Optimal design with cost functions for the pharmacokinetics of AZT and AZT-TP

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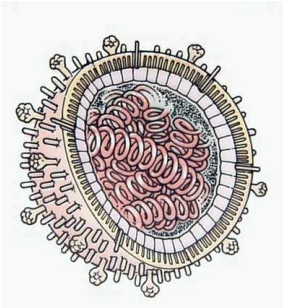
AZT & AZT-TP

- **Zidovudine or azidothymidine (ZDV or AZT)**
  - Antiretroviral drug
  - Nucleoside analog



- **First treatment approved for HIV**

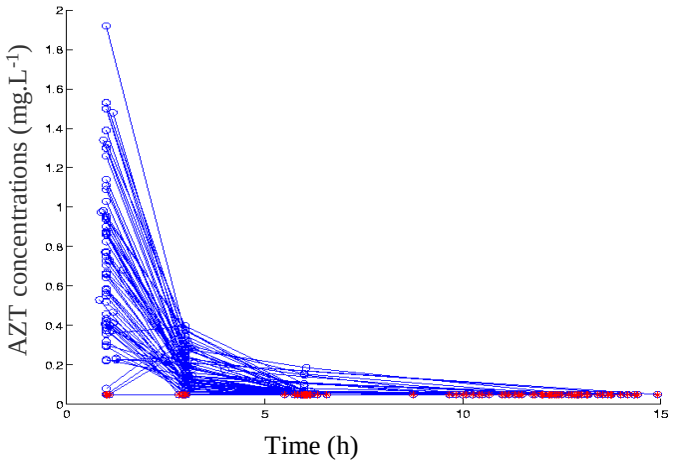
- **Metabolism AZT in AZT-TP in the cell**
  - Active metabolite AZT-TP
    - Important determinant to study the toxicity and efficacy of AZT
    - Complex and costly assay performed in few laboratories[1-2]

1. Becher F. et al. *Journal of Mass Spectrometry*, 2001
2. Pruvost A. et al. *Journal of Mass Spectrometry*, 2002

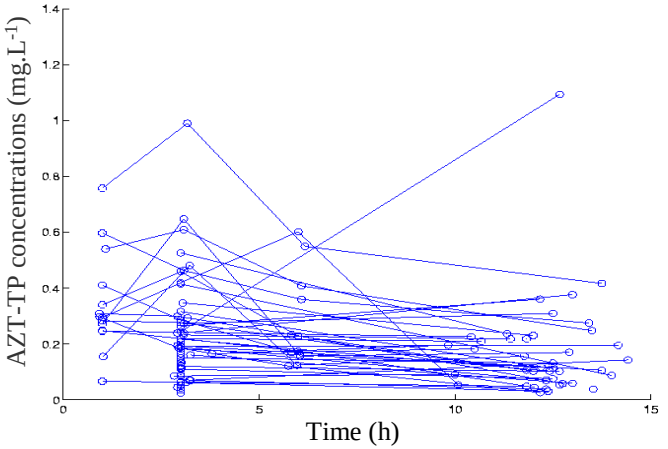
Pop PK of AZT & AZT-TP (1)

- **Data : COPHAR 2-ANRS 111 trial**
  - 73 patients with AZT concentrations after 2 weeks of treatment
    - 62 patients with AZT-TP concentrations
  - Dose of 300 mg twice daily
  - Sampling times at 1, 3, 6 and 12h (steady state)

