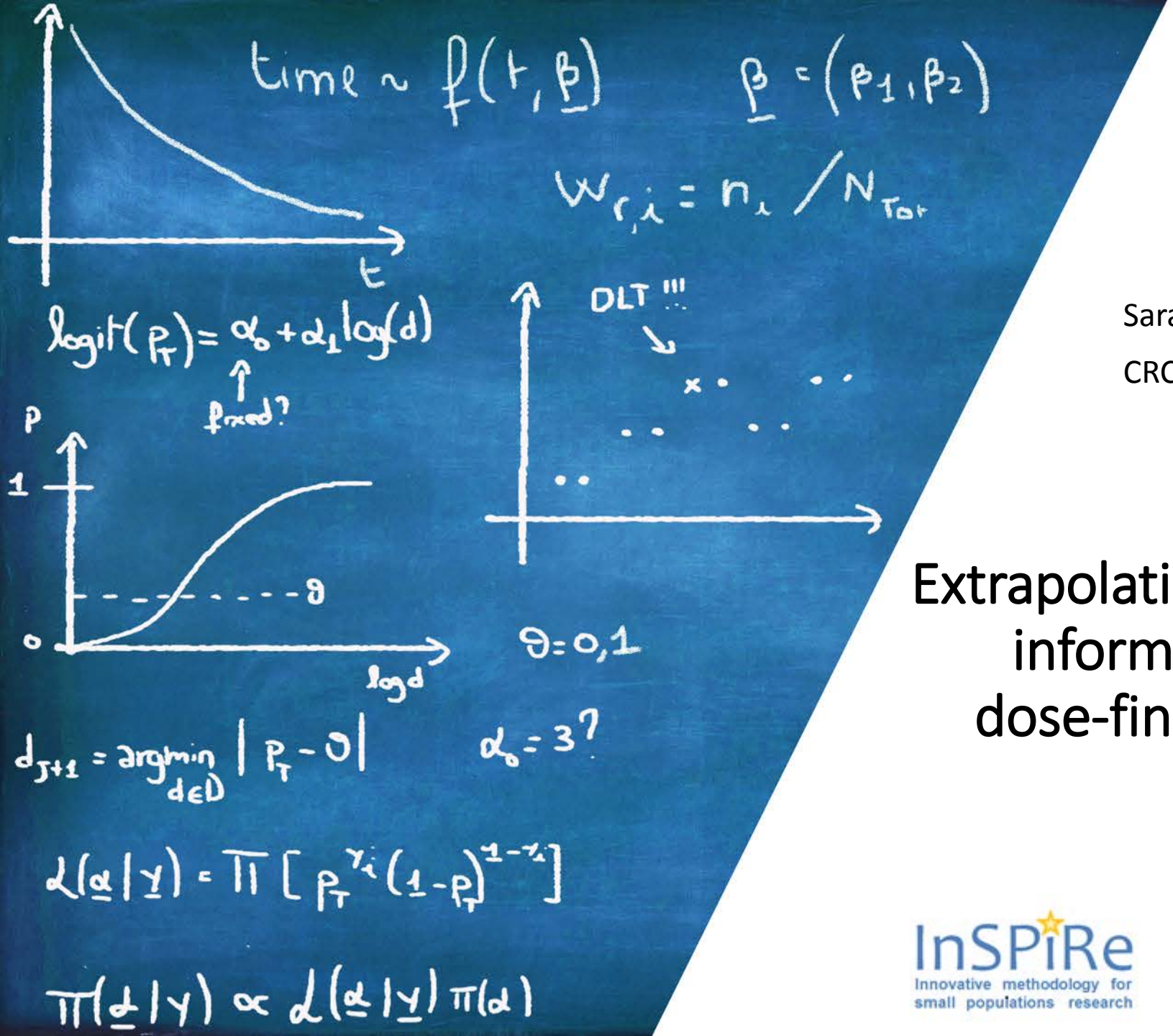

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Extrapolation and bridging of adult information in early-phase dose-finding pediatric studies

