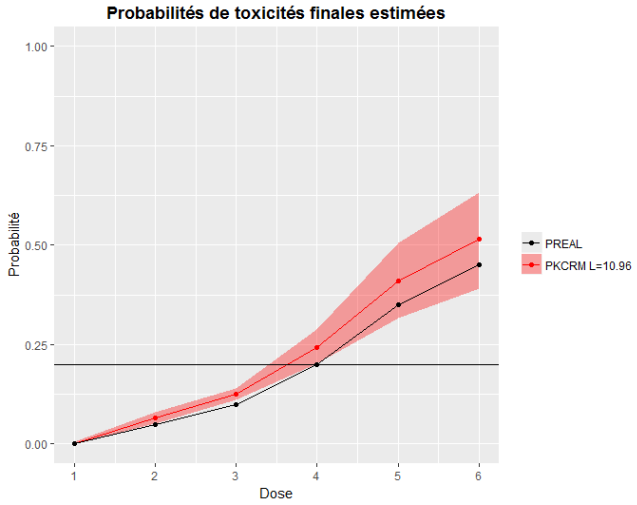
		Stop	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
6 pat	PKCOV	0.000	0.000	0.000	0.000	**0.978**	0.022	0.000
(N=96)	PKLOGIT	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	MTA	0.036	0.046	**0.324**	0.176	0.160	**0.202**	0.056
	CRM		0.000	0.000	0.000	**1.000**	0.000	0.000
8 pat	PKCOV	0.000	0.000	0.000	0.000	0.010	**0.990**	0.000
(N=96)	PKLOGIT	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	PKCRM L = 10,96	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	PKCRM L = 18,1	0.000	0.000	0.000	0.000	**1.000**	0.000	0.000
	MTA	0.000	0.006	0.016	**0.372**	0.292	**0.302**	0.012
	CRM		0.000	0.000	0.000	0.000	**1.000**	0.000

