Limited sampling strategy for population pharmacokinetic modelling of a cocktail of phenotyping drugs

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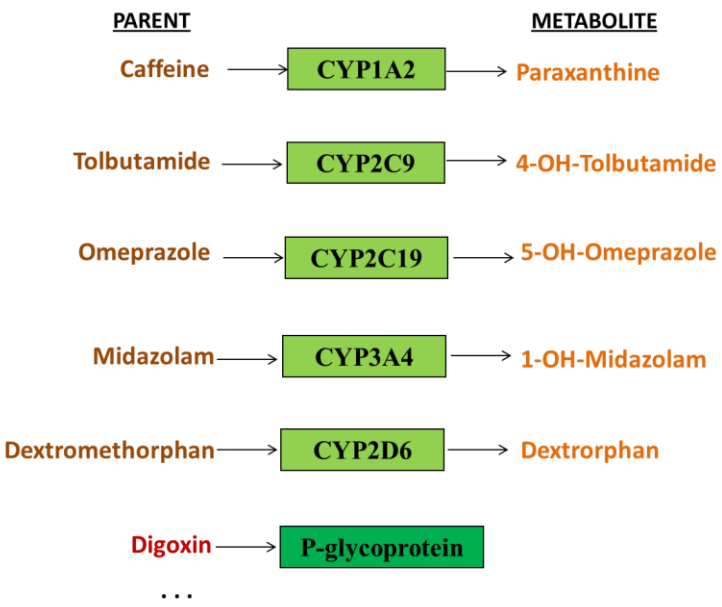
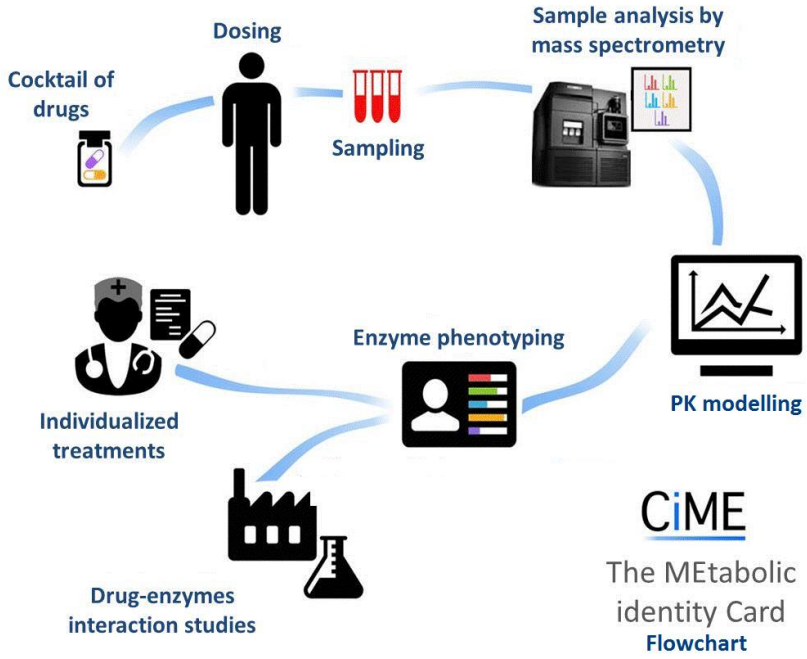
Cocktail approach (1)

Cocktail of phenotyping drugs: to determine activity of enzymes and transporters responsible for drug metabolism and pharmacokinetics (PK) [1]

CIME (MEtabolic Identity Card) project: to develop a phenotype test in clinical routine, including a pharmaceutical formulation for the drug cocktail [2]





Pilot phase 1 study CIME1 in healthy volunteers: showing the safety of the cocktail [2]

[1] Fuhr et al. *Clin. Pharmacol. Ther.*, 2007.

[2] Lenuzza et al. *Eur. J .Drug Metab. Ph.*, 2016.

Cocktail approach (2)

Phenotyping indexes (PI) to assess metabolizer status

- AUC of substrates or ratio AUC substrate/AUC metabolite [1,2]
- Derived from a few samples using nonlinear mixed effect models (NLMEM)
    - population parameter estimation by likelihood maximization
    - individual parameters obtained by Bayesian estimation

Future cocktail studies with sparse design

- Limited number of samples/subject
- Identical sampling times for substrate and metabolite concentration measurements
- Flexible sampling times

⇒ **Importance of choice of study design on the precision of parameter estimates**

[1] EMA. *Guideline on the Investigation of Drug Interactions*, 2012.
[2] Zadoyan et al. *Eur J Clin Pharmacol*, 2012.