AZT

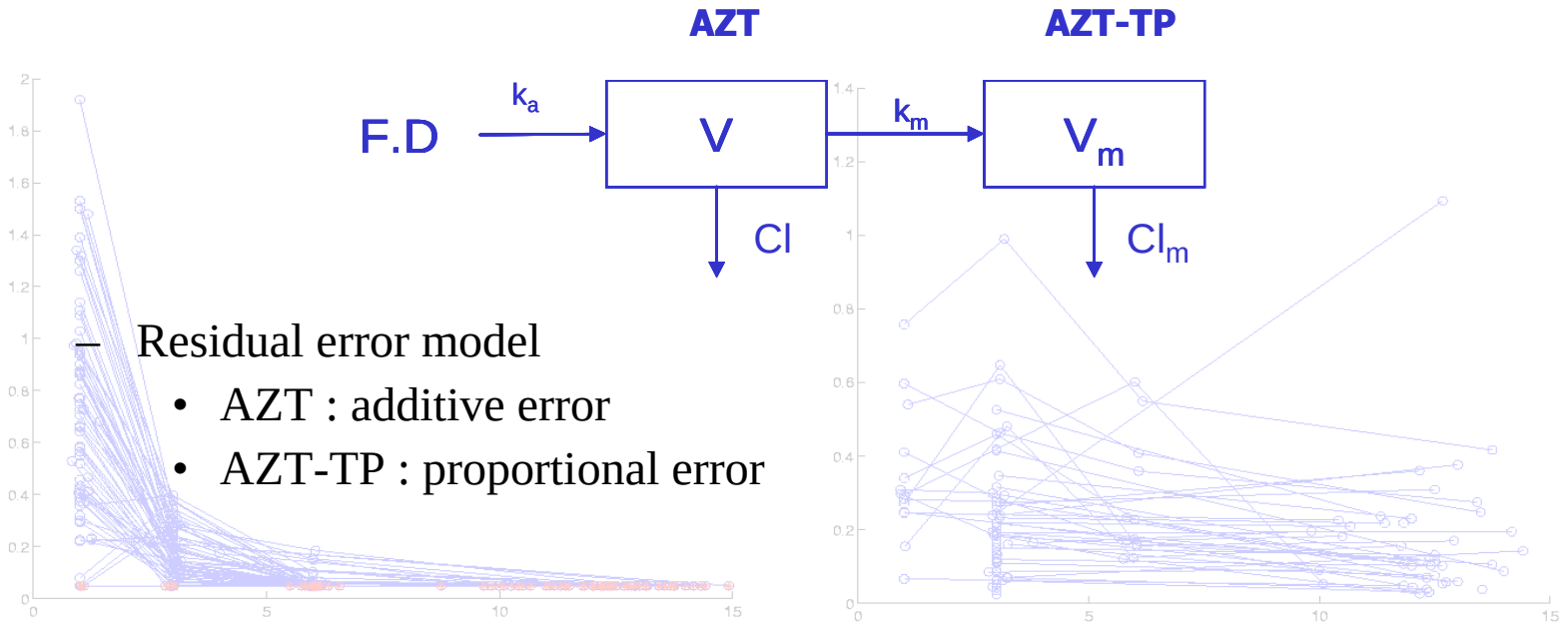


AZT-TP



Pop PK of AZT & AZT-TP (2)

- **A joint PK model for both compounds**



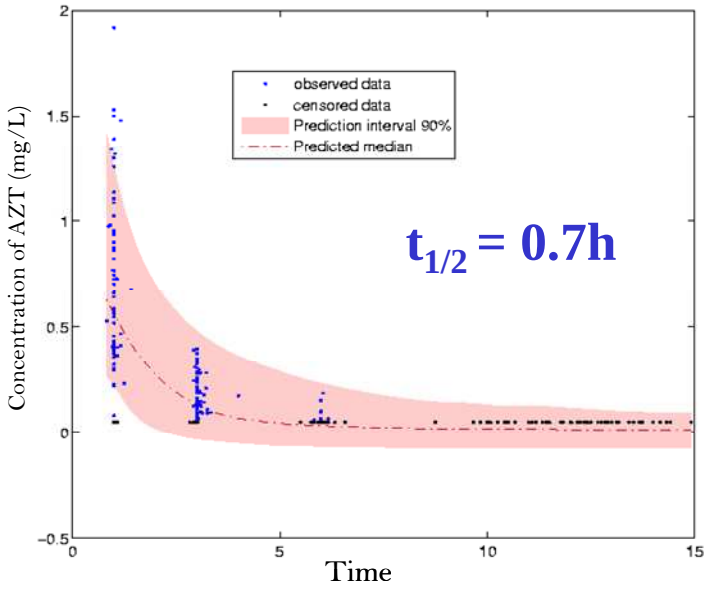
  - Residual error model
    - AZT : additive error
    - AZT-TP : proportional error