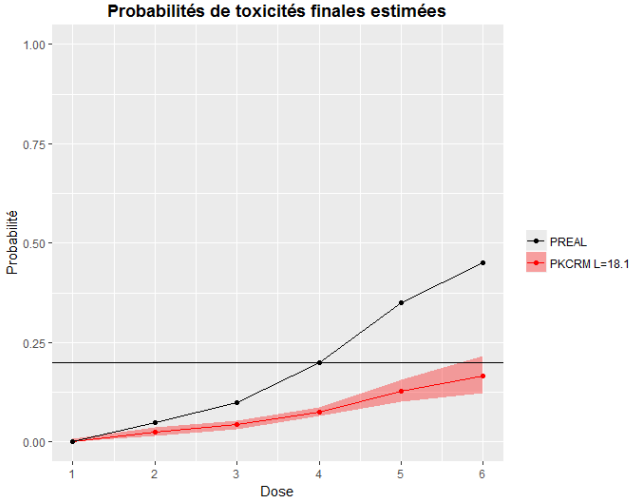
- **Simulations results : Relation 1**

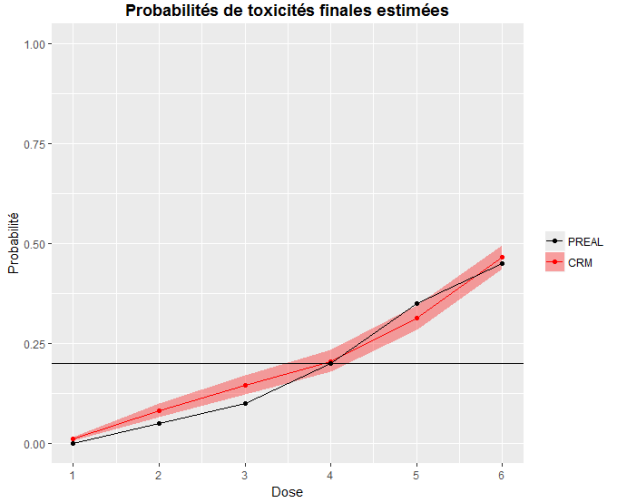
Final estimation





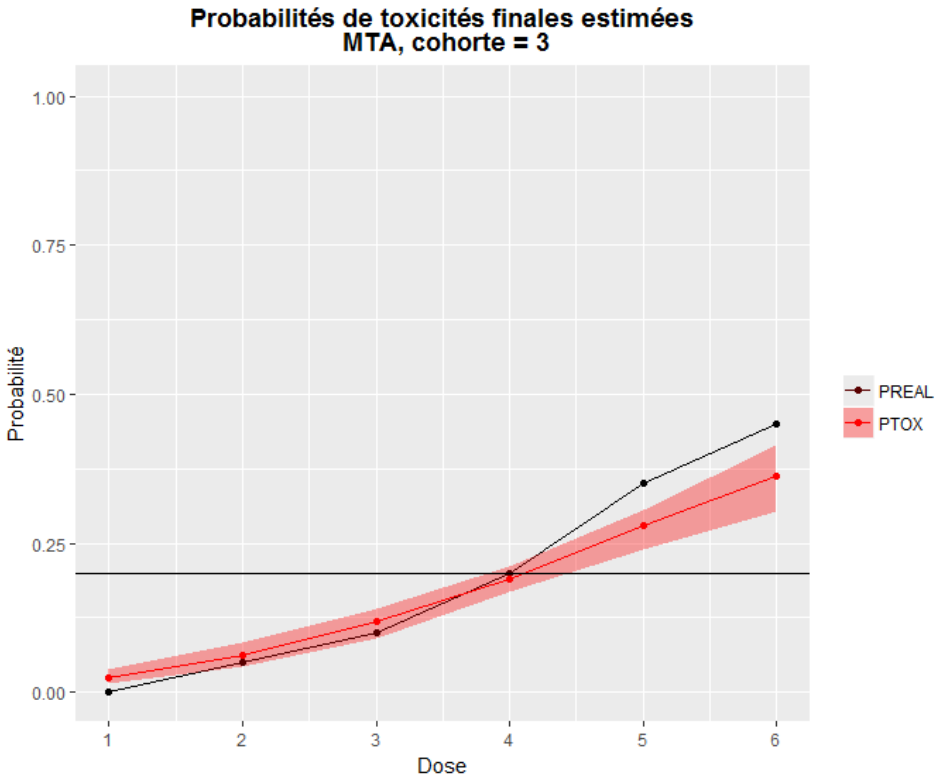


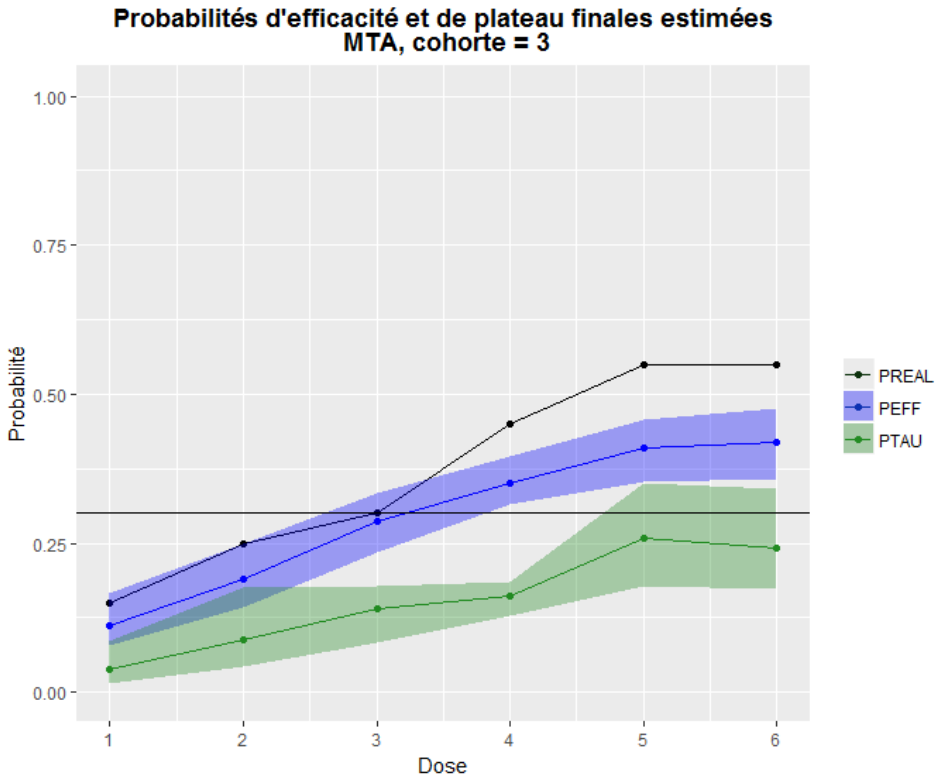




- **Simulations results : Relation 1**

Final estimation (MTA)





- **Simulations results : Relation 1**

Percentage of attribution

		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
1 pat	PKCOV	0.010	0.010	0.030	0.916	0.024	0.010
	PKLOGIT	0.010	0.018	0.184	0.733	0.037	0.018
	PKCRM L = 10,96	0.010	0.103	0.807	0.080	0.000	0.000
	PKCRM L = 18,1	0.010	0.010	0.090	0.890	0.000	0.000
	MTA	0.042	0.106	0.254	0.433	0.130	0.035
	CRM	0.010	0.020	0.050	0.900	0.020	0.000
3 pat	PKCOV	0.030	0.060	0.030	0.742	0.134	0.004
	PKLOGIT	0.103	0.100	0.226	0.571	0.000	0.000
	PKCRM L = 10,96	0.030	0.061	0.395	0.515	0.000	0.000
	PKCRM L = 18,1	0.030	0.061	0.212	0.697	0.000	0.000
	MTA	0.066	0.113	0.188	0.377	0.210	0.046
	CRM	0.030	0.091	0.242	0.636	0.000	0.000

- **Simulations results : Relation 1**

Percentage of attribution

		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
1 pat	PKCOV	0.010	0.010	0.030	0.916	0.024	0.010
	PKLOGIT	0.010	0.018	0.184	0.733	0.037	0.018
	PKCRM L = 10,96	0.010	0.103	0.807	0.080	0.000	0.000
	PKCRM L = 18,1	0.010	0.010	0.090	0.890	0.000	0.000
	MTA	0.042	0.106	0.254	0.433	0.130	0.035
	CRM	0.010	0.020	0.050	0.900	0.020	0.000
3 pat	PKCOV	0.030	0.060	0.030	0.742	0.134	0.004
	PKLOGIT	0.103	0.100	0.226	0.571	0.000	0.000
	PKCRM L = 10,96	0.030	0.061	0.395	0.515	0.000	0.000
	PKCRM L = 18,1	0.030	0.061	0.212	0.697	0.000	0.000
	MTA	0.066	0.113	0.188	0.377	0.210	0.046
	CRM	0.030	0.091	0.242	0.636	0.000	0.000

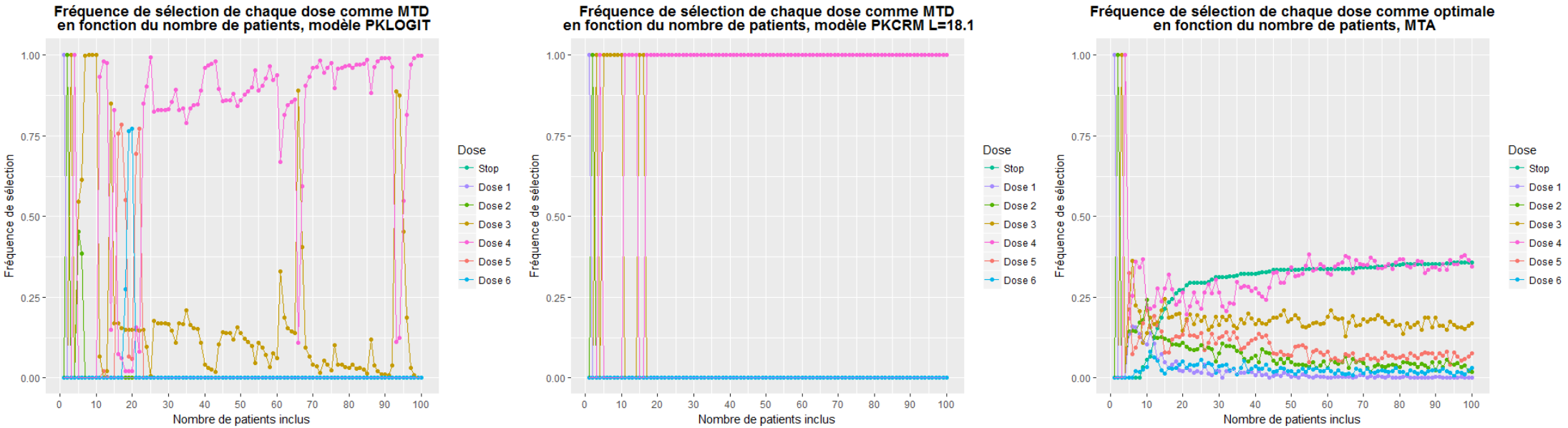
- **Simulations results : Relation 1**

Percentage of attribution

		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
6 pat	PKCOV	0.062	0.062	0.062	0.687	0.125	0.000
	PKLOGIT	0.062	0.062	0.188	0.626	0.062	0.000
	PKCRM L = 10,96	0.062	0.062	0.269	0.607	0.000	0.000
	PKCRM L = 18,1	0.062	0.062	0.062	0.814	0.000	0.000
	MTA	0.144	0.234	0.260	0.236	0.112	0.014
	CRM	0.062	0.062	0.062	0.752	0.062	0.000
8 pat	PKCOV	0.083	0.083	0.083	0.105	0.628	0.017
	PKLOGIT	0.083	0.083	0.083	0.751	0.000	0.000
	PKCRM L = 10,96	0.083	0.083	0.167	0.667	0.000	0.000
	PKCRM L = 18,1	0.083	0.083	0.083	0.583	0.168	0.000
	MTA	0.119	0.131	0.240	0.304	0.190	0.016
	CRM	0.083	0.083	0.083	0.168	0.583	0.000