Optimisation of population design in cocktail studies

To optimize joint design for several drugs = to find a compromise between informative sampling times that best characterize each drug's kinetic

- Use of the population Fisher information matrix (M_{PF}) [1]: good alternative to clinical trial simulation (CTS)
- Multi-response model approach: implemented in several software programs [2], enables selection of joint optimal times for several co-administered drugs
- Compound optimality [3] approach: weighting models of several drugs, balance between different targets in phenotyping test
- These approaches require *a priori* knowledge of models and their parameters

[1] Mentré et al. *Biometrika,* 1997.
[2] Nyberg et al. *Br J Clin Pharmacol*, 2014.
[3] Atkinson. *J. Stat. Plan. Inference*, 2008.

Objectives

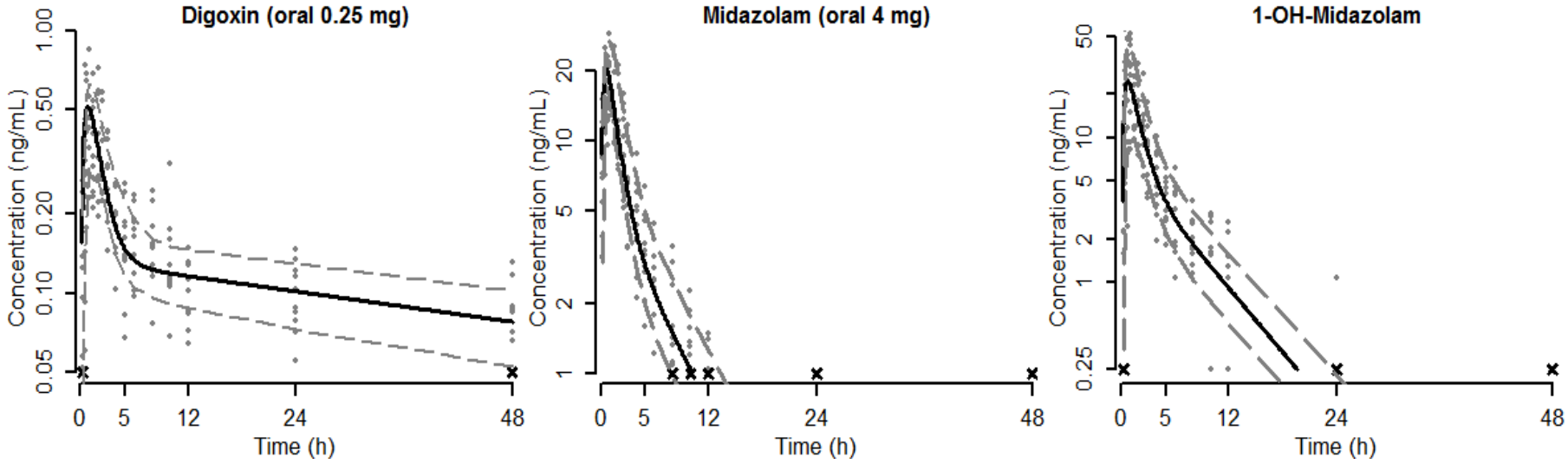
To propose a limited sampling strategy for a phenotyping study with two molecules of the CIME cocktail

- Digoxin (probe for P-glycoprotein)
- Midazolam and its metabolite 1-OH-midazolam (probe for CYP3A activity)

1. **Analysis of data from the pilot study CIME1**
2. **Optimization of joint sampling times**
3. **Computation of sampling windows for more flexibility in experiments**

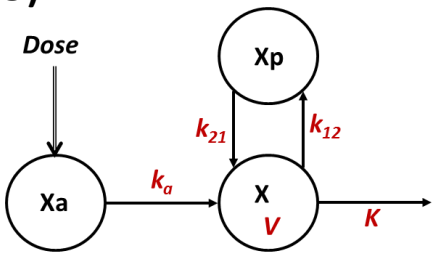
Population PK modelling of CIME1 study

Data: 10 healthy volunteers, rich PK profiles with 16 samples [0-48h]/subject

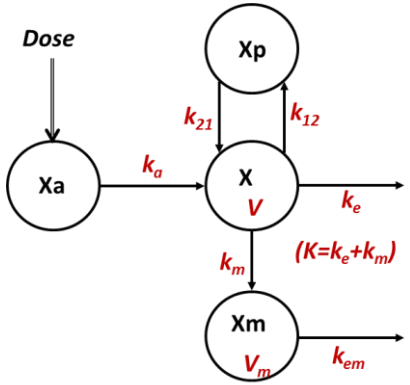


Population analysis: using MONOLIX 4.2.2 [1]

