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Optimal Design To Estimate the Time Varying Receptor Occupancy Relationship in a PET Experiment

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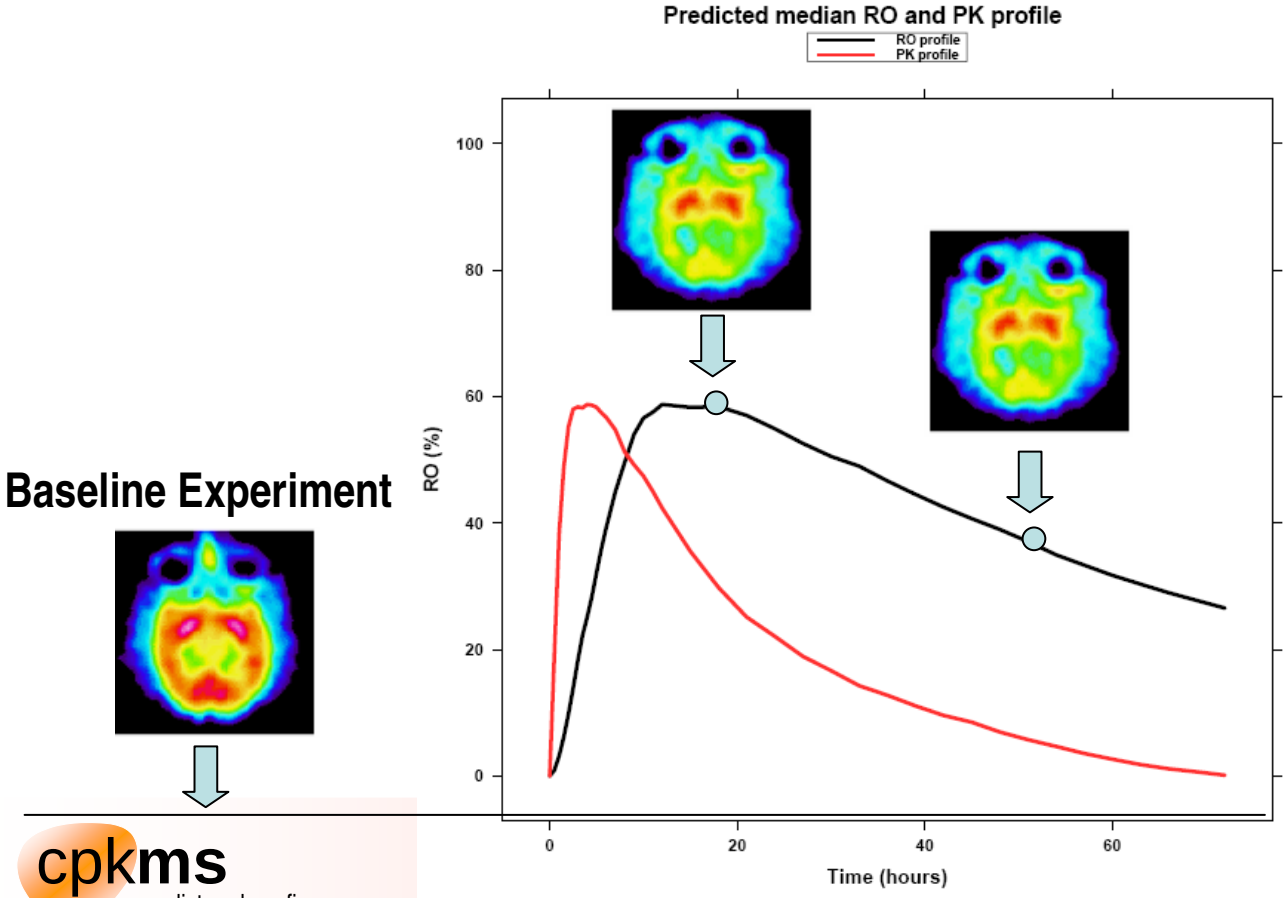
Why Study PK/RO?