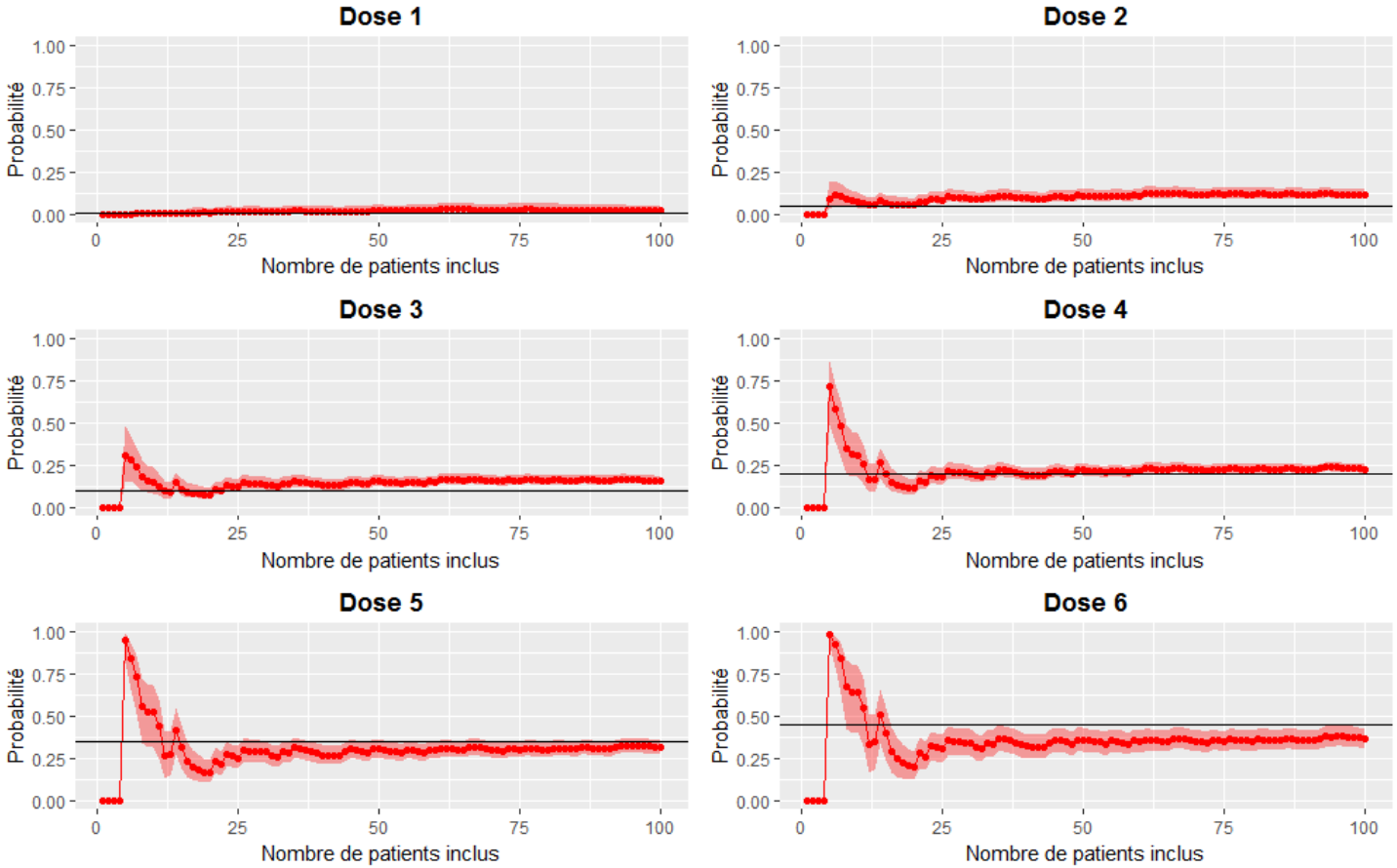
Simulations results : Relation 1

Evolution of selection



- **Simulations results : Relation 1**

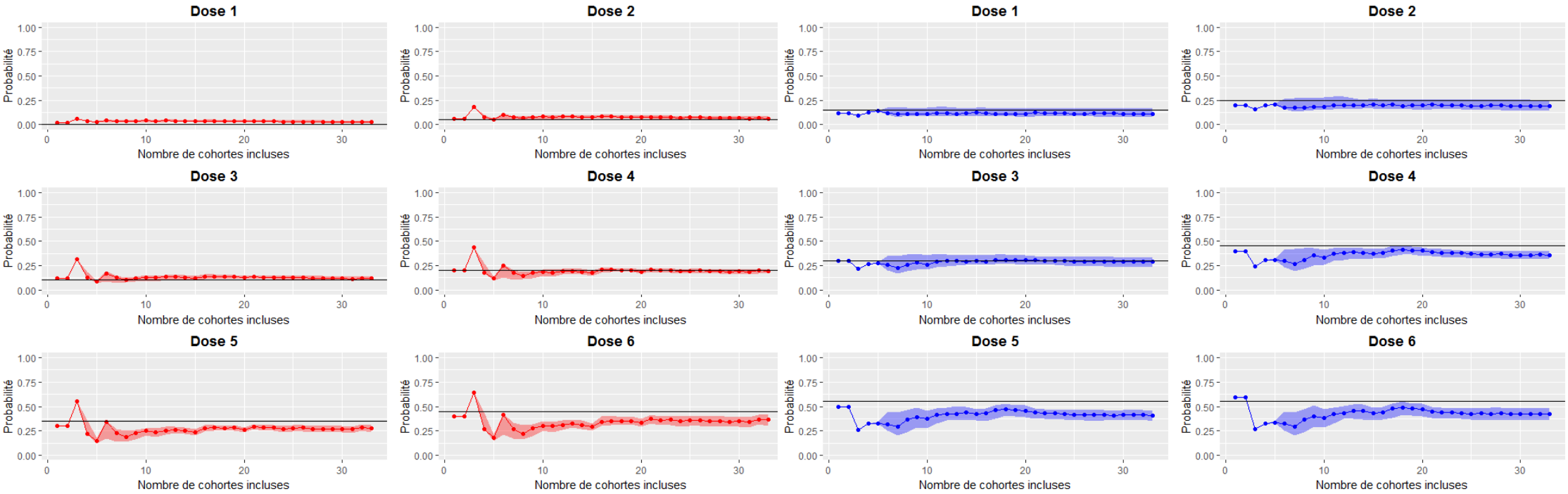
Evolution of estimation



Médiane, premier et troisième quartiles
probabilité de toxicité, modèle PKLOGIT

- **Simulations results : Relation 1**

Evolution of estimation



Médiane, premier et troisième quartiles
probabilité de toxicité, MTA, cohorte = 3

Médiane, premier et troisième quartiles
probabilité d'efficacité, MTA, cohorte = 3