Digoxin (DIGO):



Midazolam (MDZ):



Phenotyping indexes (PI)

Digoxin: AUC

Midazolam: Ratio AUC parent/metabolite

[1] www.lixoft.eu

Optimisation of joint sampling times – Methods (1)

Optimality criteria

Identical elementary design ξ= $(t_1,\ldots, t_n)$ in all subjects

- **D-optimal design for drug *m***

$$\xi_m^D = \underset{\xi}{Arg\max} \det\left(\mathbf{M}_{PF}(\Psi_m, \xi)\right)^{1/P_m}$$

Ψ_m = population parameters of each drug *m*

P_m = length(Ψ_m)

- **D-optimal multi-response (MR) design for M drugs**

$$\xi_{MR}^D = \underset{\xi}{Arg\max} \prod_{m=1}^{M} \det\left(\mathbf{M}_{PF}(\Psi_m, \xi)\right)^{1/P} = \underset{\xi}{Arg\max} \sum_{m=1}^{M} \frac{1}{P} \log\left(\det\left(\mathbf{M}_{PF}(\Psi_m, \xi)\right)\right)$$

$P = \Sigma_m P_m$

- **D-optimal compound design** [1]

$$\xi^{CD} = \underset{\xi}{Arg\max} \prod_{m=1}^{M} \left(\frac{\det(M_{PF}(\Psi_m, \xi))^{1/P_m}}{\det(M_{PF}(\Psi_m, \xi_m{}^D))^{1/P_m}} \right)^{\alpha_m} = \underset{\xi}{Arg\max} \sum_{m=1}^{M} \frac{\alpha_m}{P_m} \log\left(\det\left(\mathbf{M}_{PF}(\Psi_m, \xi)\right)\right)$$

weight α_m quantifies the balance between different models

$$\sum_{m=1}^{M} \alpha_m = 1$$

$\Rightarrow$ $\xi^{CD} = \xi_m{}^D$ when $\alpha_m = 1$ and $\xi^{CD} = \xi_{MR}{}^D$ when $\alpha_m = P_m/P$

[1] Atkinson. *J. Stat. Plan. Inference*, 2008.

Optimisation of joint sampling times – Methods (2)

Application to design a cocktail study with 2 molecules

- Based on CIME1 models and parameters: $P_{Digoxin} = 9$, $P_{Midazolam} = 16$, $P = 25$
- N = 40 subjects, sparse design of n = 6 or 5 samples/subject (chosen in CIME1 design)
- **Using PFIM 4.0** [1]
  - ξ_m^D for each drug
  - ξ_{MR}^D for both drugs jointly using a three-response model
- **Using the compound criterion approach implemented in R based on PFIM code**
  - ξ^{CD} for several values of $\alpha_{digoxin} = \{0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1\}$

    ($\xi^{CD} = \xi_{MR}^D$ for $\alpha_{digoxin} = 9/25 \approx 0.36$)

[1] www.pfim.biostat.fr

Optimisation of joint sampling times – Methods (3)

Prediction with each design

- Efficiency for estimation of population parameters

$$Eff_m(\xi) = \frac{\det(M_{PF}(\Psi_m, \xi))^{1/P_m}}{\det(M_{PF}(\Psi_m, \xi_m^{\ D}))^{1/P_m}}$$

- Relative standard errors (RSE) of phenotyping indexes (PI)

⇒ **Choice of a common design ξ* with efficiency > 90% and RSE(PI) < 30% for both drugs**

