Early phase dose-finding designs for bridging studies in pediatrics

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INTRODUCTION

Designing paediatric dose-finding (DF) I/II studies is often a challenge. Usually performed on healthy subjects, they aim at obtaining reliable information on a drug safety for several doses. The choice of the dose-range, as well as the elicitation of the probability of toxicity for each dose (working model, WM) is often a challenge due to ethical reasons and small sample size.

We propose a global approach to build a dose-finding study in paediatric using previous adult information on pharmacokinetics (PK), toxicity and efficacy. We evaluated the approach on a motivating example, erlotinib.

MODEL

A bivariate continual reassessment method [1] was used to model the dose-toxicity and dose-efficacy curves :

- toxicity $R(d_j) = \Pr(Y_j = 1|d_j)$
- efficacy $Q(d_j) = \Pr(V_j = 1|d_j, Y_j = 0)$
- success $P(d_j) = Q(d_i)(1 - R(d_i))$

where Y_j and V_j are respectively the toxicity and the efficacy of patient j, who received dose d_j.

We modeled the toxicity and efficacy with

$$R(d_i) = \psi(d_i, a) = \alpha_i^{\exp(a)}$$
$$Q(d_i) = \phi(d_i, b) = \beta_i^{\exp(b)}$$

where a and b are the parameters, and α_i, β_i the initial probability of toxicity and efficacy respectively, also called working model (WM).

WM needed to be defined.

In a bayesian view, we used priors such that $a \sim \pi_a$ and $b \sim \pi_b$. $\hat{a}$ and $\hat{b}$ are estimated for each patient from the posterior distribution and we had $\hat{R}(d_i) \cong \psi(d_i, \hat{a})$, $\hat{Q}(d_i) \cong \phi(d_i, \hat{b})$ and $\hat{P}(d_i) = (1 - \hat{R}(d_i))\hat{Q}(d_i)$. Priors needed to be defined.

The dose for the next patient is the safe most successful dose (sMSD) d^* which maximises $\hat{P}(d_1), \hat{P}(d_2), ..., \hat{P}(d_K)$ under a constraint of toxicity target τ, such that $\hat{R}(d^*) \leqslant \tau$.

EXTRAPOLATION FROM ADULTS TO CHILDREN

(1) Doses:

The paediatric doses d_i were extrapolated from the adult doses c_i through different appoaches: linear, allometric or maturation adjustment. Formulae are detailed on Figure 1. Doses related to erlotinib are in blue, with the final paediatric dose range for each approach.

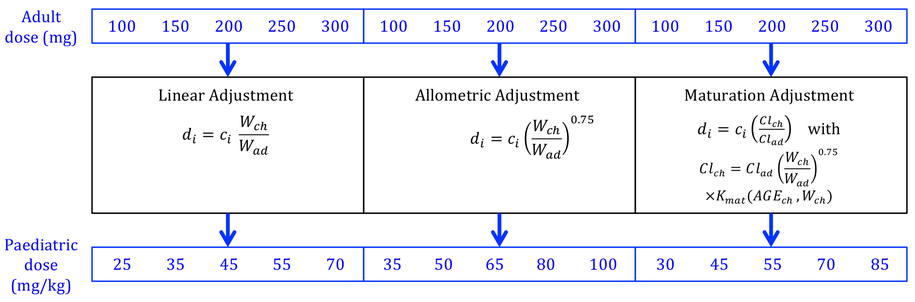


Figure 1: Dose adjustment for paediatrics

(2) Dose-Finding Model:

(i) We built WM using adult information. A dose-toxicity curve was built using mixture estimates, as described in Figure 2, from which we fitted a logit function $\eta(d)$.

In order to balance the choice of WM, we established several WMs according to:

WM1: $\alpha_i = \eta(d_i), i = 1 \dots K$

WM2: $\alpha_i = \eta(d_{i+1}), i = 1 \dots K-1, \quad \alpha_K = (\eta(d_K) + 1)/2$

