Application of optimal design methodologies in clinical pharmacology experiments

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MAIN PAPER

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Pharmacokinetics and pharmacodynamics data are often analysed by mixed-effects modelling techniques (also known as population analysis), which has become a standard tool in the

Introduction

- Clinical pharmacology experiments often involves investigation into the PK and PD of drugs

- The use of modelling in drug development has increased considerably in the last decade
  - Model-based drug development (MBDD)

- Drug development is considered a continuous process (so is modelling), knowledge about PK and PD is updated with information from new studies

- Mixed effects modelling (population approach) has become standard tool in the analysis of PK and PD data
  - Sparse data, varying sampling times between subjects, incomplete and missing data, investigation using simulations

Population PK study design

- Population PK study design is a group of **elementary designs** each composed of a set of **sampling times** to be performed in a **group of subjects**

- Population PK design factors
  - Number of groups (elementary designs)
  - Number of subjects in each elementary design
  - Number of sampling times in each elementary design
  - Sampling times within the design region

- Optimal population PK study design - careful balance of design factors

Optimal population PK study design

- Simulation - cumbersome and time consuming

- Model - Cramer-Rao inequality, inverse of the FIM is the lower bound of the variance-covariance matrix of any unbiased estimator of the parameters
  - Involves using prior information about parameter/variability
  - Optimise some criterion function of the likelihood with given constraints e.g. D-optimality: minimise uncertainty associated with parameter estimates

- Software – PopDes, PFIMOPT (PFIM), PopED, POPT, PkStaMP

Population Fisher information matrix (PFIM)

The Model

$$y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij} \qquad i = 1,\ldots,N \qquad j = 1,\ldots,n_i$$

$$\theta_i = \theta + b_i \qquad b_i \sim N(0,\Omega) \qquad \varepsilon_{ij} \sim N(0, \sigma_{add}^2 + \sigma_{prop}^2(f(\theta_i, t_{ij})))$$

$$\Psi = [\theta_1,\ldots,\theta_p, \omega_{11},\ldots,\omega_{pp}, \sigma_{add}^2, \sigma_{prop}^2]$$

FIM

$$F(\Psi, \xi_i) = -E\left(\frac{\partial^2 L(\Psi; y_i)}{\partial \Psi \partial \Psi^T}\right)$$

$$F(\Psi, \Xi) = \sum_{i=1}^{N} F(\Psi, \xi_i) = \begin{pmatrix} A(\Psi, \xi_i) & C(\Psi, \xi_i) \\ C(\Psi, \xi_i) & B(\Psi, \xi_i) \end{pmatrix}$$

PFIM

$$F(\Psi, \Xi) = \sum_{q=1}^{Q} N_q \cdot F(\Psi, \xi_q)$$

Optimisation of PFIM

- Gives best parameter estimates
  - High precision and low bias

  D-Optimal design

  $$\Xi_D = \arg\left[\max_{\Xi \in \chi} \left| F(\Psi, \Xi) \right| \right]$$

- Exact design
  - Optimise ξ_q (n_q, Q and N_q are fixed)
  - Optimisers - Fedorov exchange, simplex, simulated annealing, etc

- Continuous or statistical or approximate design
  - Optimise ξ_q, n_q, Q and N_q
  - Optimisers - First order, simplex, Fedorov-Wynn etc

Sampling windows

- Sample collection at specific time points may not be feasible – less informative
  - Delays in seeing medical personnel
  - Patients may have taken the drug before arrival at the clinic
  - Need for more immediate medical procedure
  - Un-cooperative patients (children)

- Sampling windows – sampling within pre-defined time interval
  - Allows control of sampling times, gives flexibility and informative data

Optimal sampling windows

- Stage 1 – Fixed time optimisation

$$\Xi^D = \left\{ \begin{array}{c} \xi^D \\ N \end{array} \right\} \qquad \Xi^D = \left[t_1^D, ..., t_n^D \right]$$