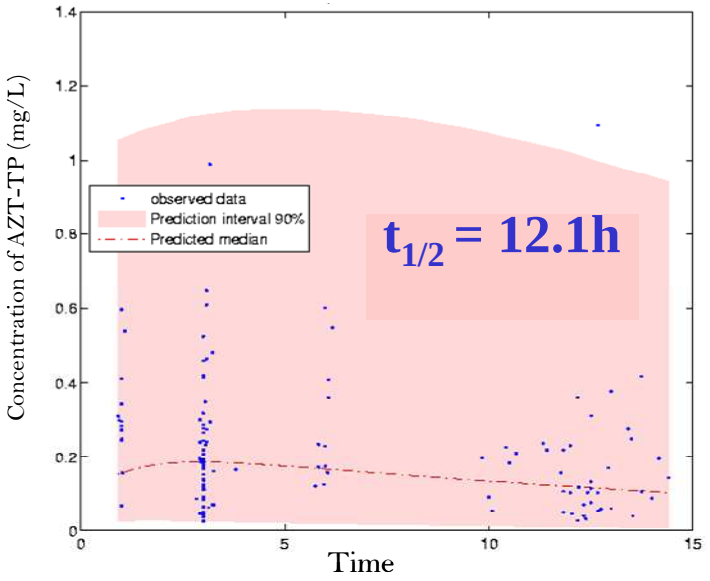
- **Estimation of the population parameters using MONOLIX[1]**

1. www.monolix.org

Pop PK of AZT & AZT-TP (2)

- **A joint PK model for both compounds[1]**





- **AZT**
  - ka = 2.86 h^{-1} (FIX)
  - Cl = 201 $L.h^{-1}$, V = 232 L
  - ω_{Cl} = 54.2 %, ω_V=78 %
  - σ_{inter} = 0.05mg.L^{-1}

- **AZT-TP**
  - Cl_m/Fk_m= 175 L
  - V_m/Fk_m= 2.67 10^3 $L.h^{-1}$
  - $\omega_{Clm/Fkm}$= 60.3 %
  - σ_{slope} = 44.9 %

1. Bazzoli et al., *Population Approach group in Europe (PAGE)*, June 2008, Marseille, France

Objective

- **To optimize a design taking into account the costly assay of AZT-TP concentrations**

Design optimization with cost functions

General Formulation

- **Population design Ξ**
  - N subjects
  - Q groups of N_q subjects with the same elementary design ξ_q
    - n_q samples
    - $\xi_q = (\xi_q^1, \xi_q^2, \ldots, \xi_q^K)$ in case of K responses

- **Objective: to find Ξ^* which maximizes $\det(M_F(\Xi))$**

- **$M_F(\Xi) = \Sigma_q(N_q M_F(\xi_q)) = N\Sigma_q(\alpha_q M_F(\xi_q))$**
  - $\alpha_q = N_q/N$ proportion of subjects in each design ξ_q

- **Optimization of α_q and ξ_q under constraints**

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- **Optimization of α_q and ξ_q under constraints**
- **Optimization for a fixed total number of samples n_{tot}**
  - $N\Sigma_q \alpha_q n_q = n_{tot}$
  - $M_F(\Xi) = n_{tot} \Sigma_q (w_q M_F(\xi_q)/n_q)$
    - w_q proportion of the total samples attributed to design ξ_q

$w_q = N\Sigma_q \alpha_q n_q / n_{tot}$

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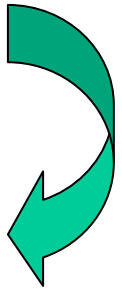
- **Extension: optimization for a fixed total cost C_{tot} [1-2]**
  - **$C(\xi_q)$** : cost for an elementary design ξ_q

    $N\Sigma_q \alpha_q C(\xi_q)) = C_{tot}$
  - **$M_F(\Xi) = N\Sigma_q(\alpha_q M_F(\xi_q)) = C_{tot} \Sigma_q(w_q M_F(\xi_q)/ C(\xi_q))$**
    - w_q proportion of the total cost attributed to design ξ_q



n_{tot} -> C_{tot}

n_q -> $C(\xi_q)$

1 Mentré et al. *Biometrika*. 1997.
2 Gagnon et al. *Journal of Biopharmaceutical Statistics*. 2005.

Statistical optimization problem

- **Optimization of both proportion w_q and elementary designs ξ_q**
  - solved assuming the proportions continuous between 0 and 1