- **Simulations results : Relation 1**

Cohorts

- No clear influence
- Better results with small cohorts

Models

- L threshold has influence for PKCRM
- PKLOGIT, PKCRM L=10,96

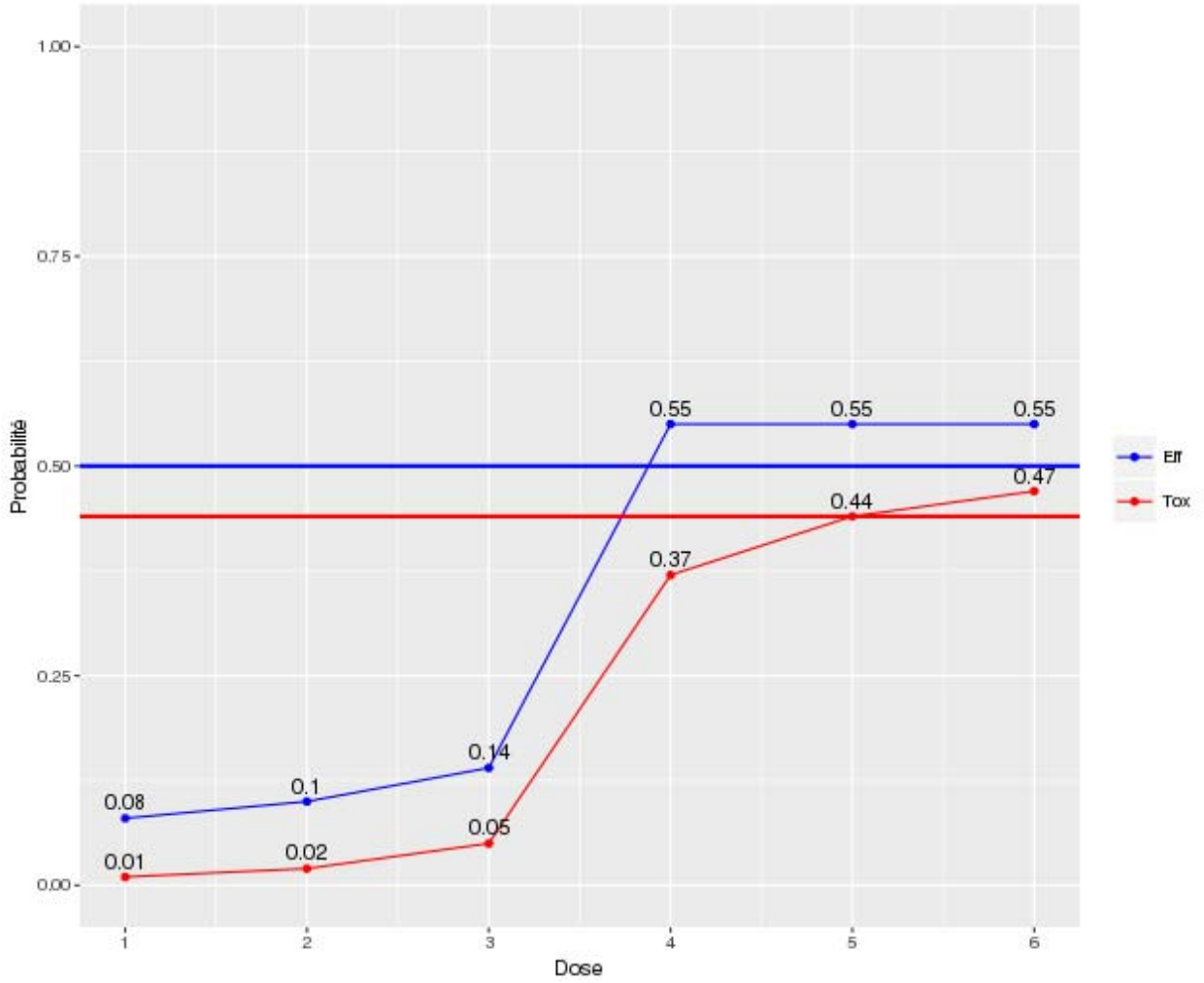
Gains

- Number of patients
- Attribution & selection

Simulations results : Relation 2

↳ Important step in reactions

↳ 3 doses in plateau



Results

- **Simulations results : Relation 2**

Cohorts

- No clear influence
- All size of cohorts give similar results

Models

- Issue when chosing between doses with close probabilities
- Acceptability range is too conservative
- MTA (3pats/coh)

Gains

- Less important for attribution and number of patients
- Wrong final selection

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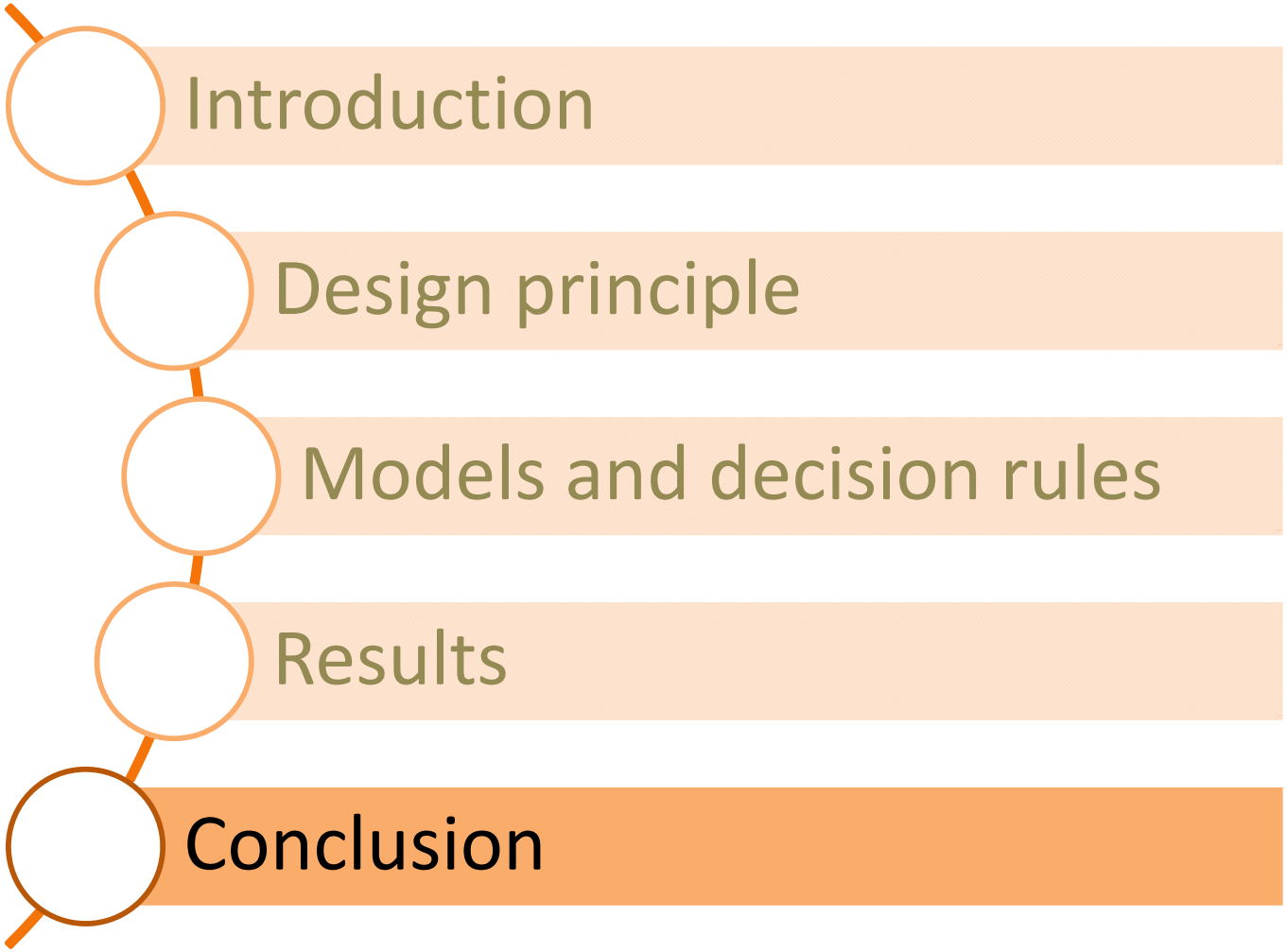