InSPiRe
Innovative methodology for small populations research

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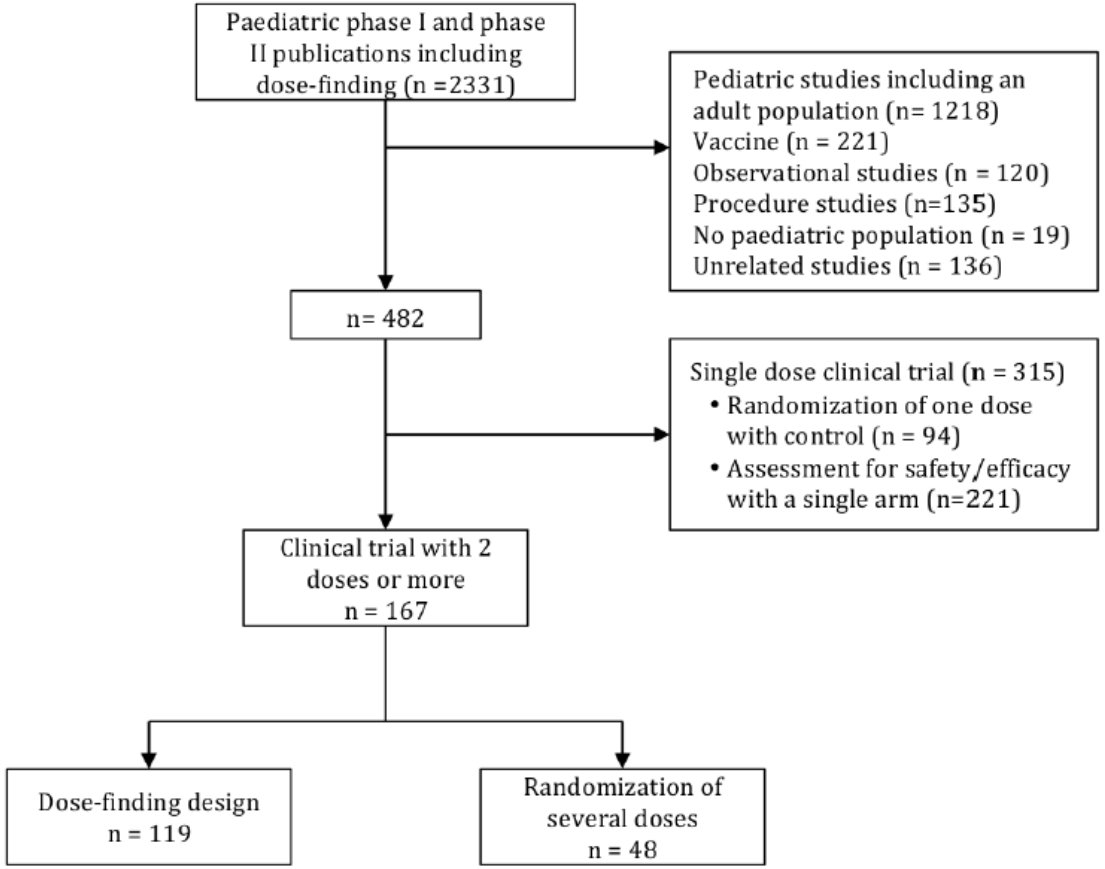
Clinical context – systematic review



How adult information is used in practice?