- Positron emission tomography (PET) is one of the most effective imaging in vivo techniques to estimate RO
- The assessment of the RO-time profile is critical to predict the time course of pharmacological response



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Why Study PK/RO?

- To characterise the shape and location of the concentration-RO curve
- To explain variability in response
- To rationalise dose/dosing regimen selection
- To predict the time course of pharmacological response (therapeutic & toxic)
- To understand complex relations (tolerance, sensitisation)

Experimental design issues in a PET study

- Cost and ethical reasons limit the total number of subjects (usually n < 20) and the number of PET scans per individual (≤ 3 scans)
- Uncertainty in the structure of the mechanistic model relating RO and PK *(Equilibration delay, Mechanistic delay, Tolerance)*
- Inter- and intra-subject variability in PK and in drug-to-receptor binding resulting in an overall inflation in variability
- Need to estimate typical exposure/RO link in a target patient population (fraction of subjects achieving an 'effective' RO in a chronic treatment)

Time course RO – Mechanistic models

- Typically a direct link between plasma concentrations and RO is assumed
- To account for delay/hysteresis between occupancy levels and plasma concentration the following models* can be applied:

Effect Compartment Model

$$\frac{dC_E}{dt} = k_{eo} \cdot (C_P - C_E) \quad \Rightarrow \quad \%RO = 100 \frac{C_E}{EC_{50} + C_E}$$

Receptor Association-Dissociation Model

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$

R_T = maximum receptor occupancy (fixed at 100%)
RO = observed receptor occupancy time course data

Combined Biophase / Receptor Association-Dissociation Model

$$\frac{dRO}{dt} = k_{on} \cdot C_E \cdot (R_T - RO) - k_{off} \cdot RO$$

*Yassen et al,. Anesthesiology. 2006; 104-1232-42

Optimal Population Design

$$CP_i = f(\theta_{CP_i}, \xi_{CP_i}) + \varepsilon_{CP_i}$$ Population PK model (fixed effect)

$$RO_i = g(CP_i, \theta_{RO_i}, \xi_{RO_i}) + \varepsilon_{RO_i}$$ Population PK/RO model (fixed effect)

$$\theta_i \in N(\Phi, \Omega)$$ Population PK/RO parameters (random effect)

Ξ Population design vector of PK and RO sampling times (ξ)

Ψ Vector of population fixed (Φ) and random effect (Ω) parameters

For a given individual with design ξ

$$M_F(\Psi, \xi) = E\left(-\frac{\partial^2 l(\Psi; y)}{\partial \Psi \partial \Psi^T}\right)$$

$l(\Psi; y)$ is the log-likelihood of vector of observation y of individual for the population parameters

Population Fisher information matrix (PFIM): $$M_F(\Psi, \Xi) = \sum_{i=1}^{N} M_F(\Psi, \xi_i)$$

Designs are optimized maximizing the determinant of the PFIM with respect to Ξ assuming known Ψ

$$\det[M_F(\Psi, \Xi)]^{\frac{1}{\dim(\Psi)}}$$

Retout S, Duffull S, Mentre F. Comput. Meth. Prog. Biomed. 2001; 65(2):141-51

Case study: Optimal study design

- PK/PD model was defined using pre-clinical data (kon/koff) and human PK data (considered fixed)
- Optimal design was performed to allocate PET scans at the most informative time-points
- Various designs exploring the influence of optimizing the PET scan time allocation, the number of subjects to elementary design and the number of dose levels were considered
- Optimisation was performed using WinPOPT®*
- Study designs: 16 subjects in total, up to 4 doses (1.5, 2.5, 4 and 6 mg), and 3 PET scans per subject

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*Duffull S, et al. J. Pharmacokinet. Pharmacodyn. 2005; 32:441-57

