Design and power PK/PD experiments using very sparse data

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Clinical PK-Modeling and Simulation, GlaxoSmithKline

Background

- The optimal design of population PK/PD studies is crucial to maximize the efficiency and information-gathering of pharmacological experiments
- The objective of optimal design is to define the best number/timing of samples, dose(s), number of subjects and groups in the trial
- Both simulation-based and analytical (Population Fisher Information Matrix) method have been proposed for evaluation/optimization of population designs

The Problem

Feasibility might limit the number of samples in PK/PD experiment to one per subject

- Dosimetry (imaging studies) / Ethical reasons in humans
- Destructive sampling in preclinical studies (binding)

The optimal design methods assume both PK/PD model parameters values (and variability) as known

Often PK/PD parameters are guessed based on:

- PK, pKi, and additional information (binding in other species, other biomarkers, etc.)

Objective

To develop a method to design and power very sparse PK/PD experiments* accounting for inter-individual variability on PK and PD measurements and uncertainty on structural model parameters^

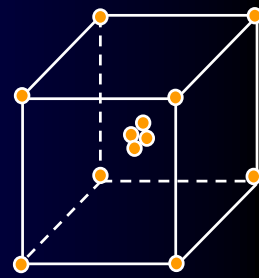
* one PK/PD sample per subject

^ assumed known in an interval

Focus is on population averages (θ). *Compelling evidence proving it is not possible to obtain realistic variability estimates* (η) *with one sample/subject*

Method Strategy

1) Set plausibility bounds for the unknown parameters (generate a hypercube in which the true parameters should fall)



2) Optimize the Population Fisher Information Matrix (Retout et al. 2001) for the vertexes of the hypercube

3) Join the local optimal designs to define a global design

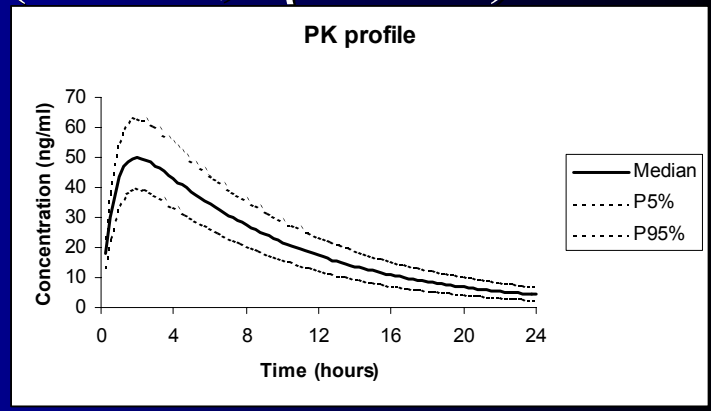
4) Evaluate the bias/precision of the global design using Monte Carlo simulation assessing the impact of PK and PK/PD variability

Initial Hypotheses

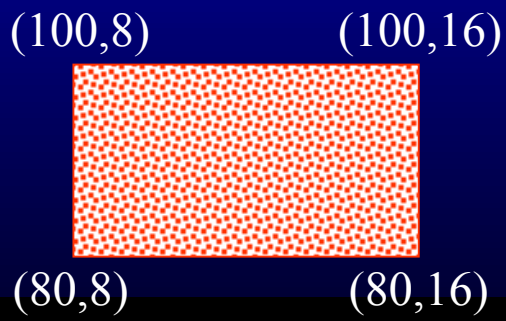
- PK parameters are assumed known (both θ, η and σ) from previous experiments

$V = 47.6$ l, $K_e = 0.115\ h^{-1}$, $K_a = 1.34\ h^{-1}$

η = 10% lognormal, σ = 10% lognormal



- The structure of PK/PD relationship is assumed (Emax)
- The PK/PD parameters are unknown but their bounds are available