Evaluation of ξ* by CTS

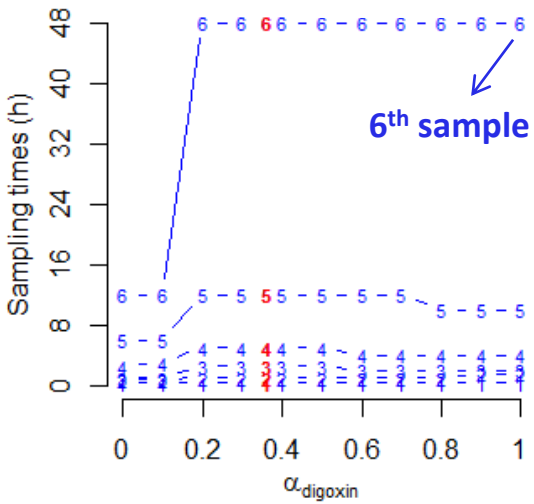
- **Simulation**: 200 datasets of 40 subjects with ξ*, analysed by MONOLIX 4.2.2 [1]
- **Comparision** SE_{CTS} = standard deviation of population estimates vs $SE_{PRED} = \sqrt{diag(M_{PF}^{-1})}$

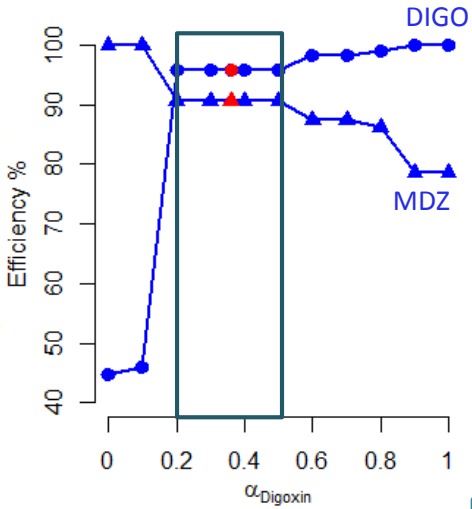
[1] www.lixoft.eu

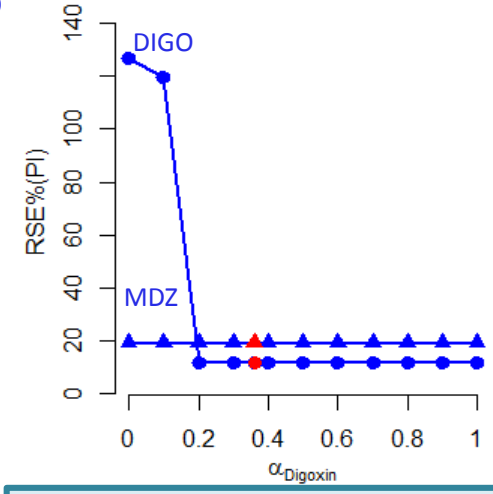
Optimisation of joint sampling times – Results (1)