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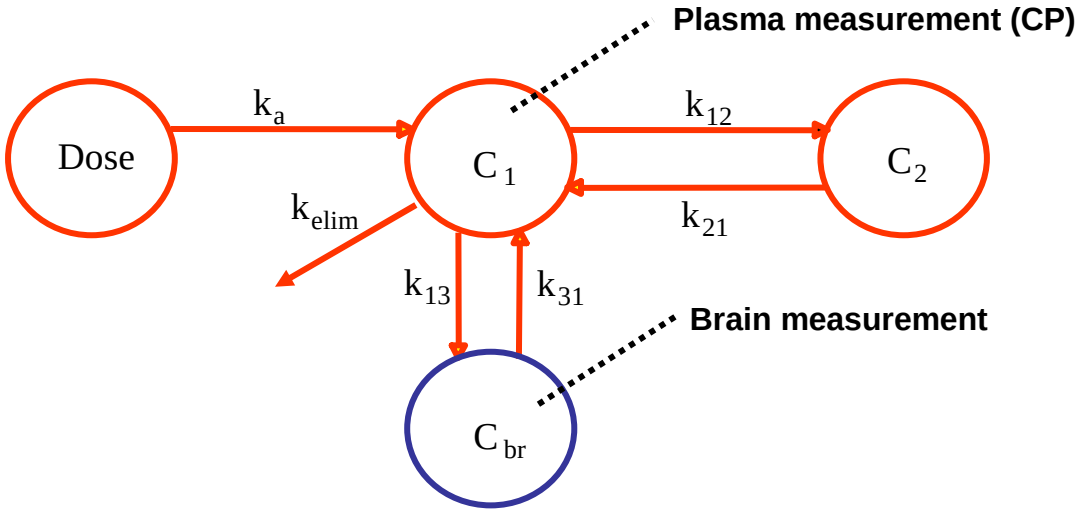
Modelling time-course RO data

- A mechanistic model was developed using pre-clinical data to estimate the RO time-course and the time-varying link between PK and RO based on k_{on} and k_{off} parameters



1) Modelling of plasma/brain data

2) Receptor Association-Dissociation Model

$$\frac{dRO}{dt} = k_{on} \cdot C_P \cdot (R_T - RO) - k_{off} \cdot RO$$

C_P = predicted plasma concentrations (input function)

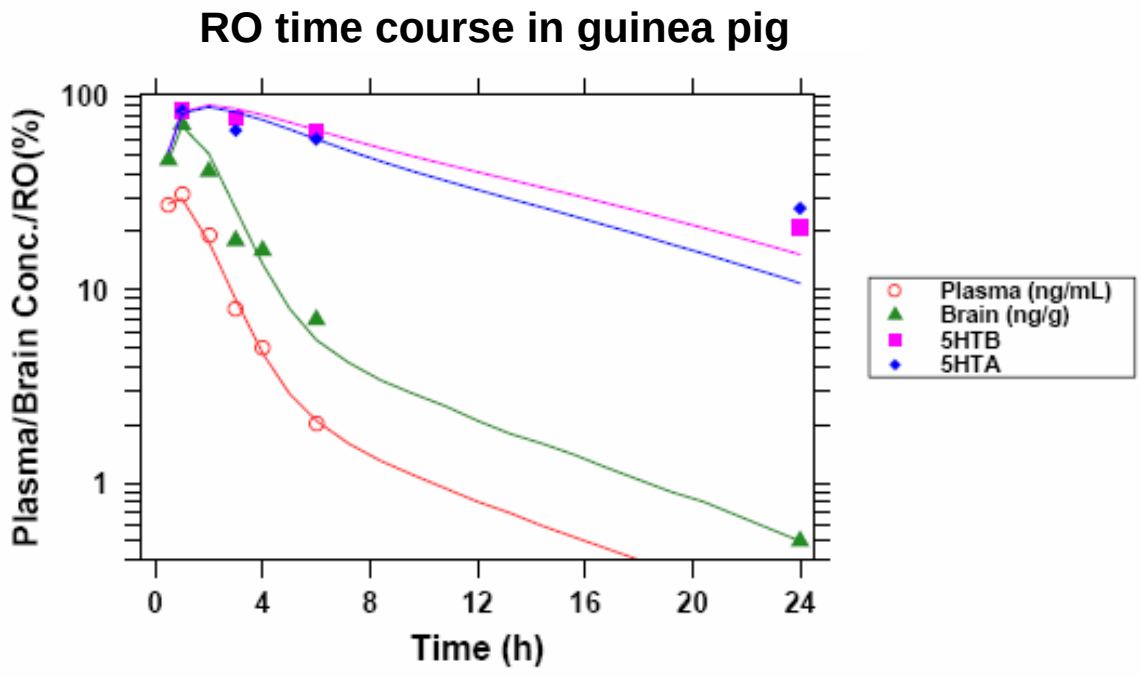
R_T = maximum receptor occupancy (fixed at 100%)