WM3: $\alpha_1 = \eta(d_1)/2, \quad \alpha_i = \eta(d_{i-1}), i = 2 \dots K$

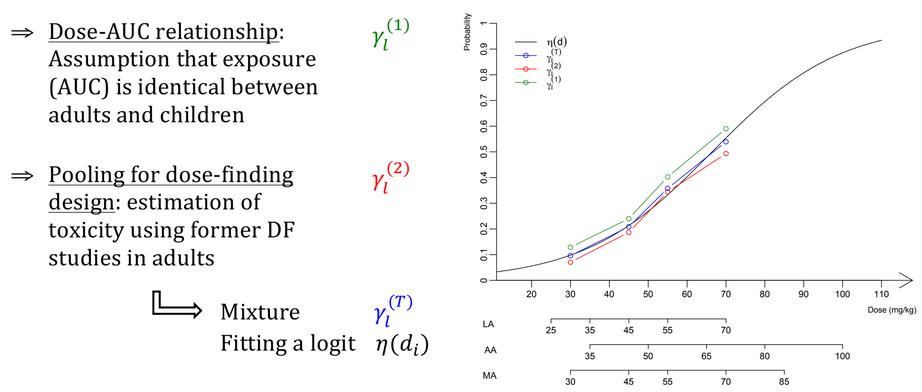


Figure 2: Working model construction

The resulting WMs in the case of erlotinib are presented Figure 3.

A model selection is used to compare the WMs: the Watanabe-Akaike information criteria (WAIC).

	Linear Adjustment					Allometric Adjustment					Maturation Adjustment				
WM1	0.07	0.13	0.21	0.33	0.55	0.13	0.27	0.48	0.70	0.88	0.10	0.21	0.33	0.55	0.76
WM2	0.13	0.21	0.33	0.55	0.78	0.27	0.48	0.70	0.88	0.94	0.21	0.33	0.55	0.76	0.88
WM3	0.04	0.07	0.13	0.21	0.33	0.06	0.13	0.27	0.48	0.70	0.05	0.10	0.21	0.33	0.55

Figure 3: Paediatric working model for each approach

(ii) Prior distributions were chosen as normal distributions $\mathcal{N}(\mu, \sigma^2)$. Parameter a was established using either

- the effective sample size (ESS) method π_a: parameters were defined such that the information brought by the prior was equivalent to the information brought by a fixed number of patient.
- the method of Zhang *et al* π_a^*: parameters were defined such that each dose had the same probability to be the most tolerated dose.

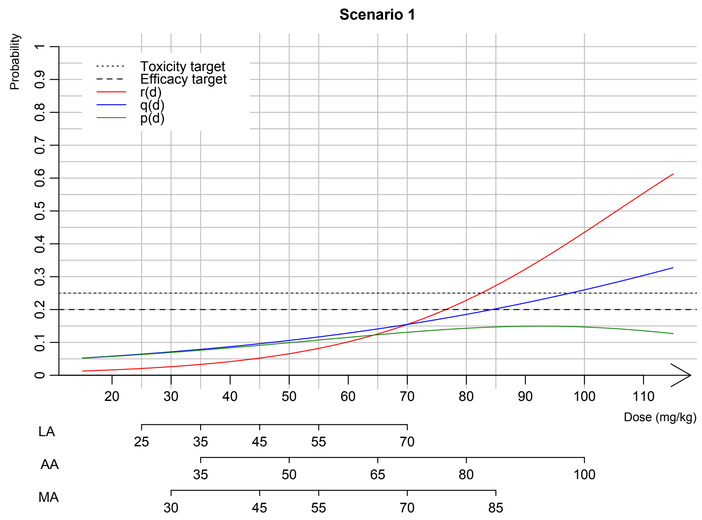
Due to stringent priors, we used an adaptive prior method: if the data seemed to indicate that the sMSD was at the extrems, we would switch to a prior with a larger variance π_a' based on Bayes factor.

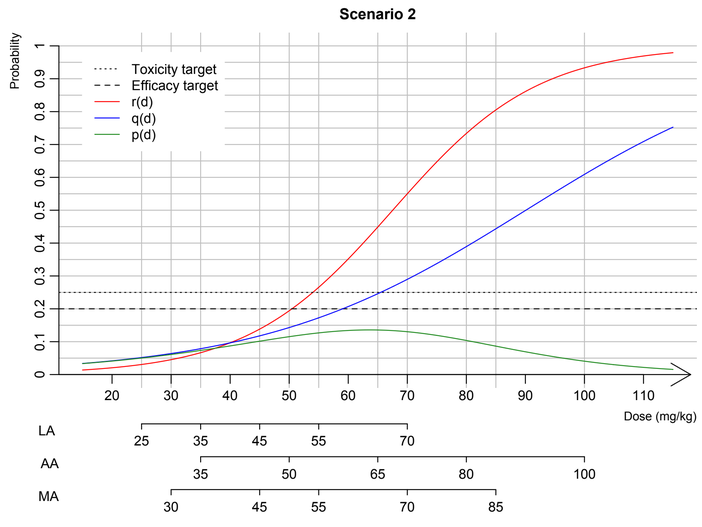
	Linear Adjustment	Allometric Adjustment	Maturation Adjustment
π_a	$\mathcal{N}(-0.31, 0.36)$	$\mathcal{N}(-0.38, 0.50)$	$\mathcal{N}(-0.34, 0.42)$
π_a^*	$\mathcal{N}(-0.31, 0.46)$	$\mathcal{N}(-0.38, 3.13)$	$\mathcal{N}(-0.34, 1.46)$
π_a'	$\mathcal{N}(-0.31, 4.33)$	$\mathcal{N}(-0.38, 15.24)$	$\mathcal{N}(-0.34, 8.88)$

