UPPSALA UNIVERSITET

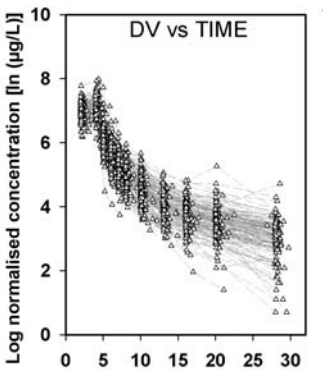
Application of the optimal design approach to improve pre-transplant drug monitoring for cyclosporine

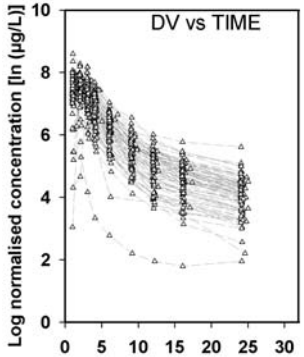
Stefanie Hennig, Joakim Nyberg, Samuel Fanta, Andrew Hooker, Mats O. Karlsson

Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University

UPPSALA UNIVERSITET

Procedures in Finland during paediatric renal transplantation





Transplantation

CyA iv test

CyA po test

CyA iv therapy

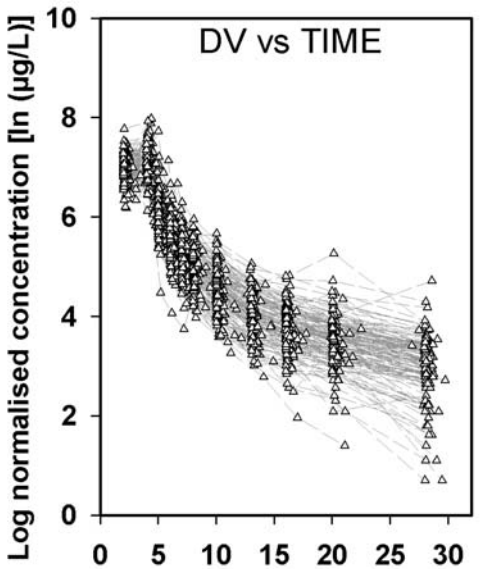
CyA po therapy

Knowledge gained used to individualize therapy initiation

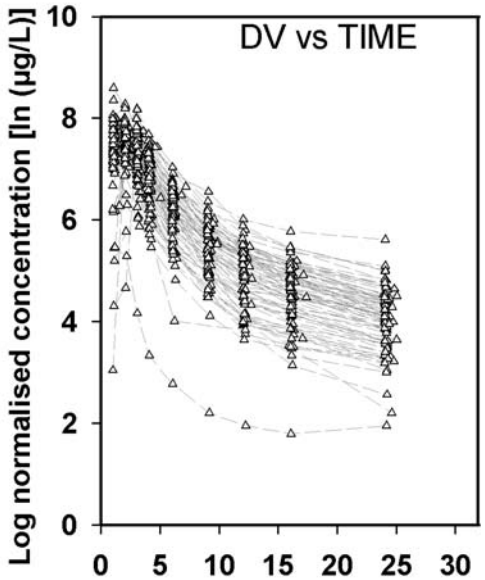
UPPSALA UNIVERSITET

Previous design

Intravenous (IV)



Oral (PO)



- 162 IV patients & 89 PO patients (77 with both) were collected (1988-2005)
  - During this time; individual models were used to predict 1st iv and 1st oral post transplant dose
- In 2007 a Population PK model was published by Fanta et al*

* Fanta S. *Br J Clin Pharmacol.* Dec 2007;64(6):772-784.

UPPSALA
UNIVERSITET

Aim

- Reduce and optimise the pre-transplant cyclosporine monitoring design for an analysis of individual parameters which used priors from the population model