RO = observed receptor occupancy time course data

kon = association binding rate constant

koff = dissociation binding rate constant.

Preclinical data - Results



PK/RO parameters estimetes			
Receptor	**k_{on}** ($ml.ng^{-1}.h^{-1}$)	**k_{off}** (h^{-1})	**$Kd=k_{off}/k_{on}$** (ng/ml)
5-HT_{1A}	0.088	0.221	2.5
5-HT_{1B}	0.088	0.183	2.1

Population PK/PD model

- Optimization was performed on the PK/PD model based on pre-clinical data (kon=0.088 and koff=0.221, variability=30%) and human PK data (first order absorption with 2 comp. model)

Parameter (units)	Fixed effects	Between-subject variance	Population distribution
CL (L/h)	34.9 Fixed	0.112 Fixed	Log normal
VSS (L)	1200 Fixed	0.134 Fixed	Log normal
Q (L/h)	21.7 Fixed	0.179 Fixed	Log normal
FVC	0.67 Fixed	0 Fixed	Normal
Ka (h^{-1})	0.605 Fixed	0.97 Fixed	Log normal
Kon (h^{-1})	0.088	0.1	Log normal
Koff (h^{-1})	0.221	0.1	Log normal
σ^2	0.1	-	Proportional

Optimality criteria improved trial efficiency

Number of doses	Number of groups (n. groups x dose)	Sampling times	Efficiency (%)
4 (2.5, 4, 6, 1.5)	4 (1, 1, 1, 1)	{6, 48}; {6, 48}; {6, 48}; {6, 48} Empirical design (1)	50
4 (2.5, 4, 6, 1.5)	4 (1, 1, 1, 1)	{6, 48}; {6, 24}; {3, 36}; {6, 48} Empirical design (2)	100 (crit = 73.57)
4 (2.5, 4, 6, 1.5)	4 (1, 1, 1, 1)	{5.21 13.9}; {3.9 13.9}; {9.83 13.9}; {5.73 15.1}	558
2 (1.5,6)	8 (4, 4)	{5.73, 15.1} {5.73, 15.1} {5.73, 15.1} {5.73, 15.1}; {10.7, 15.1} {7.54, 11.7} {4.74, 9.01} {9.83, 13.9}	563
4 (1.5, 2.5 ,4 ,6)	8 (2, 2, 2, 2)	{5.73, 15.1} {5.73, 15.1}; {4.74, 13.9} {4.74, 13.9}; {3.90, 13.9} {10.7, 15.1}; {8.24, 12.7} {10.7, 15.1}	554
3 (2.5, 4, 6)	8 (3, 2, 3)	{4.74, 13.9} {4.74, 13.9} {4.74, 13.9}; {3.9, 13.9} {3.9, 13.9}; {9.83, 13.9} {9.83, 13.9} {9.83, 13.9}	549