Optimal times allocation | **Efficiency** | **PI RSE**

n = 6

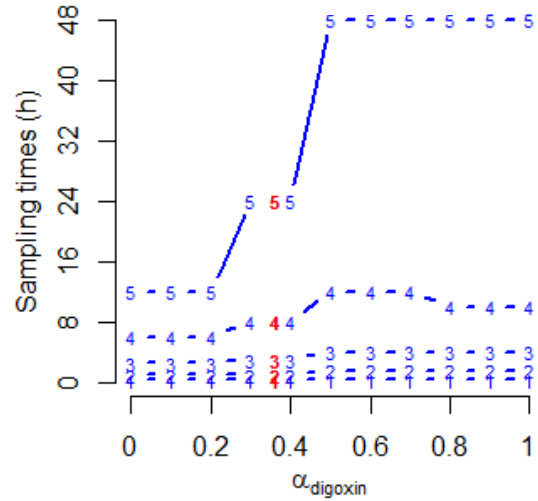


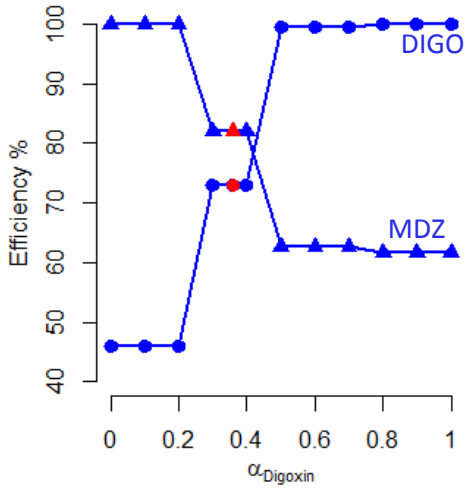


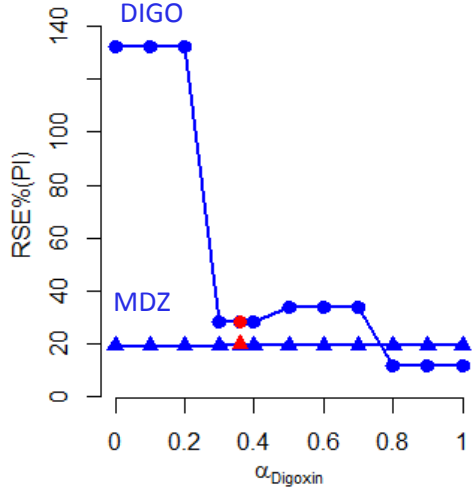


$\xi^* = \xi_{MR}{}^{D} = (0.25, 1, 2.5, 5, 12, 48h)$

n = 5

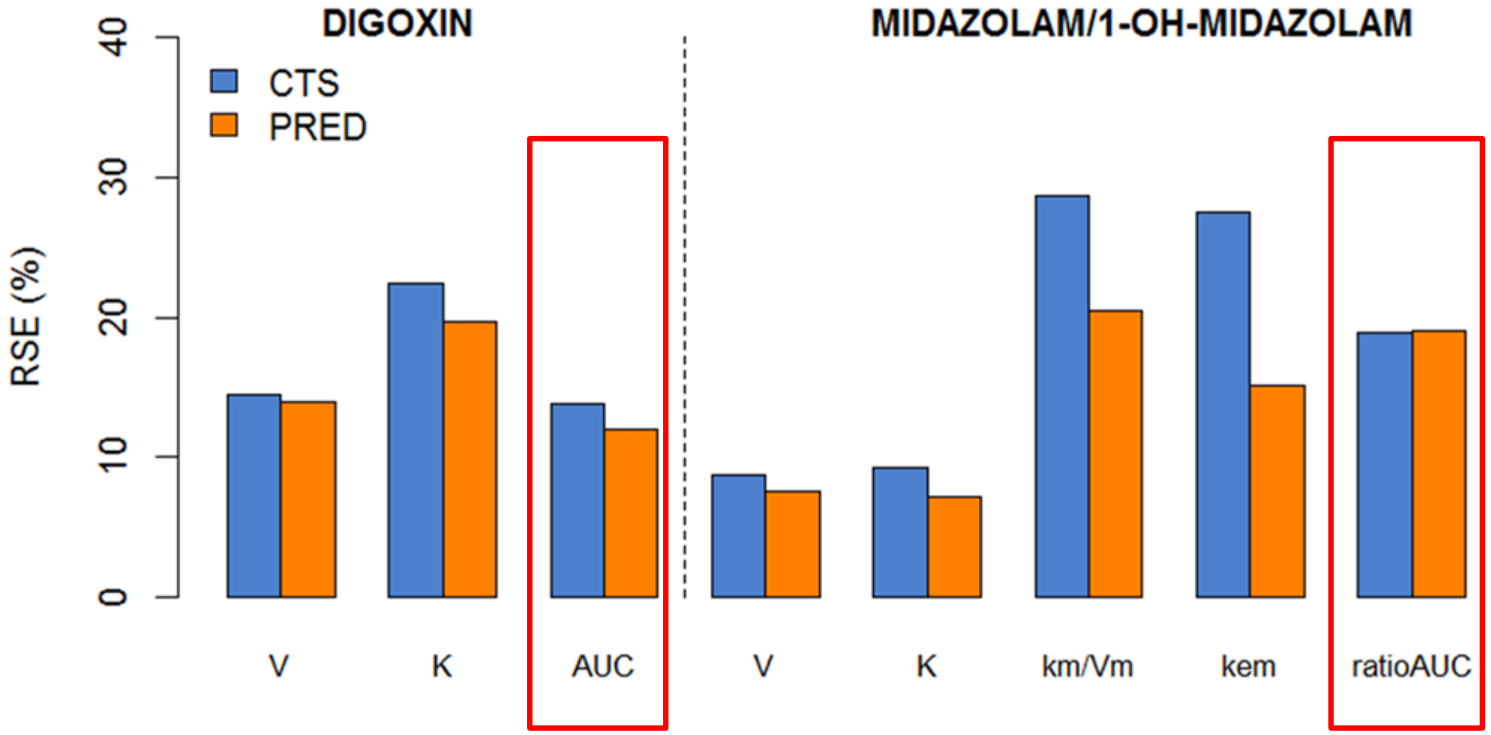






Optimisation of joint sampling times – Results (2)