Conclusion

- **Preconisations**

No out standing model

One model is promising in every situation

Simulate all methods

Right model → gain in attribution, selection and number of patients

Better results with small cohorts

Conclusion

- **Perspectives**

Joint model : MTA & PK methods

Threshold sensitivity analyses

Missing data

Rythm of PK data collection

Conclusion

Thank you for your attention !

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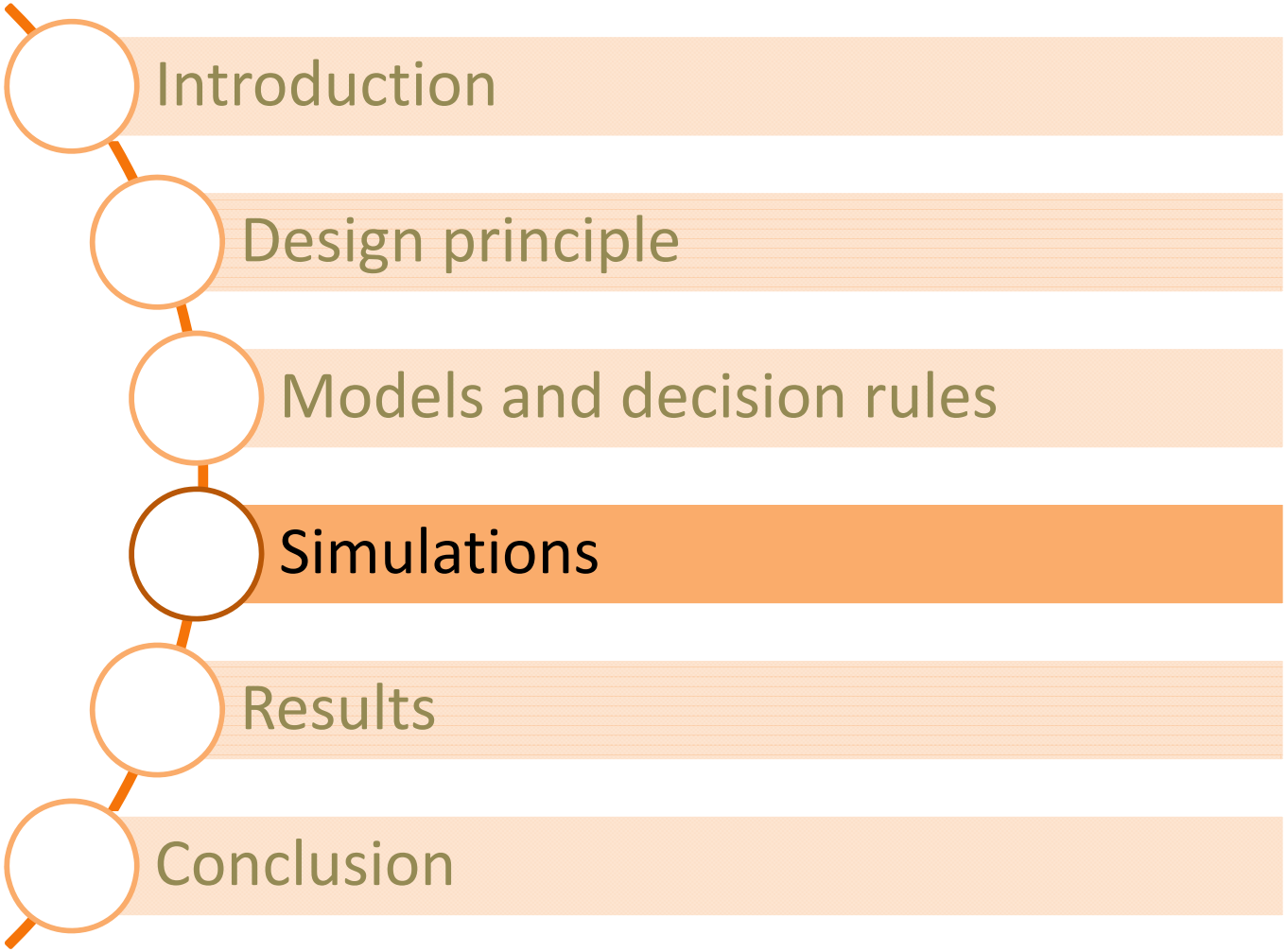


Simulations

- **R Packages : dfmta (1.5) & dfpk (3.2.0) (1/5)**

  dfmta (1/2) : Simulation

```r
sim_dfmta <- mtaBin_sim(ngroups = 1,
                        ndose = 6,
                        p_tox = c(0.005, 0.01, 0.02, 0.05, 0.10, 0.15),
                        p_eff = c(0.01, 0.10, 0.30, 0.50, 0.80, 0.80),
                        tox_max = 0.35,
                        eff_min = 0.20,
                        prior_tox = c(0.02, 0.06, 0.12, 0.20, 0.30, 0.40),
                        prior_eff = c(0.12, 0.20, 0.30, 0.40, 0.50, 0.59),
                        poisson_rate = 1,
                        n = 100,
                        cohort_start = 3,
                        cohort = 3,
                        tite = FALSE,
                        method = "MTA-RA",
                        s_1 = function(n_cur){0.2*(1-n_cur/n)},
                        nsim = 500,
                        c_tox = 0.90,
                        c_eff = 0.40,
                        seed = 1024,
                        threads = 0)
```