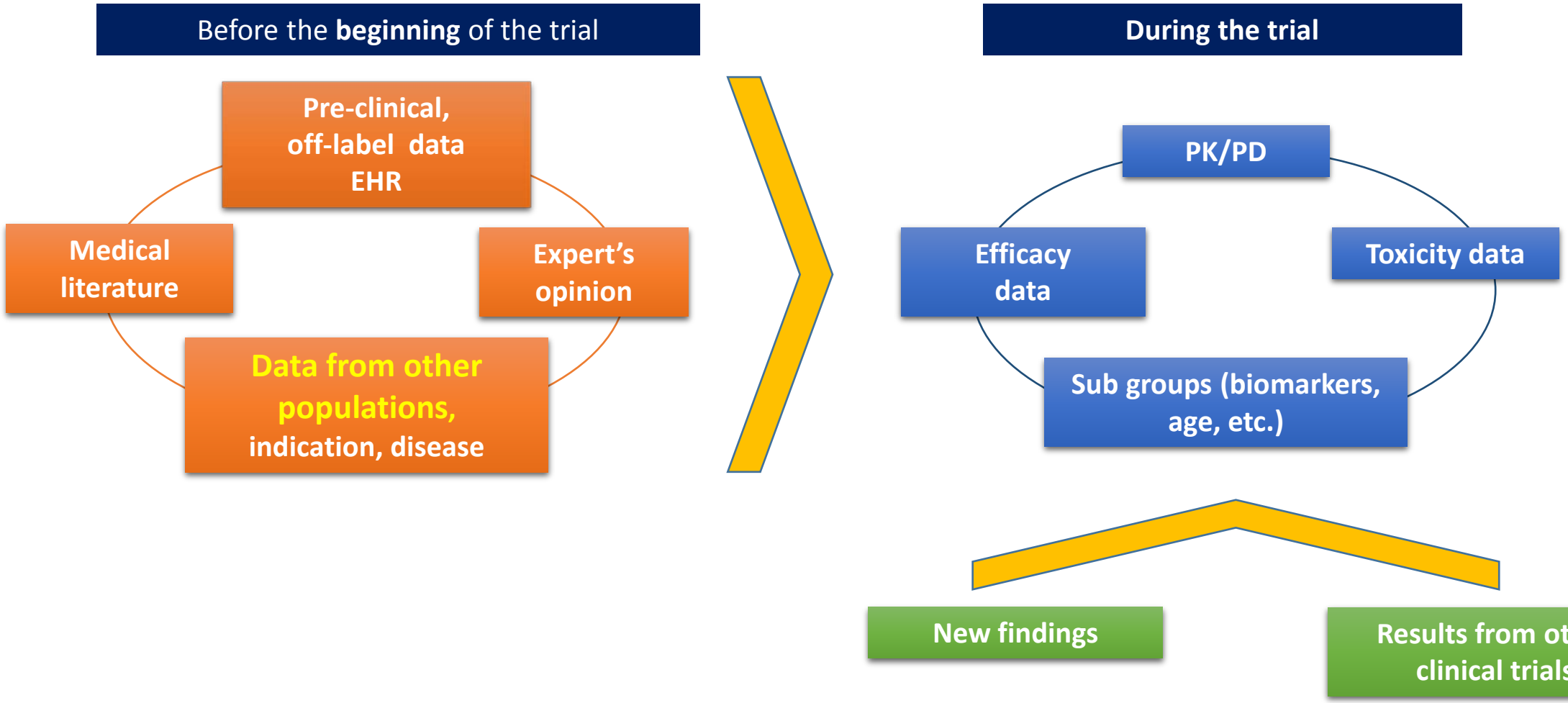
Number of publications with a dose justification	Dose-finding (n = 48)	Randomisation (n = 8)	Total (n = 56)
How are dose chosen ?			
Arbitrary choice			
From Safety: - of Adult	37 (77)	4 (50)	41 (73)
- of Children	11 (23)	2 (25)	13 (23)
- of Preclinic studies	1 (2)	2 (25)	3 (5)
From PK: - of Adult	2 (4)	1 (12.5)	3 (5)
- of Children	2 (4)	-	2 (3.5)
Modelling and simulation			
from Preclinic studies	1 (<1)	-	1 (<1)

ICH E11 - Revision

ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups).

Use of existing knowledge



Planning a pediatric dose-finding using adults information

Questions

- **How to take into account adults prior knowledge? How to down-weight this information?**
  - How to determine the dose range for the pediatrics setting?
  - How to determine the initial guessed dose-toxicity and dose-efficacy relationship?
    - Algorithm-based or model-based designs?
    - Frequentist or Bayesian inference?
  - What is the optimal dose? What are the targets according to age subgroups
  - Can the sampling number and time be optimized?