- Stage 2 – Optimisation of marginal (conditional) sampling windows

$$\Xi^W = \left\{ \begin{array}{c} t_1^U, ..., t_n^U \\ t_1^L, ..., t_n^L \end{array} \right\} \qquad t_j^U = t_j^D + \delta_j \qquad t_j^L = t_j^D - \delta_j$$

$$\delta_j = arg \left\{ \min_{\delta \in \Delta} \left[\left(eff_D(\Psi, \Xi_j^W(\delta_j)) - eff_0 \right)^2 \right] \right\}$$

- Stage 3 – Evaluate joint efficiency and adjust sampling window lengths

$$eff_D(\Psi, \Xi^W(\Delta)) = \frac{E\left[\left| F(\Psi, \Xi^W(\Delta)) \right|^{1/\dim(\Psi)} \right]}{\left| F(\Psi, \Xi^D) \right|^{1/\dim(\Psi)}}$$

Optimisation of sampling windows
Ogungbenro and Aarons (2009), JPP 35: 465-482

- Define candidate sampling windows instead of fixed sampling time
  - Taking practical and ethical constraints into consideration

FIM

$$W_i = \left[w_{i1}, ..., w_{in_i} \right] = \left[\begin{pmatrix} a_{i1} \\ b_{i1} \end{pmatrix}, ..., \begin{pmatrix} a_{in_i} \\ b_{in_i} \end{pmatrix} \right]$$

$$E\left[F(\Psi, \xi_i^w) \right] = \int_{a_{in_i}}^{b_{in_i}} ... \int_{a_{i1}}^{b_{i1}} F(\Psi, \xi_i^w) U(a_{i1}, b_{i1}) ... U(a_{in_i}, b_{in_i}) dt_{i1}^w ... dt_{in_i}^w \approx \frac{1}{H} \sum_{h=1}^{H} F(\Psi, \xi_i^{w(h)})$$

PFIM

$$\Xi^w = \left\{ W_q, p_q \right\} = \left[\begin{pmatrix} W_1 \\ p_1 \end{pmatrix}, ..., \begin{pmatrix} W_Q \\ p_Q \end{pmatrix} \right]$$

$$F(\Psi, \Xi^w) = \sum_{q=1}^{Q} N_q E\left[F(\Psi, \xi_q^w) \right]$$

Optimisation of sampling windows
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Equivalence theorem

$$\psi(W_x, \Psi, \Xi^{w(D)}) = tr\left(F(\Psi, W_x)\left[F_N(\Psi, \Xi^{w(D)})\right]^{-1}\right) \leq \dim(\Psi)$$