- **R Packages : dfmta (1.5) & dfpk (3.2.0) (2/5)**

  dfmta (2/2) : In a trial

```
id_dose <- c(1,1,1,2,2,2,3,3,3,4,4,4,5,5,5,4,4,4,5,5,5,6,6,6,3,3,3,4,4,4,3,3,3)
toxicity <- c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,0,1,1,0,0,0,0,0,1,0,0,0,0)
efficacy <- c(0,0,0,0,0,0,0,0,1,0,0,0,1,1,0,0,1,0,0,1,0,0,1,0,0,1,1,0,1,0,0,1,1)

next_mta <- mtaBin_next(ngroups = 1,
                        group_cur = 1,
                        ndose = 6,
                        prior_tox = c(0.02, 0.06, 0.12, 0.20, 0.30, 0.40),
                        prior_eff = c(0.12, 0.20, 0.30, 0.40, 0.50, 0.59),
                        tox_max = 0.35,
                        eff_min = 0.20,
                        cohort_start = 3,
                        cohort = 3,
                        final = FALSE,
                        method = "MTA-RA",
                        s_1 = function(n_cur){0.2*(1-n_cur/n)},
                        group_pat = rep(1,length(id_dose)),
                        id_dose = id_dose,
                        toxicity = toxicity,
                        tite = FALSE,
                        efficacy = efficacy,
                        c_tox = 0.90,
                        c_eff = 0.40,
                        seed = 1024)
```

Simulations

- **R Packages : dfmta (1.5) & dfpk (3.2.0) (4/6)**

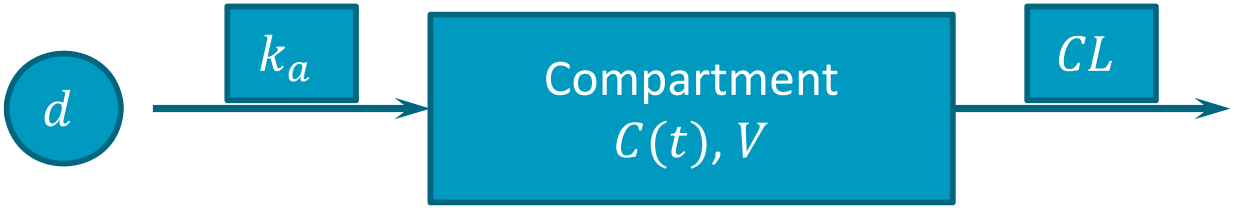
dfpk (1/3) : Simulation

```
simulatedData <- sim.data(PKparameters = c(2, 10, 100),
                          omegaIIV = 0.7,
                          omegaAlpha = 0,
                          sigma = rep(0.2, length(timeSampling)),
                          doses = c(12.59972, 34.65492, 44.69007, 60.80685, 83.68946, 100.37111),
                          limitTox = 10.96,
                          timeSampling = seq(0, 24, length.out=48),
                          N = 100)

sim_dfpk <- nsim(doses = c(12.59972, 34.65492, 44.69007, 60.80685, 83.68946, 100.37111),
                 N = 100,
                 cohort = 3,
                 icon = c(2:6, round(seq(9, 48, ((48-9)/4)))),
                 theta = 0.20,
                 model = "pktox",
                 simulatedData = simulatedData,
                 TR = 500,
                 prob = 0.9,
                 AUCmethod = 2,
                 options = list(nchains = 4, niter = 4000, nadapt = 0.8),
                 betapriors = c(10,10000,20,10),
                 thetaL = NULL,
                 p0 = NULL,
                 L = log(18.1))
```

- **R Packages : dfmta (1.5) & dfpk (3.2.0) (5/6)**

dfpk (2/3) : Simulation



$$C(t) = \frac{d.k_a}{V.k_a - CL}\left(exp\left(-\frac{CL}{V}t\right) - exp(-k_a.t)\right)$$

$$AUC = \int_0^T C(t)dt \xrightarrow{T\to\infty} \frac{d}{CL}$$

Toxicity if $\alpha_i.AUC_{i,k} > \tau_T$

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

- k_a (h^{-1}) : absorption rate
- CL $(L.h^{-1})$: clearance of elimination
- V (L) : compartment volume
- α : sensitivity parameter for the AUC
- τ_T : AUC threshold for toxicity

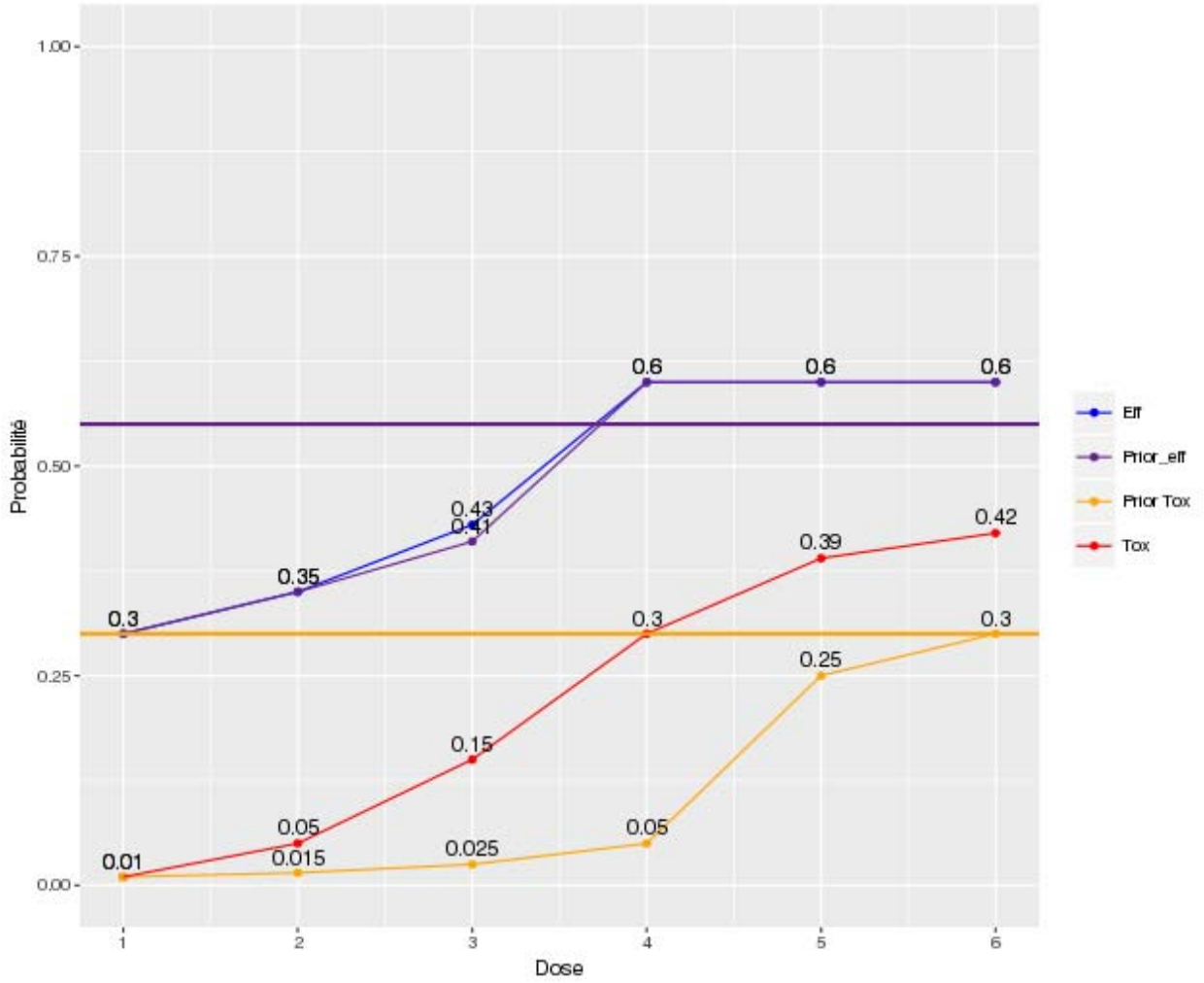
- **R Packages : dfmta (1.5) & dfpk (3.2.0) (6/6)**