- Work within clinical restrictions

UPPSALA UNIVERSITET

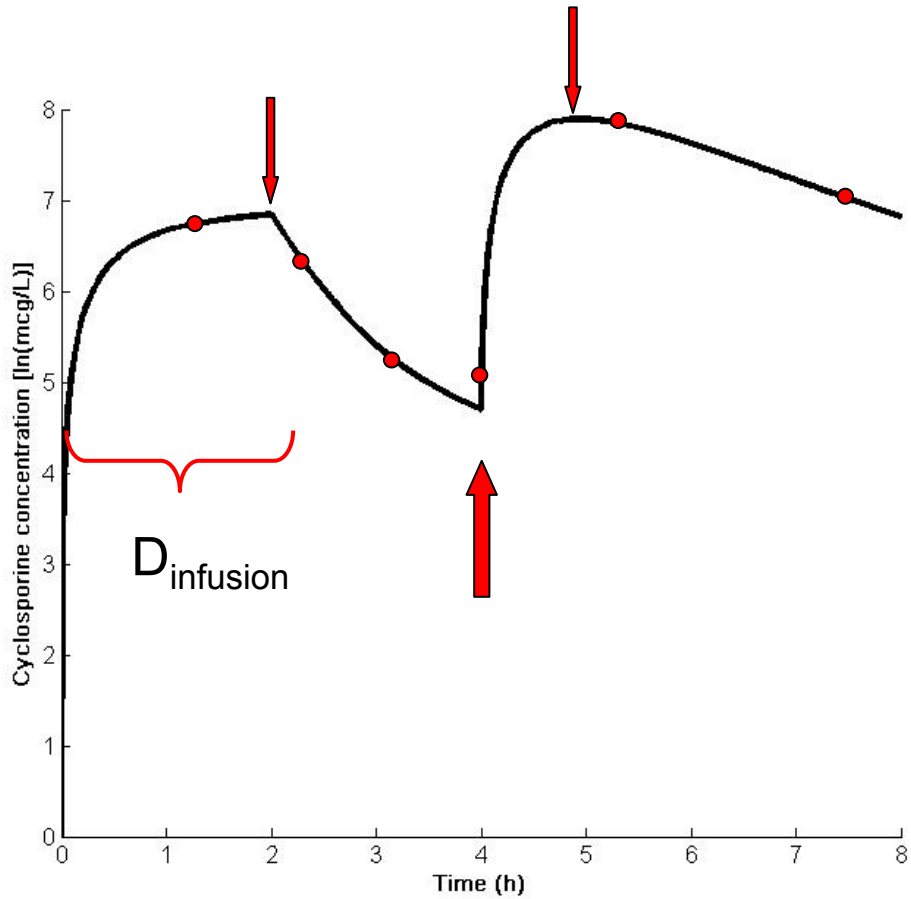
Clinical Restrictions

- Maximum of 3 samples per dose
- Maximum total cyclosporine dose (IV+PO) of 10 mg/kg
- Maximum infusion rate for IV: 0.75 mg/kg/h
- Fit both doses IV+PO within 8 hour time limit

UPPSALA UNIVERSITET

What can we optimize on?

- Sampling times IV, PO
- Doses IV, PO
- Durations of infusion for IV
- Start of second dose
- IV first then PO and vice versa



UPPSALA UNIVERSITET

Methods used

- 8 individual parameters (EBEs) transformed to fixed effect parameters
- Continuous distributions (variances of parameter distributions) to represent prior information on the **individual level**
- Discrete distributions for ED-sampling
- Optimization of all design variables simultaneously
- WT as covariate, Doses were optimized as mg/kg

- ED_s-optimality used for following parameter subsets of interest:
  - EBEs of CL and F only
  - EBSs of all 6 parameters
  - EBEs of all 6 parameters and 2 of the RUV (eta on eps)