- **Specific algorithm adapted to this context: Fedorov-Wynn algorithm**
  - convergence toward the D-optimal design
  - optimisation of both the proportions and the elementary designs
  - sampling times taken in a user-defined set of possible times
    - more clinically relevant
  - implemented in C and linked with PFIM

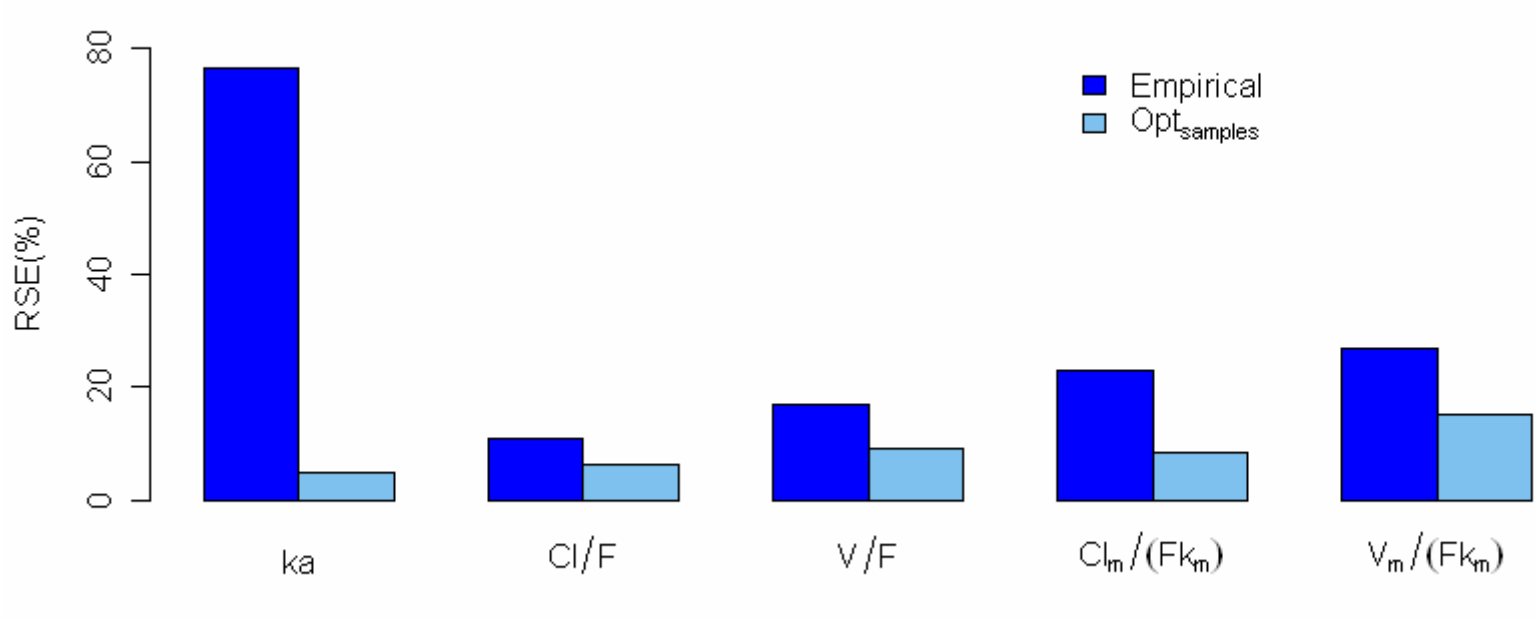
- **Number of subjects per group**
  - Derived using $N_q = w_q C_{tot}/C(\xi_q)$
  - Rounded to an integer under the constraints that $\Sigma_q (N_q C(\xi_q)) \leq C_{tot}$

Application to the joint modeling of AZT and AZT-TP

- **Use of the previous joint PK model**
  - Estimation of ka
- **Empirical design**
  - 50 patients
  - Sampling times at 1, 3, 6 and 12 h for AZT and AZT-TP (COPHAR2 trial)
- **Constraints**
  - From 1 to 4 samples per patient
  - Set of allowed sampling times
    - For AZT : 0.5, 1, 1.5, 2, 3 and 4h
    - For AZT-TP : 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h
  - Fixed total cost $C_{tot} = 400$ for both responses
- **Optimization using 4 cost functions**
  - Number of samples to analyse : $C_{samples}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP}$
  - Cost of an intracellular concentration analyse : $C_{intra}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP} * 10$
  - Cost of the addition of a new patient in the study : $C_{patient}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP} + 8$
  - Both cost of an intracellular concentration analyze and cost of a new patient : $C_{intra\_patient}(\xi_q) = n_q^{AZT} + n_q^{AZT\text{-}TP} * 10 + 8$