  dfpk (3/3) : In a trial

```
next_dfpk <- nextDose(model = "pktox",
                      y = c(0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 0, 0),
                      AUCs = c(1.208339,  5.506040,  6.879835,  3.307928,  3.642430,
                               10.271291,  3.885522,  3.086622,  2.537158,  5.525917,
                               8.522176,  4.642741, 11.048531, 10.246976,  5.226807),
                      doses = c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111),
                      x = c(1, 2, 3, 4, 5, 6, 4, 4, 4, 5, 5, 4, 4, 5, 5),
                      theta = 0.2,
                      options = list(nchains = 4, niter = 4000, nadapt = 0.8),
                      prob = 0.9,
                      betapriors = c(10,10000,20,10),
                      thetaL = NULL,
                      p0 = NULL,
                      L = log(18.1))
```

- **Simulations results : Relation 3**

↳ Bad priors on toxicity

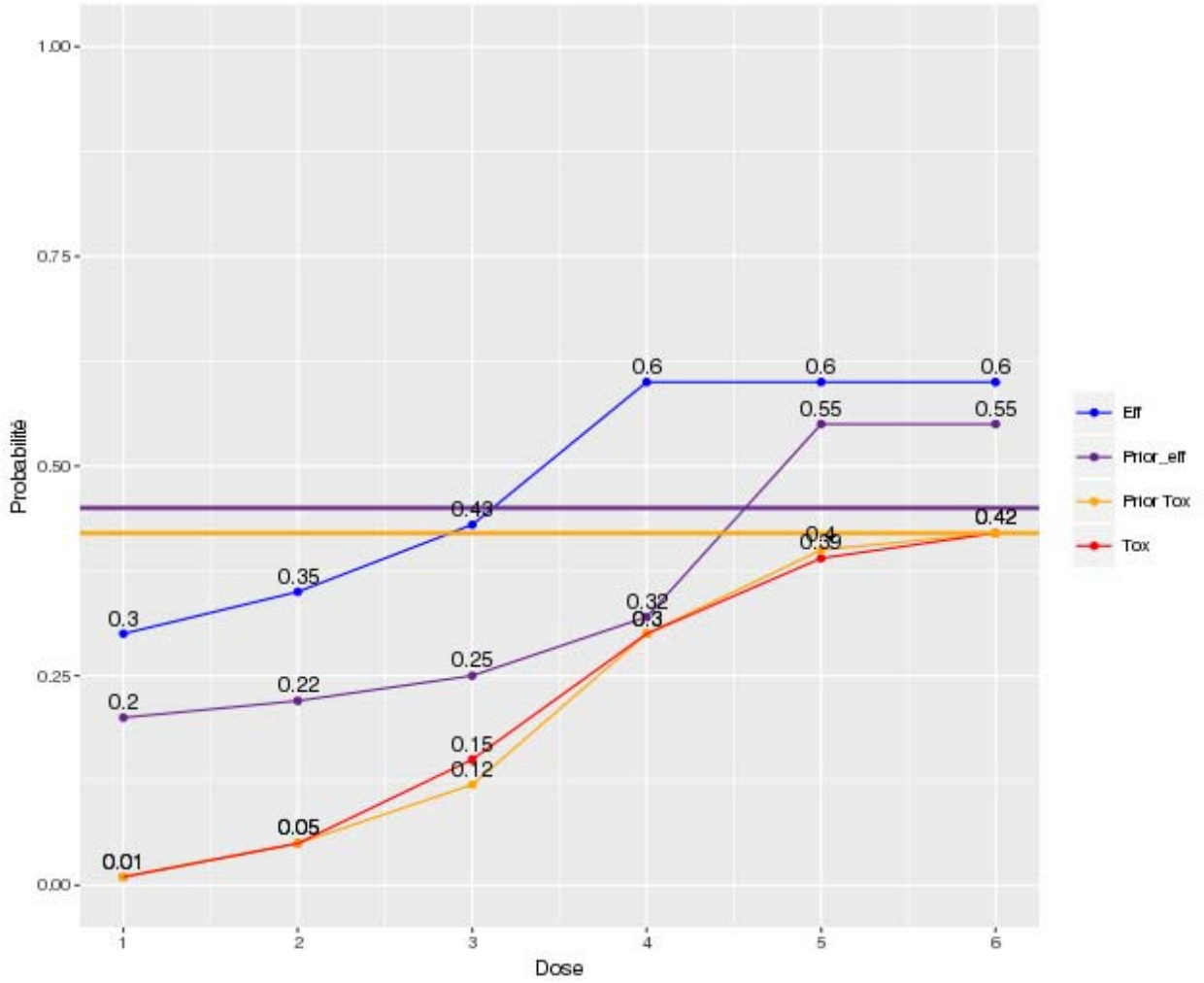


- **Simulations results : Relation 3**

Cohorts	• Better results with cohorts of 3 patients
Models	• Acceptability range rule is too conservative
Gains	• Final levels reached early (25-30 patients)
Priors	• Low influence on the estimations