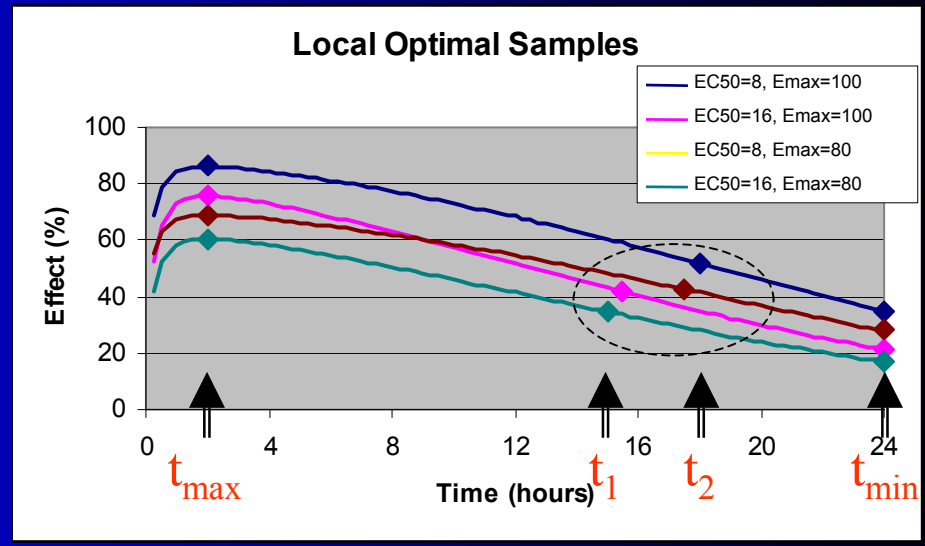
$EC_{50} \in$ 8-16 ng/ml

$E_{max} \in$ 80-100 %

- PD η (10% lognormal) and σ (25 additive)

The Method

Selection of optimal local design (vertex) (1 sample/subject - 3 subjects) using PFIM & grid search. Assume error free PK but inter-individual variability and noise on PD



The 3 samples local designs differ for the intermediate point: global design is constructed taking the common samples and the lower and upper intermediate points (total 4 subjects)

The proposed optimal time-points are : $[t_{max}, t_1, t_2, t_{min}]$

corresponding ~ to $[C_{max}, \max(EC_{50}), \min(EC_{50}), C_{min}]$

This design can be replicated (8, 12 ... subjects)

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Simulation Rationale

Is the proposed design sufficient to yield unbiased (θ) estimates?

Is it possible to properly power the proposed design in order to obtain a predefined precision?

We answered to these questions in a simulation context

Simulations (Bias)

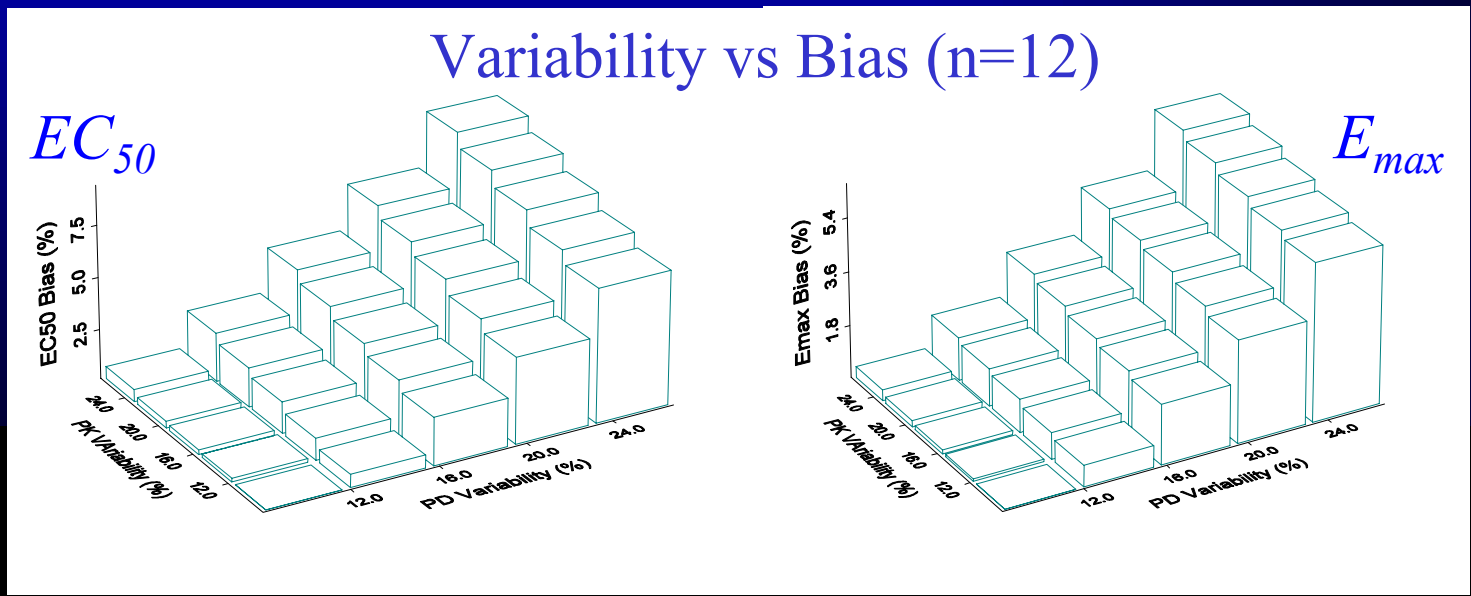
- Randomly select 20 (EC_{50}, E_{max}) pairs within the plausibility range
- For each (EC_{50},E_{max}) pair generate 100 realizations of the sparse sampling design
- Estimate (EC_{50},E_{max}) for each realization to evaluate bias of the proposed design
- Assess the impact of variability in PK (10-25%) and PD (10-25%) on the bias