- Sampling windows
- Efficiency loss compare to previous rich design

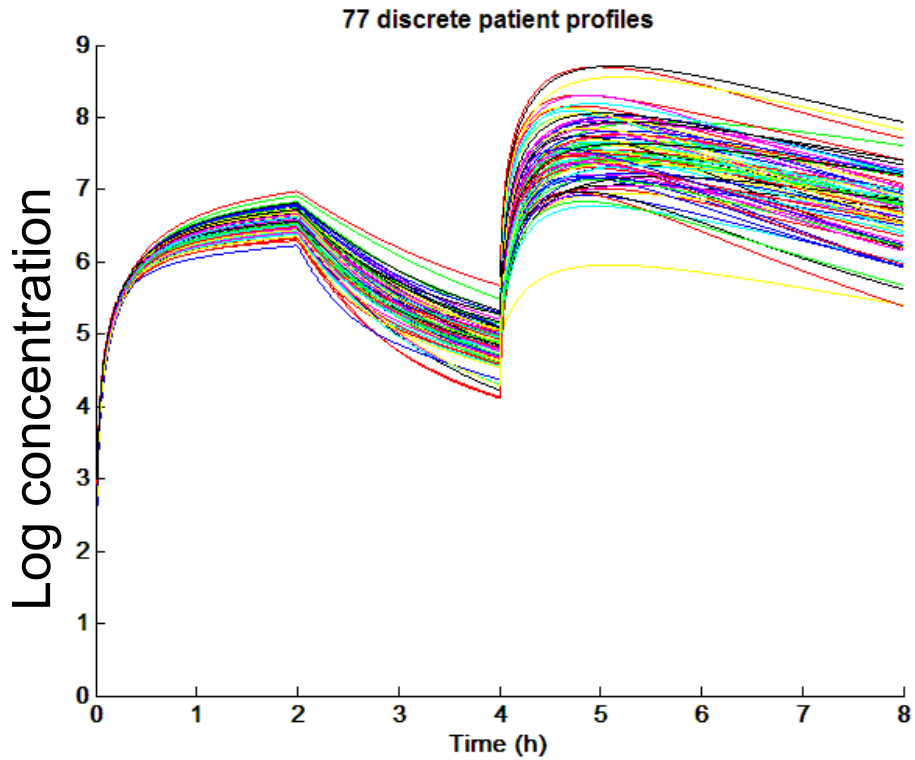
- Optimization was performed in PopED v.2

UPPSALA UNIVERSITET

Methods

ED samples from discrete distributions

- Optimization across a discrete distribution of 77 individual parameter vectors
- Includes correlation between parameters
- Reflect future patients distribution, however bias to previous patients
- η-Shrinkage was on average 6%



UPPSALA UNIVERSITET

Methods
Focus on some parameters (CL & F)

- Focus on CL and F as during chronic dosing
  - Average concentration = Dose rate * F / CL

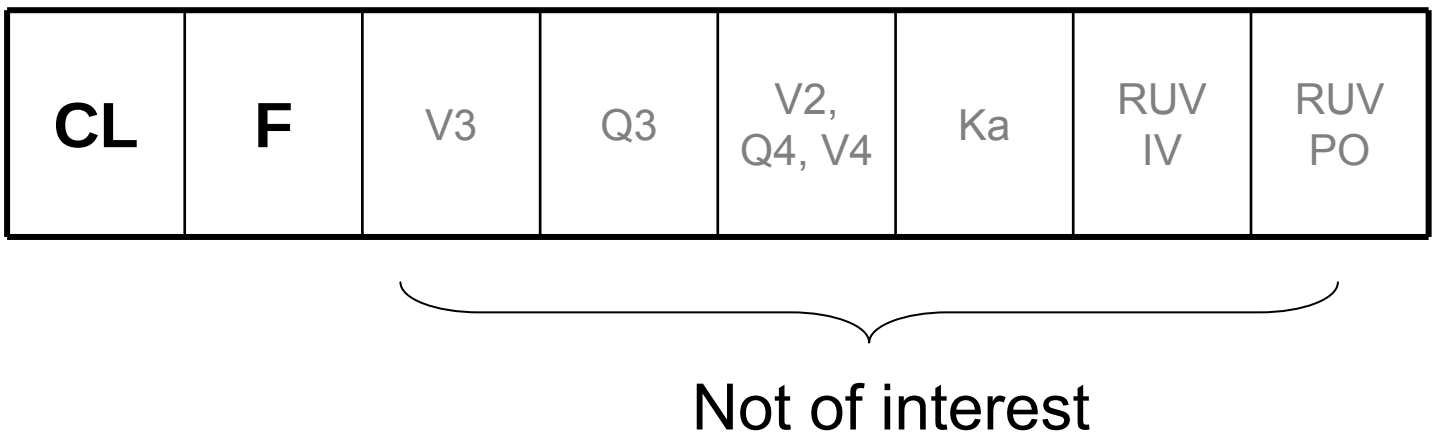
CL	F

Assume all other known

UPPSALA UNIVERSITET

Methods
Focus on some parameters (CL & F)

- Focus on CL and F as during chronic dosing
  - Average concentration = Dose rate * F / CL



UPPSALA UNIVERSITET

Methods

ED_s- optimality

$$ED_s = \max\left(E\left[\frac{|FIM_{total}|}{|FIM_{uninteresting}|}\right]\right)$$