Results (1)

Design	Q	Elementary designs			Total number of subjects	Information value
		ξ_q		N_q		
		AZT	AZT- TP			
Empirical	1	1, 3, 6, 12	1, 3, 6, 12	50	50	1.17
Opt_samples	2	0.5, 1, 3, 12 0.5, 2	3, 12 3, 12	78 2	80	2.52

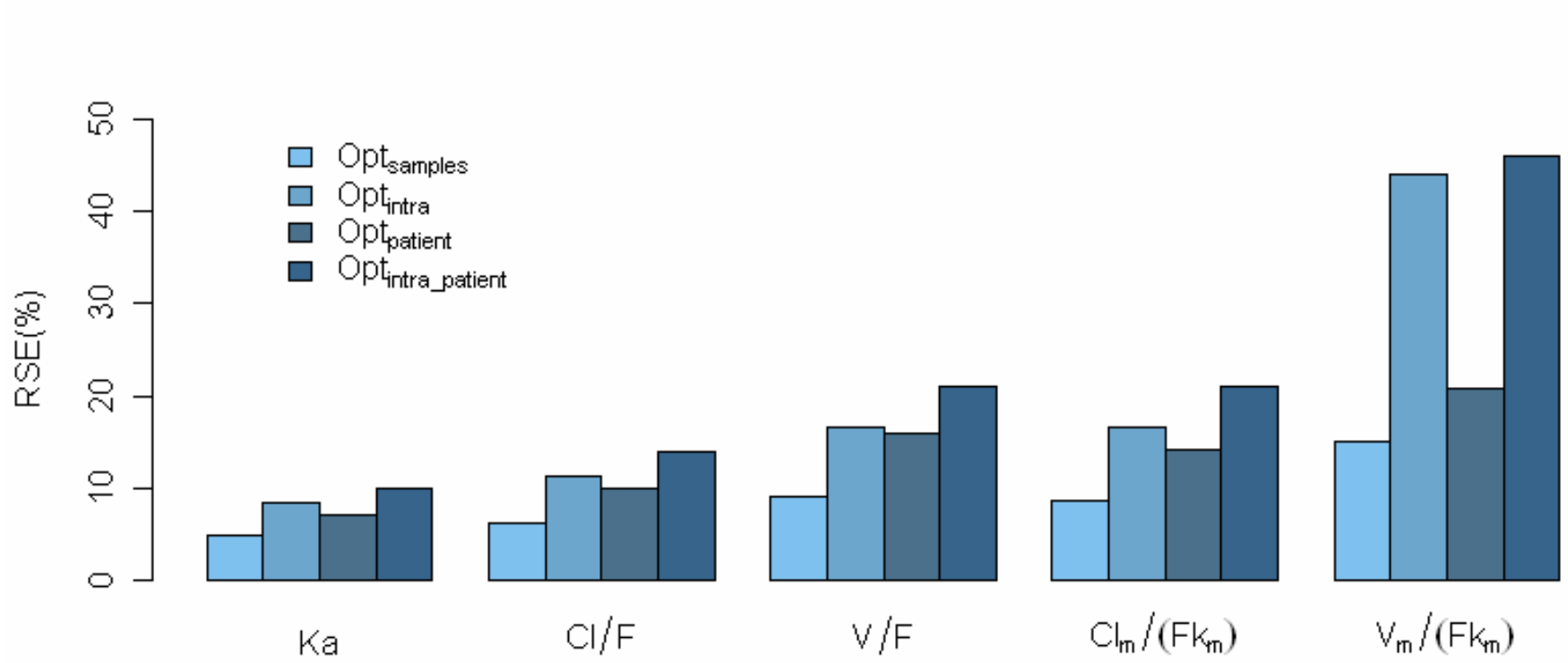


Results (2)