- number of groups and number of doses appear not to be relevant
- sampling time has been identified as the key driver to optimize the design

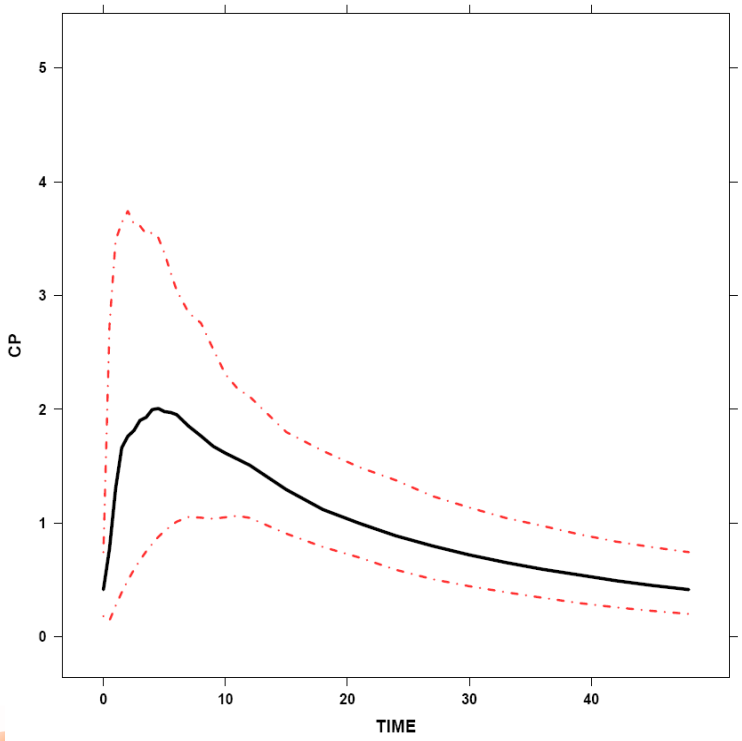
Simulation approach to assess the design performance

- Simulate RO time course with optimal and empirical time-points (~ Cmax and trough levels)
- Study design: 4 doses (1.5, 2.5, 4 and 6 mg); 4 subjects per dose (16 subjects in total)
- RO were sampled at two time-points
  - Empirical design: {6, 48} {6, 24} {3, 36} {6, 48}
  - Optimal design (at least 4 hours between two PET scans): {5.21 13.9} {3.9 13.9} {9.83 13.9} {5.73 15.1}
- Test the performance of the two approaches (bias, precision and accuracy)

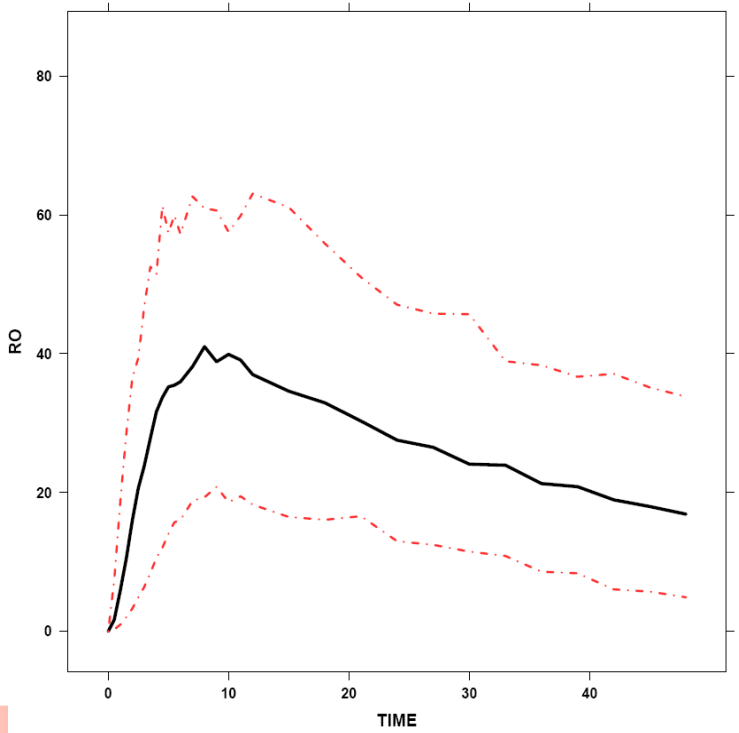
PK and RO profile (typical dose)