Simulations (Power)

- Use the selected 20 (EC_{50}, E_{max}) pairs
- Simulate different # of subjects (4, 8, 12, ...) and different levels of PK variability (10-25 %)
- Estimate 100 realizations of each (EC_{50}, E_{max}) pair to assess the precision obtained with the proposed design
- Change the PD variability (up to 25%)

Results (Bias)

- The proposed method yields unbiased estimates even with the 4 subject design (with η = 10% on the PD)
- Bias increases with increasing PK variability (but always NS)
- Change PD variability (η =10 - 25%) changes significantly bias (16 subjects needed for unbiased estimates at top η)
- Combined increases in PD and PK variability amplifies the bias



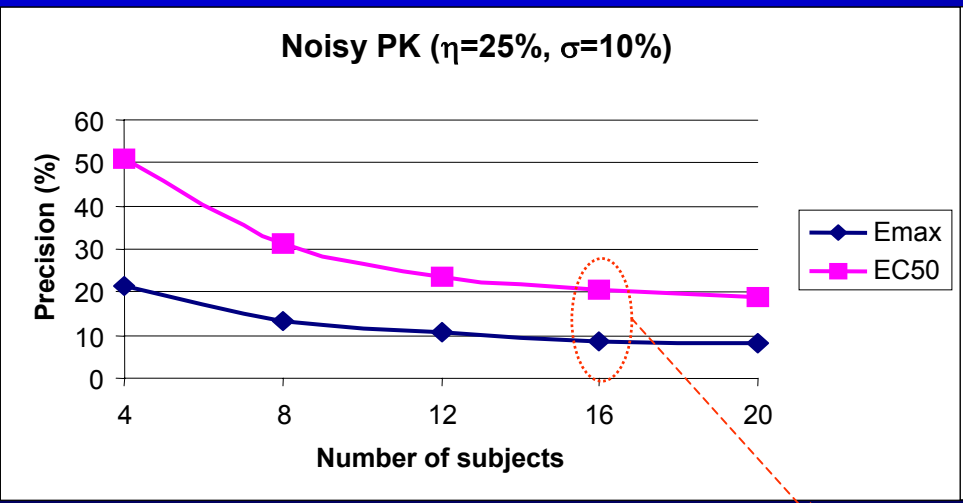
Results (Power)

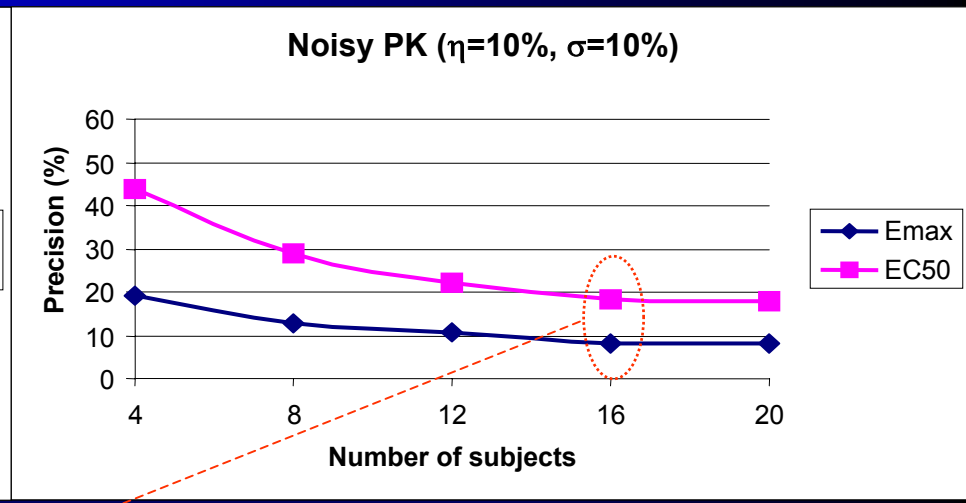
Monte Carlo simulations indicate that:

1) The influence of PK variability is small but significant

2) Precision increases with the number of subjects as a power low

3) Emax is always better estimated than EC50





E.g. precision 20% (E_{max}, EC_{50}) can be obtained with 4 replicates of the basic design and 1 PK/PD sample per subject (total n=16)

4) Change PD variability changes significantly precision (doubling η error ~ doubles)

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Conclusions

- A novel method has been proposed to optimally design population PK/PD experiments with very sparse sampling and a priori uncertainty on the parameters to be estimated
- The method is based on PFIM and grid search to select the optimal time-points. Monte Carlo simulations are used to estimate the power of experiments and assess the impact of different variability levels
- The results indicate that this method can be a valuable tool to optimally design and conduct pharmacological experiments with a minimal number of subjects and measurements/subject