Illustration

Neuro-Oncology 13(1):109–118, 2011.
doi:10.1093/neuonc/noq141
Advance Access publication October 25, 2010

NEURO-ONCOLOGY

Innovative Therapies for Children with Cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors

Birgit Geoerger, Darren Hargrave, Fabienne Thomas, Anna Ndiaye, Didier Frappaz, Felipe Andreiuolo, Pascale Varlet, Isabelle Aerts, Riccardo Riccardi, Timothy Jaspan, Etienne Chatelut, Marie-Cecile Le Deley, Xavier Paoletti, Christian Saint-Rose, Pierre Leblond, Bruce Morland, Jean-Claude Gentet, Valérie Méresse, and Gilles Vassal, on behalf of the ITCC (Innovative Therapies for Children with Cancer) European Consortium

Use of adult knowledge:

- Starting dose was 80% of the MTD found in adults

Can we do better?

How to determine the dose range?

- Available data: PK model in adults
  - Assumption: similar AUC target
- Extrapolation[1,2]

$$d_{ch} = d_{ad} \times \underbrace{\left(\frac{BW_{ch}}{BW_{ad}}\right)^{0.75}}_{\text{Allometry}} \times \underbrace{K_{mat,ch}(AGE)}_{\text{Maturation}}$$

$K_{mat,ch}$ is a combination of several physiological process

- Illustration

Adults doses (mg)	100	150	200	250	300
Pediatric dose with maturation adjustment. Ex: 2-5 years old	30	45	55	70	85

1 West, G et al. Science 276 (April 1997), 122–126.
2 Anderson, B. et al. Eur. J. Pediatr. 165 (2006), 819–829.

How to determine the initial guessed dose-toxicity and dose-efficacy relationship?

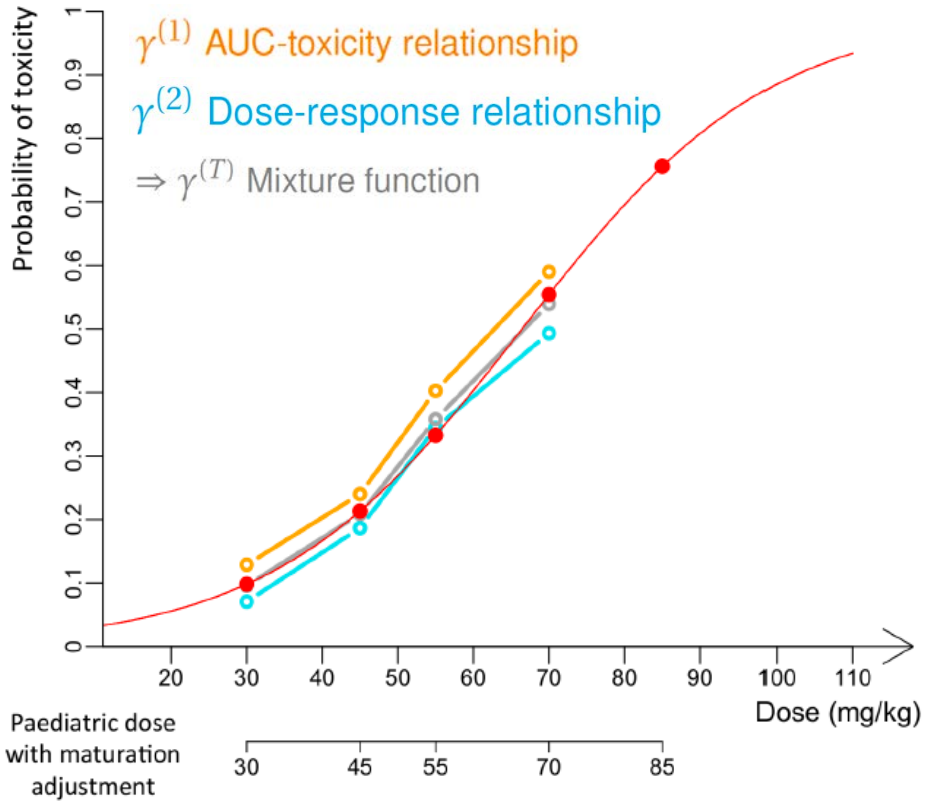
- Available data (i): AUC-toxicity relationship in adults[1]