Relative standard errors obtained by CTS vs predictions by M_{PF}



Sampling windows

Computation of population window design ξ^W

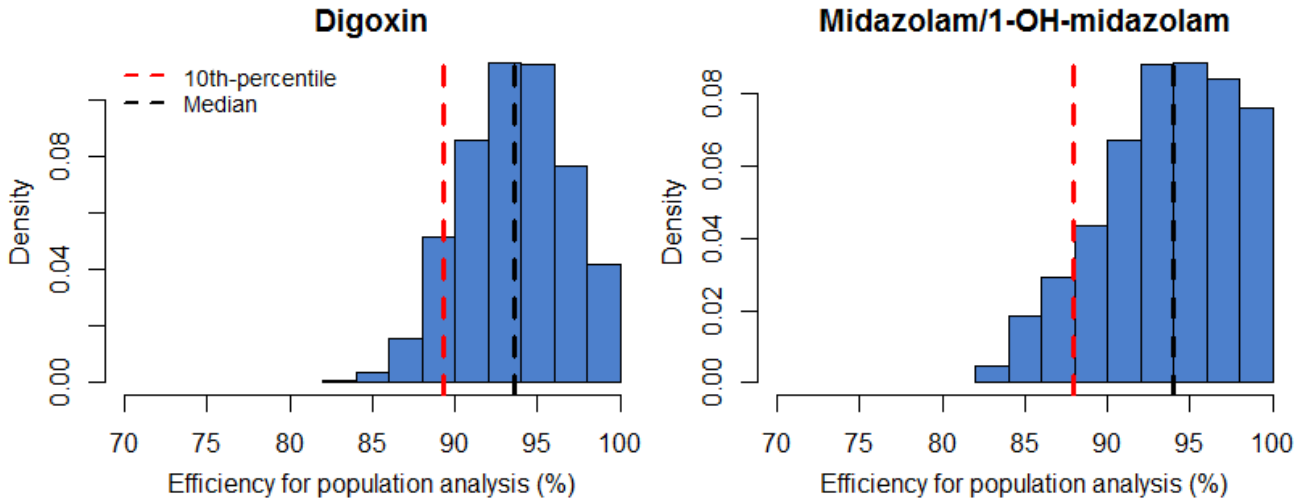
1. Recursive random sampling [1] to obtain time intervals around each optimal time of ξ^*
2. Evaluating the joint efficiency of the window design by Monte-Carlo simulation and adjustment/reduction of the length of all time intervals simultaneously [2]

$\Rightarrow$ ensuring an expected loss of efficiency below 10% for each molecule

ξ^W	0.19-0.40	0.92-1.48	2.38-3.48	4.51-7.94	9.93-27.04	43.21-48

Satisfactory expected efficiency of ξ^W for population analysis

Expected efficiency of 1000 designs generated within ξ^W



[1] Foo et al. *Pharm. Stat.*, 2012.

[2] Ogungbenro and Aarons. *J. Biopharm. Stat.*, 2009.

Discussion

- By combining NLMEM, compound design and sampling windows based on the **population Fisher information matrix**, we were able to determine sparse and flexible samples allowing correct estimation of PK parameters for two drugs [1]
  - **Compound criterion**: taking into account the importance accorded to each target in phenotyping test
  - **Sampling windows**: compromise between the allocation of informative times and clinical constraints

⇒ Relevant approach to efficiently optimize population design for cocktail studies including more drugs [2]

- Using the **Bayesian information matrix** implemented in PFIM 4.0 [3]: optimal design for Bayesian estimation of individual parameters in a five-probe cocktail study [4]

- Other criteria (Ds-optimality or C-optimality) could be used to accommodate situations in which only a subset of the model parameters or its linear combination is of interest

[1] Nguyen et al. *Pharm. Stat.,* 2016.
[2] Lenuzza et al. *Eur. J .Drug Metab. Ph.*, 2016.
[3] Combes et al. *Pharm. Res.,* 2012.
[4] Nguyen et al. *Eur. J. Clin. Pharmacol.,* 2016.

Thank you for your attention !