Equivalence theorem - sensitivity
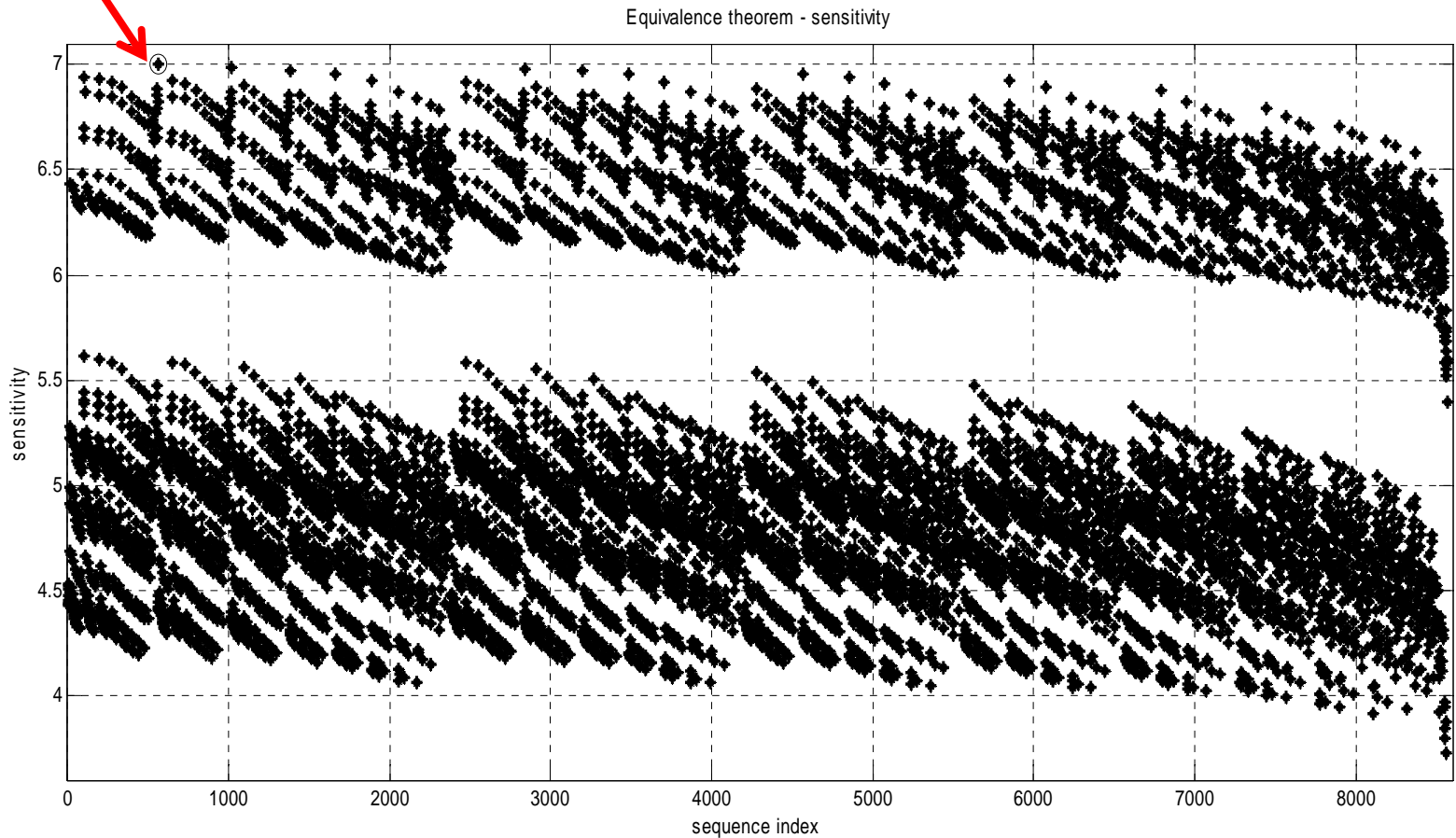
Areas of application of optimal design – clinical drug development

- Preclinical and Phase 1 trials – limited use (dense sampling)
  - Learning stage

- Phase II and Phase III – useful to increase the information content of the data
  - Constraints – clinic opening times, feeding times, sleeping time, number of time points
  - Cost – useful to balance recruitment and increasing number of time points (hospital visits)

Example 1

Optimal Blood Sampling Time Windows for Parameter Estimation Using a Population Approach: Design of a Phase II Clinical Trial

Marylore Chenel,[1] Kayode Ogungbenro,[2] Vincent Duval,[3] Christian Laveille,[3] Roeline Jochemsen,[3] and Leon Aarons[1,*]