Design	Q	Elementary designs			Total number of subjects	Number of samples	
		ξ_q		N_q			
		AZT	AZT- TP			**AZT**	**AZT-TP**
Empirical	1	1, 3, 6, 12	1, 3, 6, 12	50	50	**200**	**200**
Opt_samples	2	0.5, 1, 3, 12 0.5, 2	3, 12 3, 12	78 2	80	**238**	**160**
Opt_intra	4	0.5, 1, 3, 4 0.5, 1, 3, 4 0.5, 1, 1.5, 3 0.5, 1, 1.5, 3	12 3 3, 12 3	11 1 7 5	30	**96**	**31**
Opt_patient	2	0.5, 1, 3, 4 0.5, 1, 1.5, 3	2, 3,12 2, 3, 4, 12	15 11	26	**104**	**89**
Opt_intra_patient	3	0.5, 1, 3, 4 0.5, 1, 3, 4 0.5, 1, 1.5, 3	12 3 3,12	5 1 8	14	**56**	**22**

Results (3)

Precision of estimation on the fixed effects according optimized designs



Conclusion (1)

- **Illustration of the interest of cost functions on AZT and AZT-TP taking into account the cost of each compound analysis**
  - Possibility to take into account the real cost

- **Optimal design in agreement with the cost**
  - Group structure
  - Sampling times

Conclusion (2)

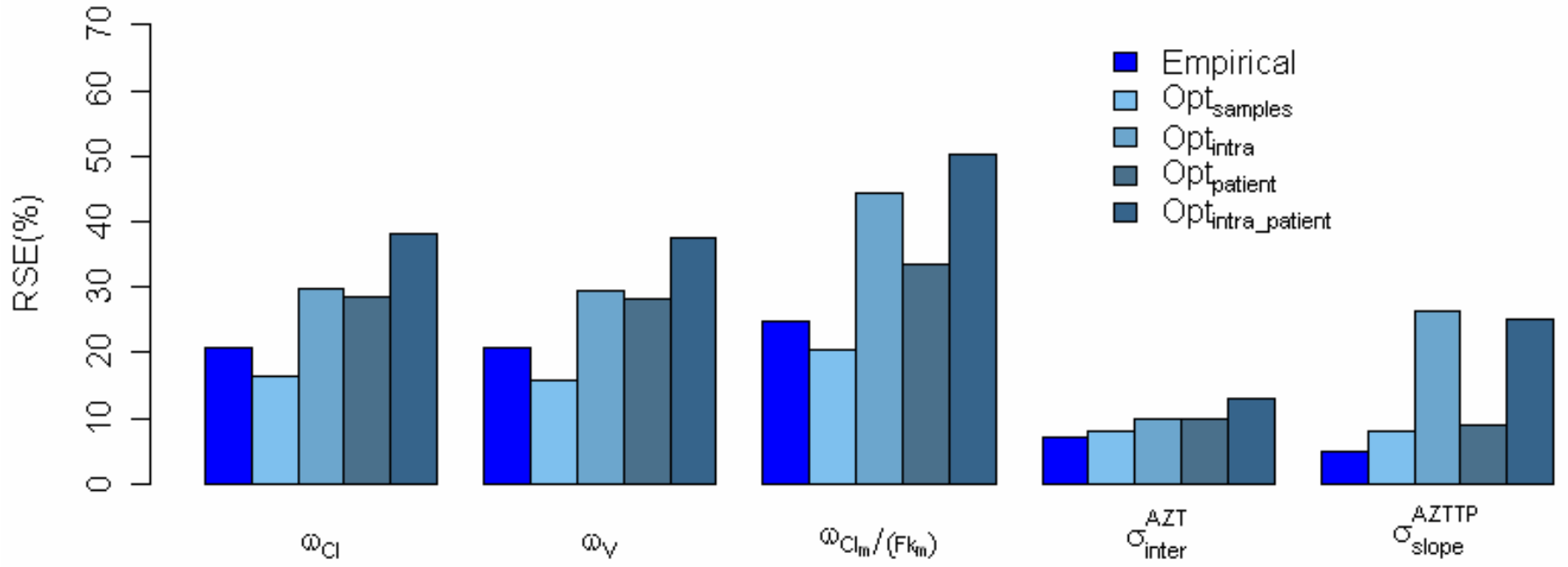
- **Cost functions combined with Fedorov-Wynn algorithm**
  - powerful tool to derive informative designs suitable to clinical conditions
  - even for multiple response models with different time scales[1]