- **Simulations results : Relation 4**

↳ Priors underestimate efficacy

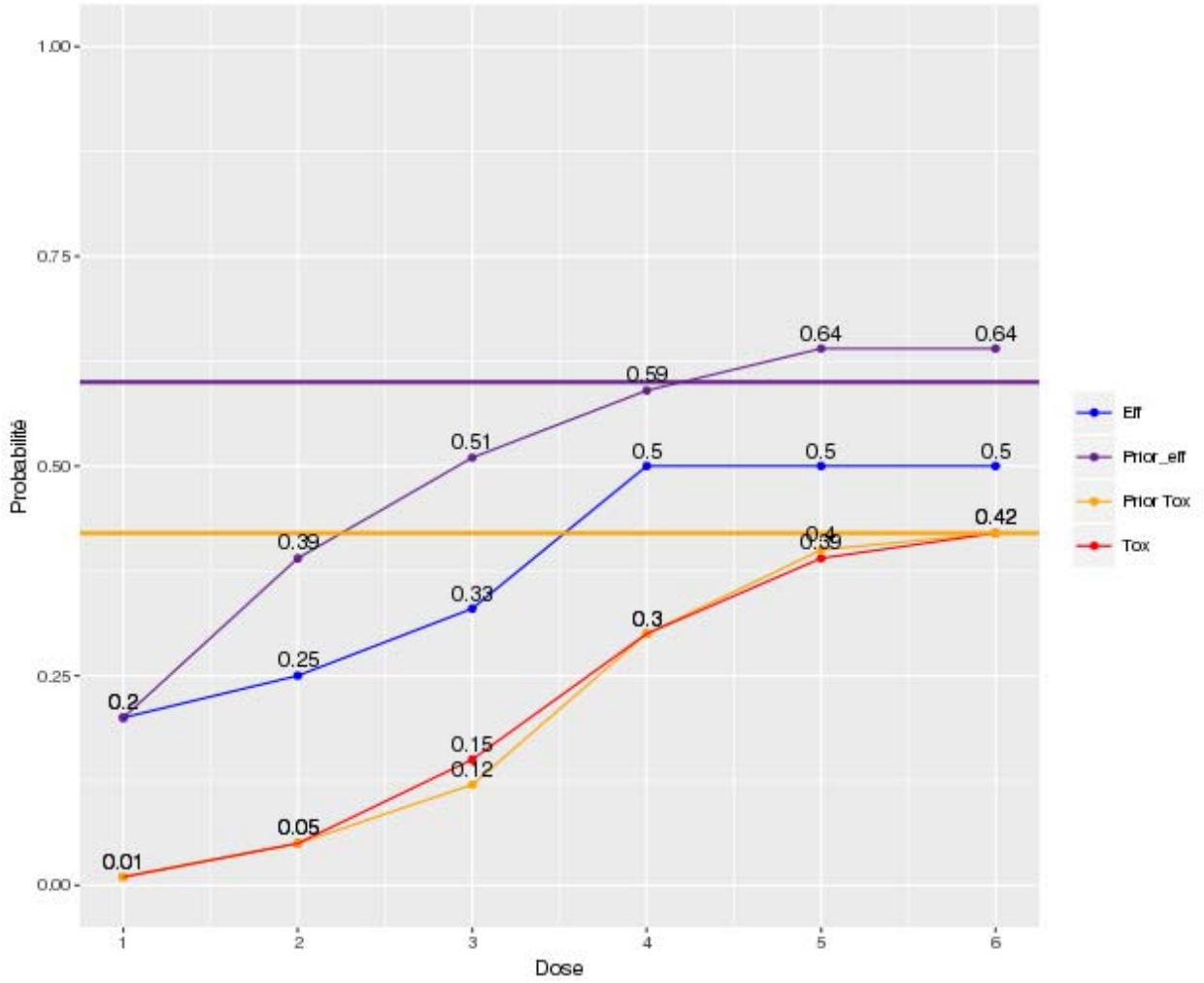


- **Simulations results : Relation 4**

Cohorts	• No clear influence • Better selection and attribution with cohorts of 1 or 3 patients
Models	• Good estimation of plateau probability • Lower number of trials stopped for cohorts of 3 patients
Priors	• No real influence

- **Simulations results : Relation 5**

↳ Priors overestimate efficacy

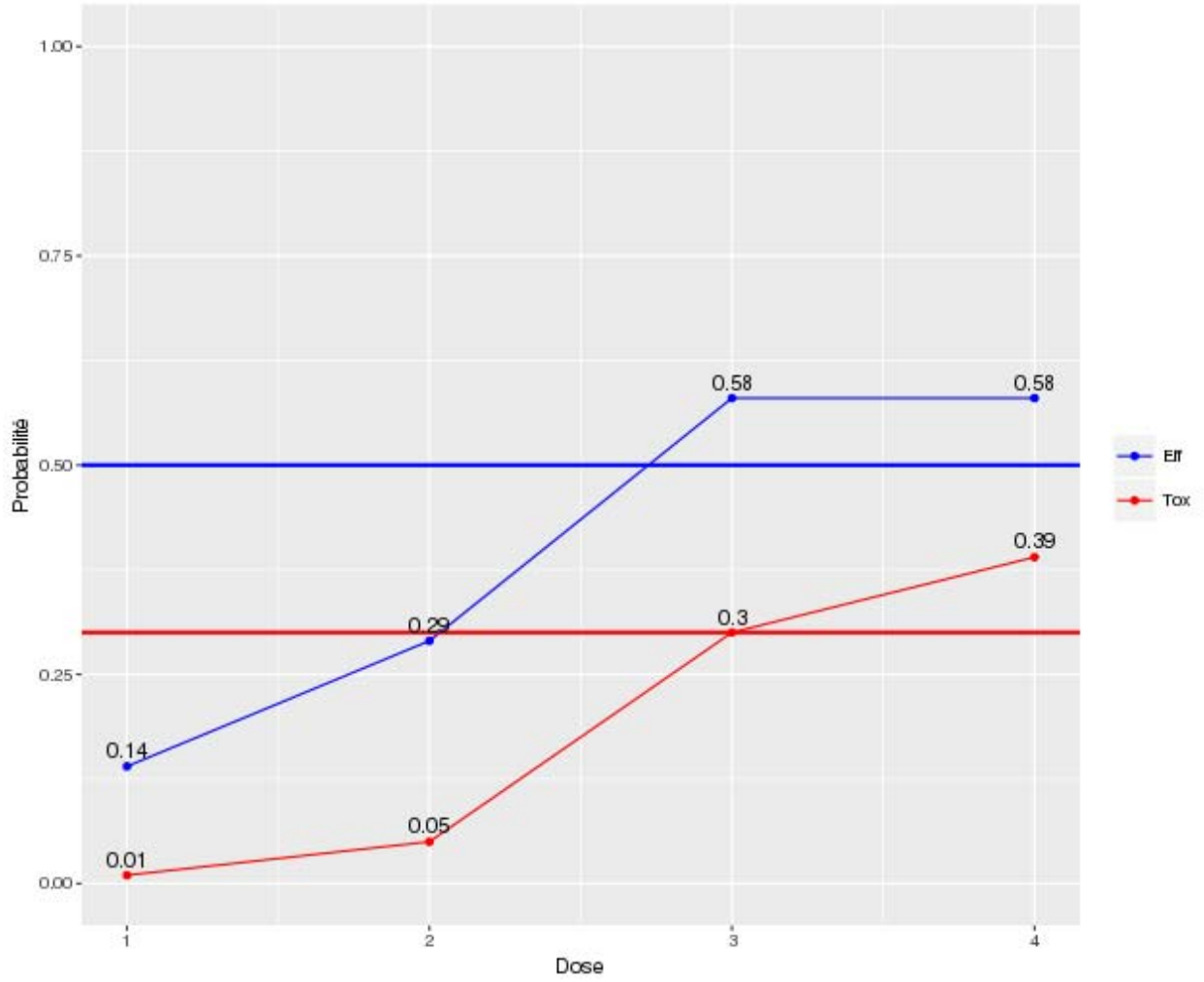


- **Simulations results : Relation 5**

Cohorts	• Less patients necessary for small cohorts
Models	• Good selection, poor estimation of efficacy and plateau
Priors	• Estimations are close to priors • Early stopping rule prevent accurate estimation

- **Simulations results : Relation 6**

↳ 4 doses



- **Simulations results : Relation 6**

Cohorts	• No clear influence • Better selection and attribution with cohorts of 1 or 3 patients
Models	• Acceptability range rule is too conservative • PKLOGIT, MTA (3pats/coh)
Gains	• Number of patients • Attribution & selection