The objective of this paper is to determine optimal blood sampling time windows for the estimation of pharmacokinetic (PK) parameters by a population approach within the clinical
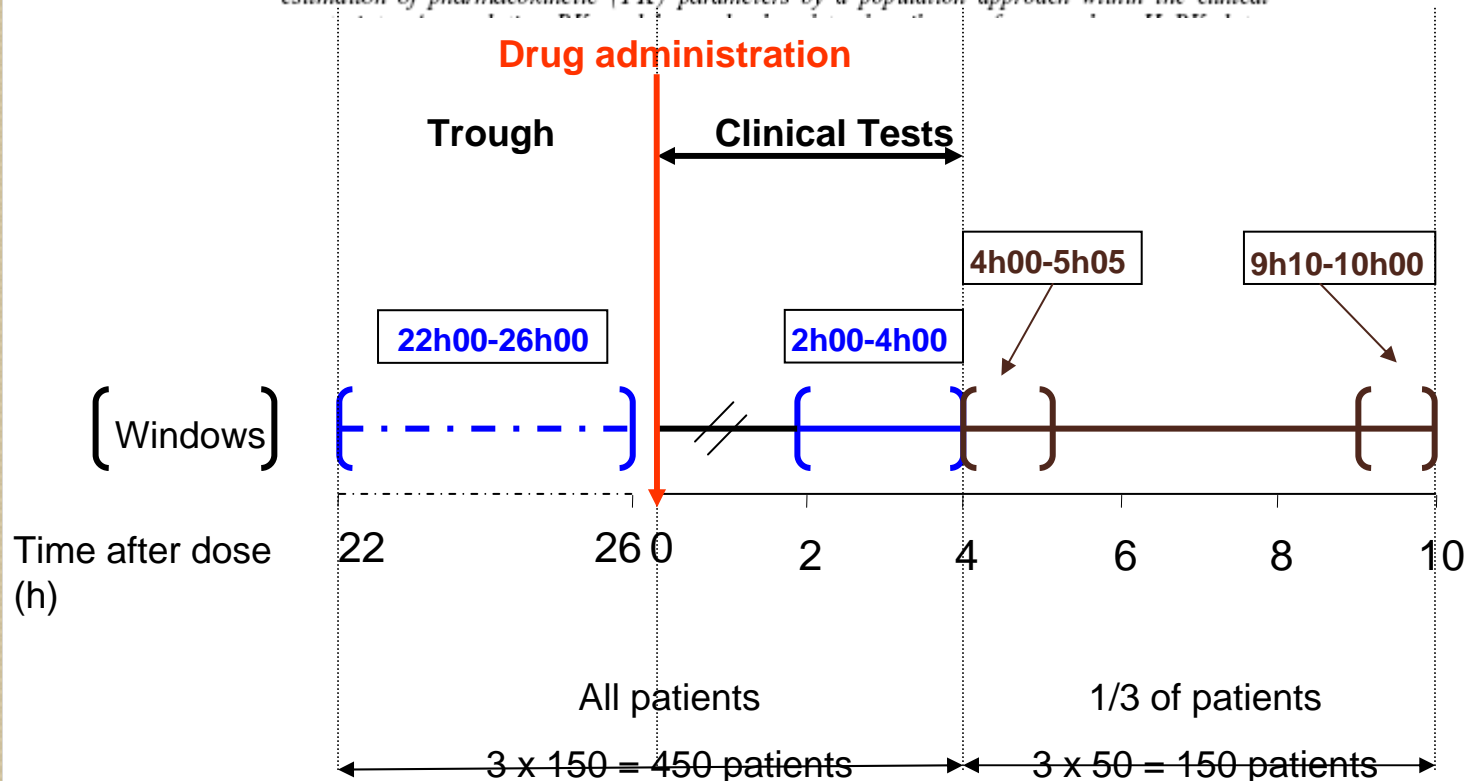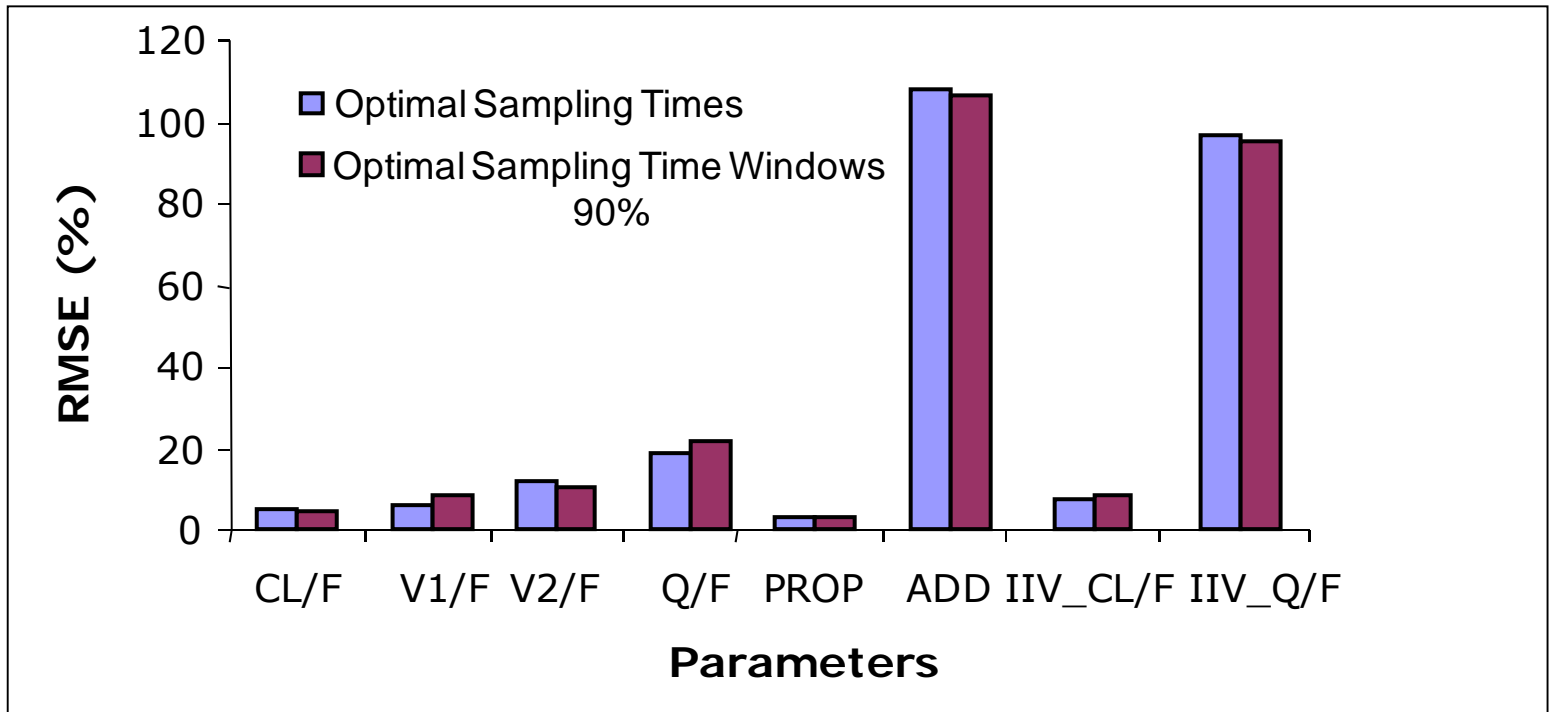
Drug administration