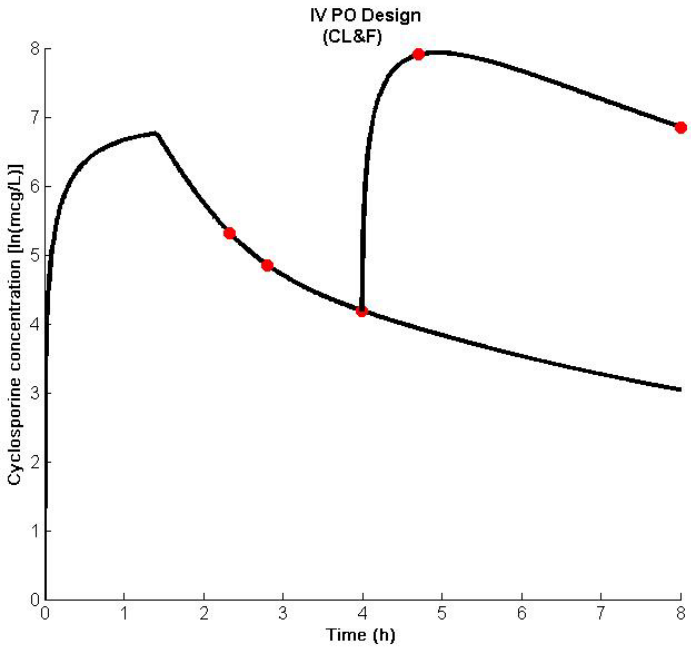
- The smaller the $|FIM_{uninteresting}|$ the larger the D_s
- Keeps correlation between all parameters of the model compared to not including certain parameters in the FIM calculation (fixing parameters)

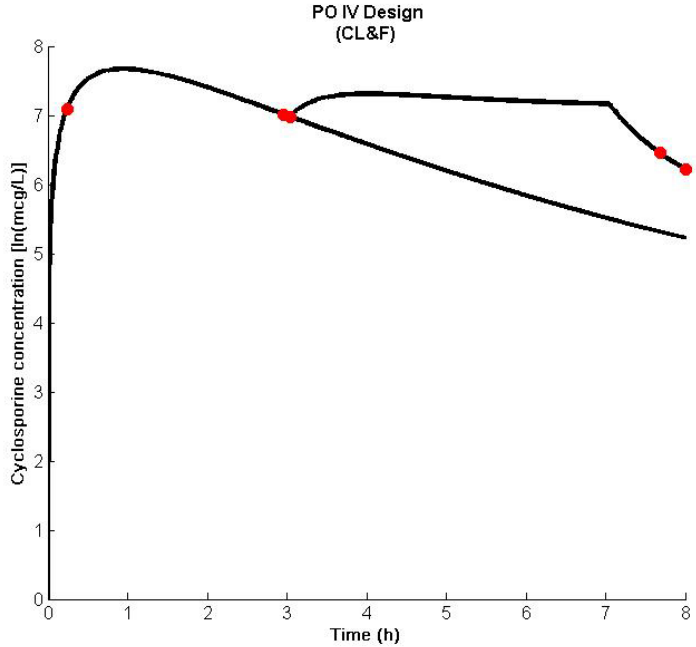
Atkinson et al. Chemometrics Intel Lab Sys 2002;61:17-33.

UPPSALA UNIVERSITET

Results

Designs optimized for CL & F





		IV PO design	PO IV design
Sampling Times	IV	2.33	3.04
		2.81	7.68
		3.98	8.00
	PO	4.71	0.24
		8.00	2.96
		8.00	2.96
Other design variables	Dose IV (mg/kg)	1.05	3.00
	Dose PO (mg/kg)	8.95	7.00
	Infusion time	1.41	4.00
	Infusion Rate	0.75	0.75
	Time of second dose	4.00	3.04

UPPSALA UNIVERSITET

Results

Comparison to previous designs

- Showing the individual expected precisions (CVs) obtained from PopED

	Originial design Individual	Optimal design		Priors
		IV PO design	PO IV design	
V3	26.2%	41.1%	40.1%	41.9%
Q3	18.0%	30.2%	31.0%	32.2%
V2 Q4 V4	53.9%	34.7%	37.9%	40.0%
CL	**6.7%**	**9.3%**	**10.7%**	**17.0%**
KA	21.1%	19.4%	19.0%	34.6%
F	**10.8%**	**13.5%**	**13.5%**	**46.7%**
EPS RUV IV	20.5%	29.6%	29.6%	43.0%
EPS RUV PO	22.5%	32.1%	32.1%	51.9%

UPPSALA UNIVERSITET

Results

Comparison with original design (individual)