- PK/PD model defined using pre-clinical data (kon=0.088 and koff=0.221, variability=30%) and human PK data (first order absorption with 2 comp. model)
- N=1600 subjects were generated from the PK/RO model

PK profile (Median with 5th and 95th perc.)

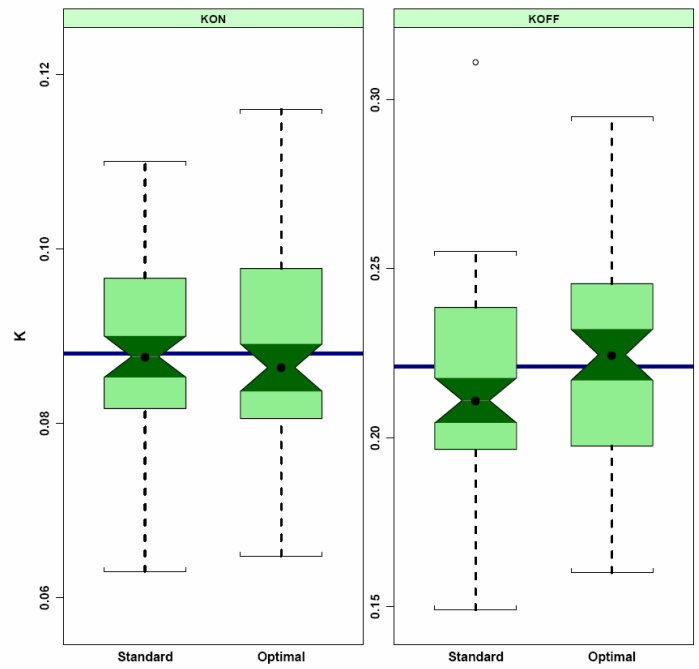


RO profile (Median with 5th and 95th perc.)



Simulation – Results

- 100 trials (with 16 subject/trial) where generated using a Monte Carlo simulation approach
- A non-linear mixed-effect methodology was used to estimate the kon and koff parameters with their inter-individual variability
- Performances were measured as bias, precision and accuracy on kon and koff estimates