Trough   **Clinical Tests**

4h00-5h05   **9h10-10h00**

22h00-26h00   **2h00-4h00**

Windows

Time after dose (h)   22   26 0   2   4   6   8   10

All patients   1/3 of patients

3 x 150 = 450 patients   3 x 50 = 150 patients

12

Example 1

Example 2

Drug–drug interaction predictions with PBPK models and optimal multiresponse sampling time designs: application to midazolam and a phase I compound. Part 1: comparison of uniresponse and multiresponse designs using PopDes

Marylore Chenel · François Bouzom · Kayode Ogungbenro

Abstract *Purpose* To determine the ...
interaction (DDI) study for the estima...
co-administered drugs (SX, a phase I ...

Drug–drug interaction predictions with PBPK models and optimal multiresponse sampling time designs: application to midazolam and a phase I compound. Part 2: clinical trial results

Marylore Chenel · François Bouzom · Fanny Cazade · Kayode Ogungbenro · Leon Aarons · France Mentré

Abstract *Purpose* To compare results of population PK analyses obtained with a full empirical design (FD) and an optimal sparse design (MD) in a Drug–Drug Interaction (DDI) study aiming to evaluate the potential CYP3A4 inhibitory effect

Areas of application of optimal design – population paediatric studies

- Special application of population pharmacokinetics and optimal design methodologies – practical and ethical constraints
  - Limited number of samples and sample volumes
  - Unbalanced designs

- Optimal design methodologies allow sampling from the most 'information rich' areas of the drug concentration-time profile
  - Optimal use of resources – balance sample size and sampling times
  - Incorporate design constraints into the optimisation

Example 1

Population pharmacokinetics and optimal design of paediatric studies for famciclovir

Kayode Ogungbenro, Ivan Matthews,[2] Michael Looby,[1] Guenther Kaiser,[1] Gordon Graham[2] & Leon Aarons[3]

Centre for Applied Pharmacokinetics Research, [3]School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, [2]Pfizer Limited, Sandwich, UK and [1]Novartis Pharma AG, Basel, Switzerland

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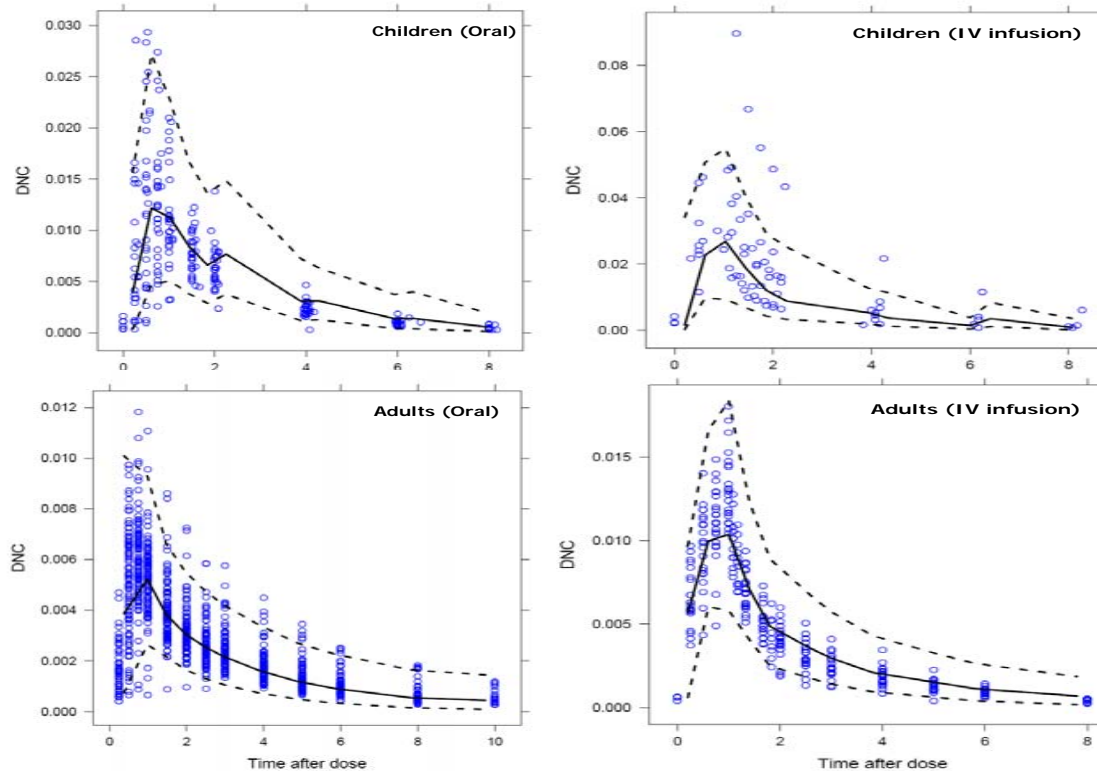
Example 1