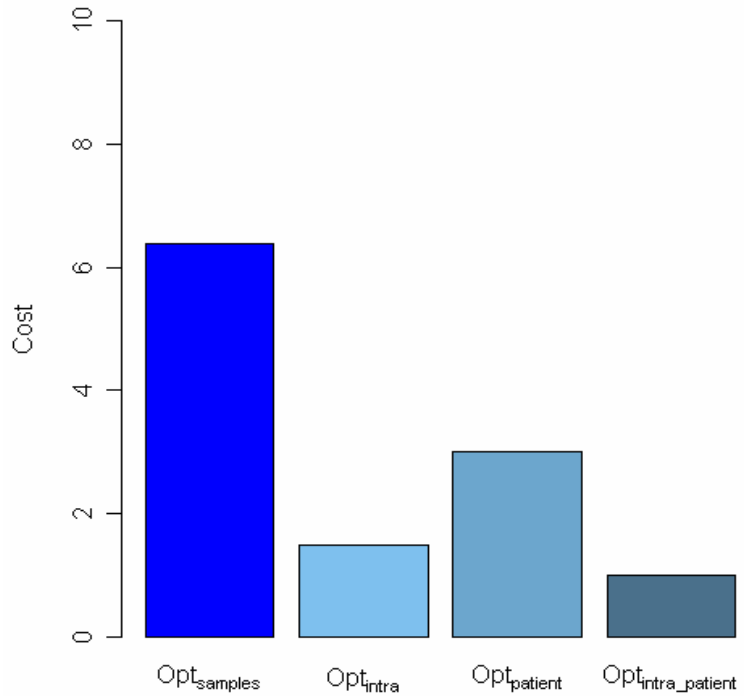
- **Fedorov-Wynn algorithm**
  - available in PFIM Interface 2.1 and in PFIM 3.0 for multiple responses with the total number of samples as cost function.
  - **www.pfim.biostat.fr**
  - more general user-defined cost functions

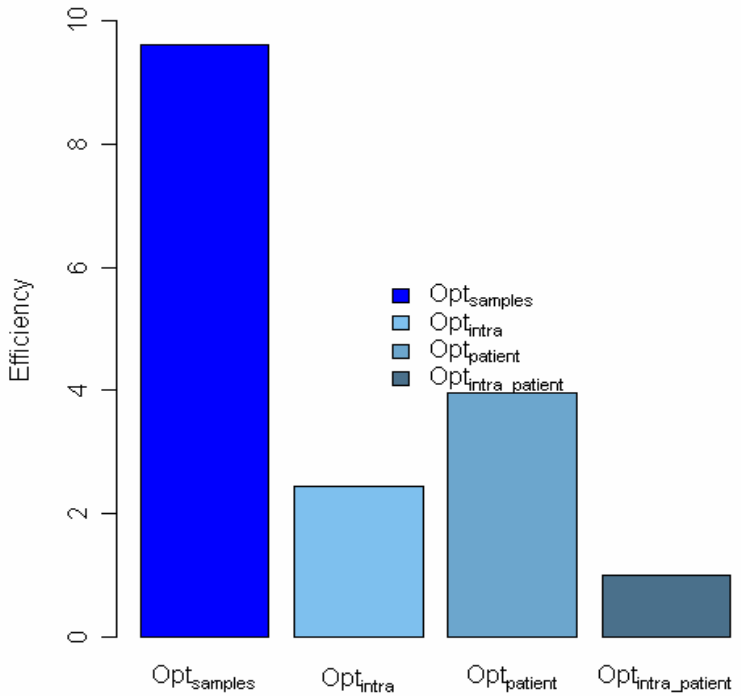
    $\Rightarrow$ future version!

1. Retout et al., *Population Approach group in Europe (PAGE)*, juin 2008, Marseille, France

Precision of estimation on variance and residual parameters according optimized designs




Cost
0
2
4
6
8
10
Opt_samples
Opt_intra
Opt_patient
Opt_intra_patient


Efficiency
0
2
4
6
8
10
Opt_samples
Opt_intra
Opt_patient
Opt_intra_patient
Opt_samples
Opt_intra
Opt_patient
Opt_intra_patient