- Comparison of the efficiency of the reduced optimal vs. the Rich Design Individual

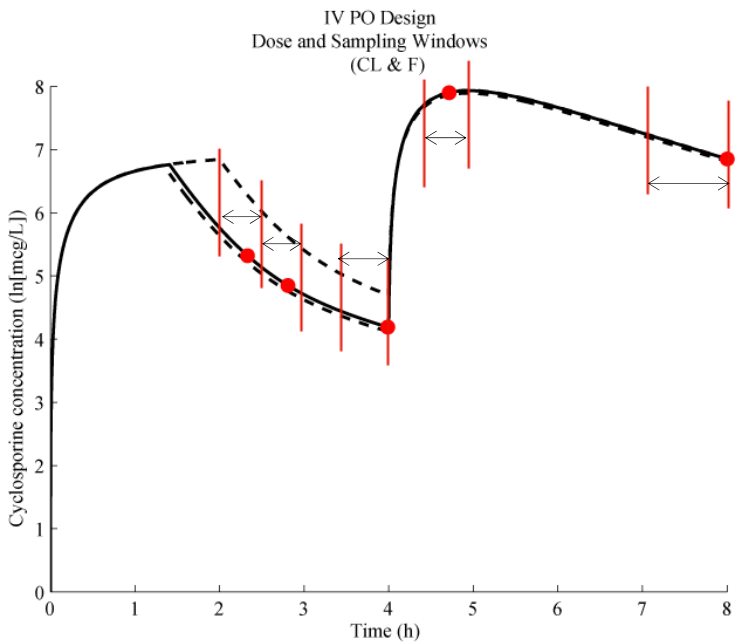
$$\text{Efficiency} = \frac{E\left[\left(\frac{|FIM_{total}|}{|FIM_{uninteresting}|}\right)^{1/s}\right]_{\text{optimal reduced design}}}{E\left[\left(\frac{|FIM_{total}|}{|FIM_{uninteresting}|}\right)^{1/s}\right]_{\text{original full design}}}$$

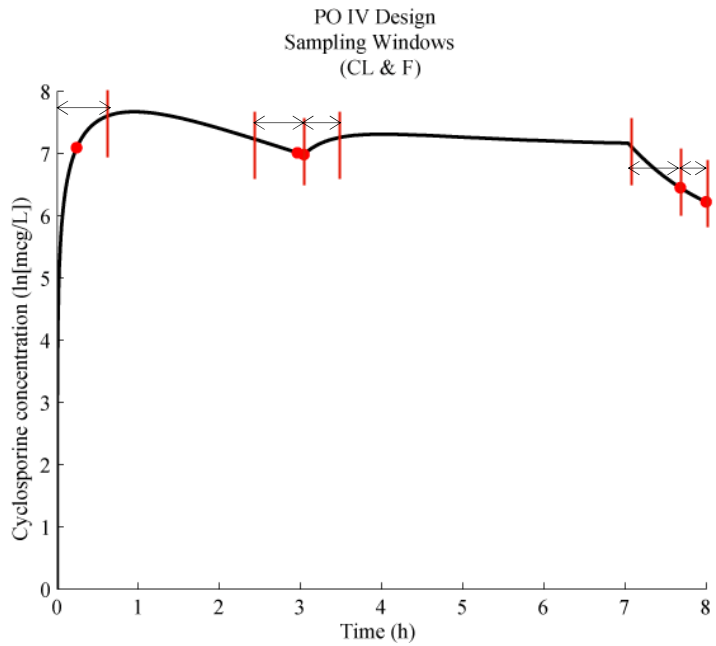
- Efficiency ~ 47%

UPPSALA UNIVERSITET

Results

Sampling and Dose windows





- Defining windows and then calculating the efficiency for 100 samples from the windows

- Efficiency reduction of 5-10% when applying sampling windows, further 3% efficiency reduction with dose windows

UPPSALA UNIVERSITET

Conclusions

- A new method were developed for optimization of EBEs with inclusion of prior information
- Multiple design variables were optimized simultaneously
- Reduction to 6 blood samples within 8 hours possible including constrains and sampling/dose windows for clinical practicality
- CVs on the EBEs for CL and F could be reduced on average by 60% compared to the Prior information
- The gain of performing the Rich Design compared to the optimal reduced designs with regards to the precision of the parameters is small

UPPSALA
UNIVERSITET

Acknowledgements

Kalle Hoppu