Sampling Properties	Sample Number	Age Groups		
		1 - 2 yr	2 - 5 yr	5 - 12 yr
Optimal Sampling Times (hr)	1	0.25	0.25	0.25
	2	0.70	0.70	0.85
	3	1.35	1.30	1.00
	4	3.05	3.00	2.80
	5	8.00	8.00	8.00
Normalised Determinant		3.32	3.42	3.57
Optimal Sampling Windows (hr)	1	0.25 - 0.28	0.25 - 0.28	0.25 - 0.27
	2	0.58 - 0.82	0.58 - 0.82	0.62 - 1.08
	3	0.70 - 2.00	0.66 - 1.94	0.26 - 1.73
	4	2.47 - 3.63	2.48 - 3.52	2.61 - 2.99
	5	7.45 - 8.00	7.48 - 8.00	7.78 - 8.00
Normalised Determinant		3.15	3.25	3.38
Efficiency		0.95	0.95	0.95

0.25-0.4, 0.5-1, 1.25-1.75, 2.75-3.5, 7.25-8 hr (Efficiency=85%)

Example 2

Population Pharmacokinetic Analysis and Optimization of the Experimental Design for Mizolastine Solution in Children

France Mentré,[1,3] Catherine Dubruc,[2] and Jean-Paul Thénot[2]

Mizolastine is a second generation antihistamine agent approved in Europe for the treatment of allergic rhinitis and skin conditions for which Sanofi~Synthélabo is developing a pediatric solution. Our objective was to design the population pharmacokinetic (PK) study of mizolastine pediatric solution in children. A bioavailability study of this solution compared to the marketed tablet was performed in 18 young volunteers. These PK data were analyzed by nonlinear regression using a

Table II. Comparison of Optimal Population Designs Involving 60 Samples, with at Most $n = $ 5, 4, 3, 2, or 1 Samples per Child[a]

n	Population design	N_{tot}	$Cri^{1/20}$	$1/e$	n_{eq}
10^{b}	10 (0.25, 0.5, 0.75, 2, 3, 6, 8, 12, 24, 36)	6	9.66	1	60
5	8(0.5, 0.75, 2, 8, 36) + 4 (0.5, 0.75, 3, 8, 36)	12	12.15	0.79	48
5^{c}	12 (0.5, 0.75, 2, 8, 36)	12	9.93	0.97	58
4	4 (0.25, 0.5, 0.75, 3) + 3 (0.25, 0.5, 0.75, 6) + 3 (0.25, 0.5, 2, 8) + 3 (0.5, 0.75, 2, 8) + 2 (0.25, 0.75, 2, 8)	15	5.52	1.75	105
3	4 (0.5, 2, 8) + 3 (0.25, 0.5, 0.75) + 3 (0.25, 0.75, 6) + 2 (0.75, 2, 8) + 2 (0.25, 0.5, 3) + 2 (0.25, 0.75, 2) + 2 (0.5, 0.75, 4) + 1 (0.25, 0.5, 6) + 1 (0.25, 2, 8)	20	4.27	2.26	136
2	4 (0.5, 0.75) + 4 (0.75, 1) + 4 (0.75, 6) + 4 (6, 8) + 3 (0.25, 3) + 3 (0.75, 3) + 3 (2, 3) + 3 (3, 6) + 2 (1, 2)	30	0.81	11.9	713
1	11 (0.25) + 10 (3) + 9 (2) + 8 (0.5) + 7 (0.75) + 3(1) + 3 (8) + 3 (36) + 2 (4) + 2 (24) + 2 (36)	60	0.02	538	32,297