Adult doses (mg)	100 mg	150 mg	200 mg	250 mg
$AUC = d/Cl_{ad}$	25.3	37.9	50.6	63.3
Probability of toxicity $\gamma^{(1)}$	0.13	0.24	0.40	0.60

- Available data (ii): Early phase trials toxicity observations in adults[2]

Publication	Number of toxicity (Number of patient)			
	100 mg	150 mg	200 mg	250 mg
Prados *et al.*	0 (3)	1 (3)	0 (3)	3 (6)
Raizer *et al.*	-	11 (99)	-	-
Thepot *et al.*	0 (5)	3 (25)	-	-
Calvo *et al.*	-	1 (25)	-	-
Van den Bent *et al.*	-	-	6 (54)	-
Sheikh *et al*	-	167 (307)	-	-
Essai ROCHE	-	11 (59)	-	-

Adult doses (mg)	100 mg	150 mg	200 mg	250 mg
Probability of toxicity $\gamma^{(2)}$	0.07	0.19	0.34	0.49



Adults doses (mg)	100	150	200	250	300
Pediatric dose with maturation adjustment	30	45	55	70	85
Probability of toxicity	0.1	0.21	0.33	0.55	0.76

1 Thomas, F. et al., Eur J Cancer 45 (2009), 2316–23
2 Zohar, S., Katsahian, S., and O'Quigley, J., Stat. Med. 30 (2011), 2109–2116

Under Bayesian inference : How to incorporate information into the dose-finding model parameters prior?

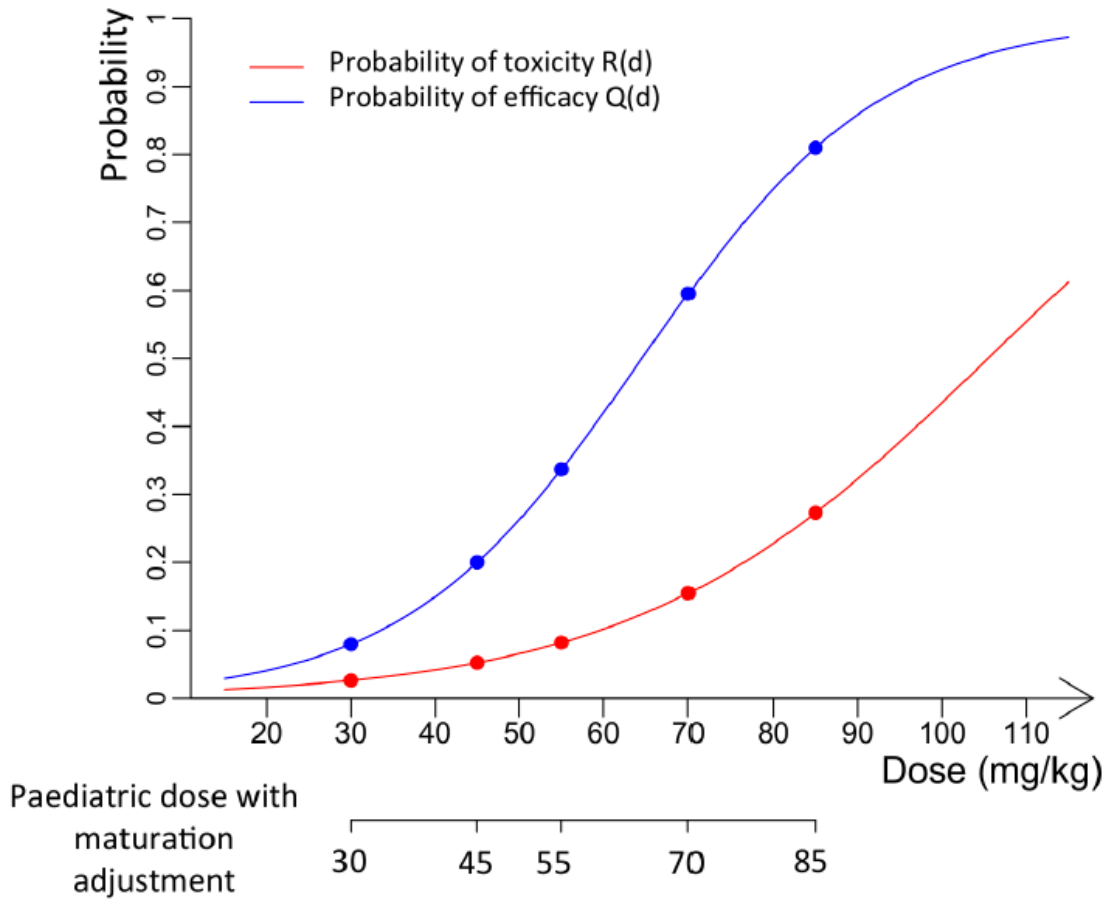
Available data: Early phase trials toxicity observations in adults