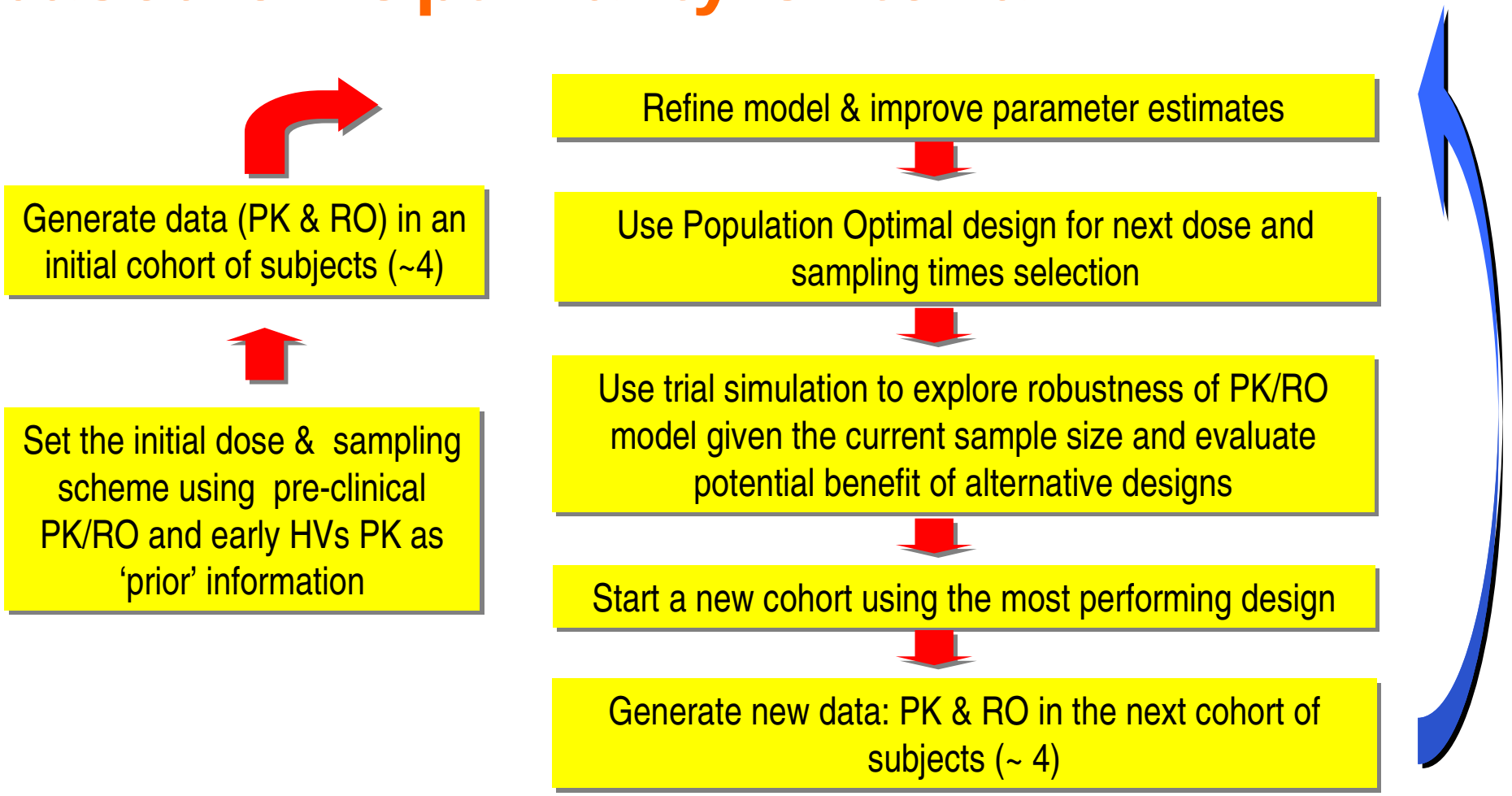


Performance	Measure	Standard		Optimal	
		Kon	Koff	Kon	Koff
Unscaled measures					
Bias	**ME**	3.32	6.84	0.0274	0.0799
Precision	**Var**	216	898	0.0692	0.614
	SD	14.7	30.0	0.263	0.783
Accuracy	**MSE**	227	944	0.0699	0.620
Scaled measures					
Bias	**SME**	37.7	31.0	0.311	0.361
Precision	**CV**	431	424	228	260

ME = mean error, Var = variance, SD = standard deviation, MSE = mean square error, SME = scaled mean error, CV = coefficient of variation

As expected the optimal study design approach provided more accurate and reliable model parameter estimates

Design of sequential PET experiments based on Optimality Criteria



Conclusions

- A mechanistic model has been proposed to estimate the RO time-course and the time-varying link between PK and RO
- Optimal study design approach provided more accurate and reliable model parameter estimates
- The use of sequential model design could increase the efficiency of the study for the PK/RO assessment especially when the human receptor kinetic model cannot be properly inferred from animal estimates
- Further work to develop a standardized methodology for the use of sequential optimal design approach is in progress