Example 2

Table III. Comparison of the Population Designs for Older Children (6 to 12 Years) Including Six Samples during the First Six Hours or Single Sample Designs (see Table II for Legend)

n	Design (sampling times)	N_{tot}	$Cri^{1/20}$	$1/e$	n_{eq}
10^a	10 (0.25, 0.5, 0.75, 2, 3, 6, 8, 12, 24, 36)	6	9.66	1	60
6	8 (0.25, 0.5, 0.75, 2, 3, 6) + 2 (0.25, 0.5, 0.75, 1.5, 2, 6)	10	6.00	1.61	97
6	10 (0.25, 0.5, 0.75, 2, 3, 6)	10	5.99	1.61	97
6^b	8 (0.25, 0.5, 0.75, 2, 3, 6) + 3 (8) + 3 (12) + 3 (24) + 3 (36)	20	5.29	1.83	110
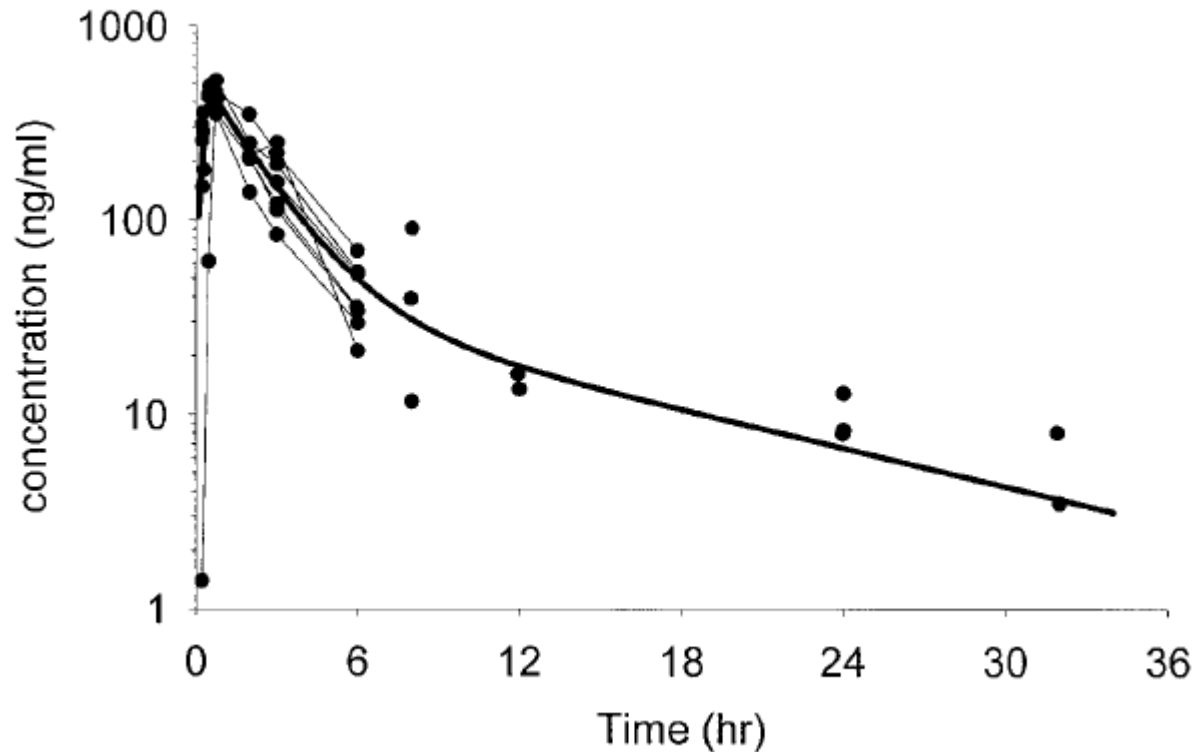
Practical issues and limitations in the application of optimal design

- Prior information
  - PBPK models

- Local validity of the assumptions
  - Bayesian approach – parameter and model uncertainties
  - Sampling windows

- Replicate designs
  - Discrete time points (possible/candidate time points)
  - Continuous/statistical/approximate design
  - Additional constraints

Conclusion

- Optimal design is a useful tool that fits naturally in the context of clinical pharmacology experiments
    - Practical and ethical constraints
    - Sparse designs – Phase II, III clinical trials, paediatric studies and TDM

- Sampling windows is particularly useful by allowing flexibility in sampling and yet provide designs that is informative

- Drawbacks in the use of optimal design methodologies in clinical pharmacology can be overcome