Toxicity :

$$R(d_k) = \mathbb{P}(Y = 1 | d_k)$$
$$R(d_k) = \psi(d_k, \boldsymbol{a})$$

Efficacy :

$$Q(d_k) = \mathbb{P}(Z = 1 | Y = 0, d_k)$$
$$Q(d_k) = \phi(d_k, \boldsymbol{b})$$



Construction of the prior distribution:

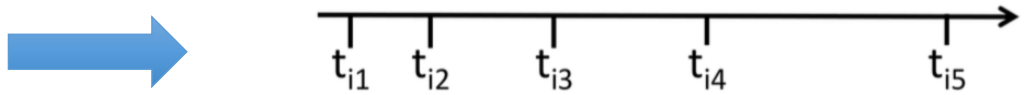
- In terms of the effective sample size[1]. More informative a prior is, more patients are needed to compensate for it.
- If the chosen prior is too informative or misspecified ->introducing the concept of 'adaptive-prior'[2] (switch during the trial to a less informative prior)

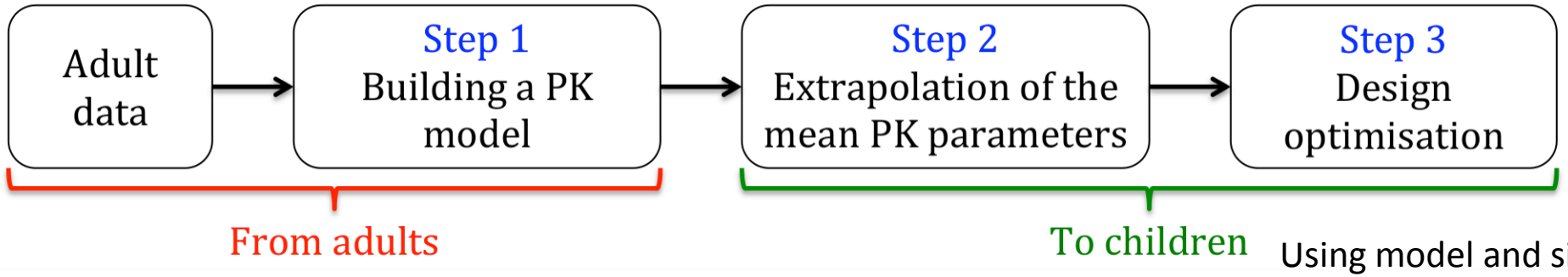
2 Morita, S., Thall, P., and Müller, P., Biometrics 64 (June 2008), 595–602.
1 Zhang, J., Braun, T., and Taylor, J., Stat. Med. 32 (2013), 2221–34.

How to optimize the sampling time?

- Available data: PK measures in adults

- Pediatrics PK sampling can be associated with some constraints





Using model and simulation approach for optimization according to each pediatric sub group of age

Conclusions and discussion

- Several tools and methods have been proposed for extrapolation in early phase dose-finding trials.
- From our simulation study the methods seems robust.
- More extrapolation should be used when planning clinical trials in pediatrics.

References

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- Petit C, Jullien V, Samson A, Guedj J, Kiechel JR, Zohar S, Comets E**. Designing a Pediatric Study for an Antimalarial Drug by Using Information from Adults**. Antimicrob Agents Chemother. 2015 Dec 28;60(3):1481-91.

- R package « dfped » should be realeased end of April 2017

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