Figure 4: Priors used for erlotinib

The different priors in the erlotinib setting are presented in Figure 4. We chose π_b as $\mathcal{N}(0, 1.34)$.

SCENARIOS





RESULTS

We compared (1) the WAIC selection using all WMs with the ESS prior (WAIC-bCRM) or a non-informative prior $\mathcal{N}(0, 1.34)$ (WAIC*-bCRM) and (2) the adaptive prior with the prior π_a (AP-bCRM) or π_a^* (AP*-bCRM). We also simulated the bCRM for each WMs with a non-informative prior $\mathcal{N}(0, 1.34)$. We performed 1,000 simulated trial and evaluated the percentage of right selection (PCS). Results are presented in table 1 for scenarios 1 and 2.

Method	Linear Adjustment							Allometry Adjustment							Maturation Adjustment						
Dose (mg/kg)	25	35	45	55	70	SR	AD	35	50	65	80	100	SR	AD	30	45	55	70	85	SR	AD
Scenario 1																					
WAIC-bCRM	0	0	0.3	13.1	*76.6*	10	**89.7**	0	2.1	44.6	*51.7*	1.2	0.4	**96.3**	0	0.3	10.6	58.9	*29.2*	1	**88.1**
WAIC*-bCRM	0	0	0.2	8.1	*81.7*	10	**89.8**	0	1.2	37.2	*59.1*	2.3	0.2	**96.3**	0	0.3	6.3	53.4	*38.3*	1.7	**91.7**
AP-bCRM	0	0	0	14.4	*77.9*	6.2	**92.2**	0	1.4	50.9	*45.2*	2.2	0.2	**96.1**	0	0.2	12.2	59.5	*26.8*	1	**86.2**
AP*-bCRM	0	0	0.1	13.9	*77.1*	7.1	**91**	0	1.1	35.1	*59.8*	3.9	0.1	**94.9**	0	0.1	7.3	58.3	*32.3*	2	**90.6**
bcrm-WM1	0	0	0.3	7.8	*81.8*	10.1	**89.6**	0	1.4	39.6	*56.8*	2.1	0.1	**96.4**	0	0.1	8.2	60.4	*30*	1.3	**90.4**
Scenario 2																					
WAIC-bCRM	0	0.4	41.3	*57.6*	0.7	0	**98.9**	1.5	*88.9*	7.9	0	0	1.7	**88.9**	0	38.5	*60.8*	0.6	0	0.1	**99.3**
WAIC*-bCRM	0	0.2	26.2	*72*	1.6	0	**98.2**	1.3	*88.1*	10.2	0	0	0.4	**88.1**	0	25.4	*73.5*	1.1	0	0	**98.9**
AP-bCRM	0	0.4	26.1	*73*	0.5	0	**99.1**	1.2	*89*	9.5	0	0	0.2	**89**	0.1	27	*71.9*	1	0	0	**98.9**
AP*-bCRM	0	0.1	24.9	*74.2*	0.8	0	**99.1**	0.6	*83.6*	14.6	0	0	0.9	**83.6**	0.4	22	*77.1*	0.4	0	0.1	**99.1**
bcrm-WM1	0	0.2	18.7	*80.1*	0.9	0.1	**98.8**	1	*86.6*	12	0	0	0.4	**86.6**	0	18.7	*79.6*	1.5	0	0.2	**98.3**

Table 1: Results for simulated scenarios

The WAIC model selection allows good PCS when combining all WMs. Likewise for the adaptive prior. The ESS method did not seem to improve results significantly.

CONCLUSION

- Adjustment of the dose-range with maturation is closer to the paediatric reality. Extrapolation could be improved with alternative methods such as PBPK models.
- The WAIC-bCRM allows to counterbalance the choice of WMs. Choice of an informative prior seems not to improve the results.
- Using adult information to built a paediatric dose-finding study allows for a more appropriate design.

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