PK/PD sampling design optimization following a sustained release formulation of triptorelin using optimal experimental design

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Objectives

- Sustained release administrations of drugs have improved long-term treatments for the patient.
- The design of clinical trials in such situations is complex due to the high number of samples required to obtain a precise prediction of the drug response.
- In the case of triptorelin (TPT) administered to supress testosterone (TST) levels in prostate cancer patients the study duration was 4 month and involved 32 samples per patient.
- The aim of this work was to use optimal design theory to reduce the number of samples per patient based on a previously developed receptor-based pharmacokinetic-pharmacodynamic (PK/PD) model for the TST effects of TPT.

Methodology

Pharmacometric Model

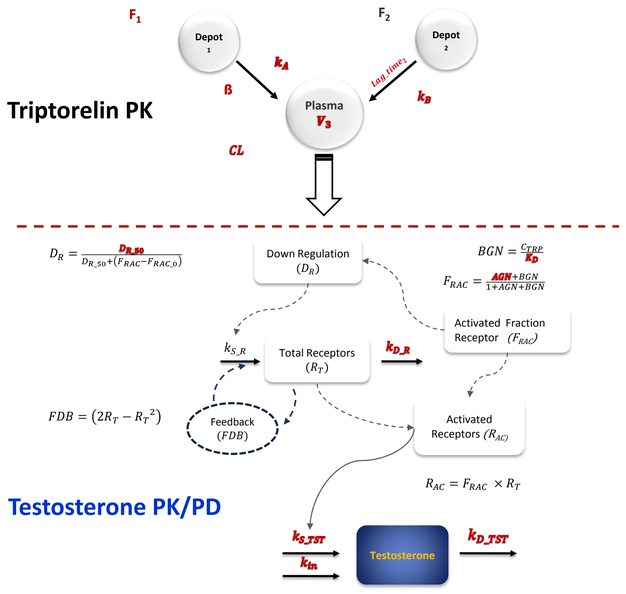
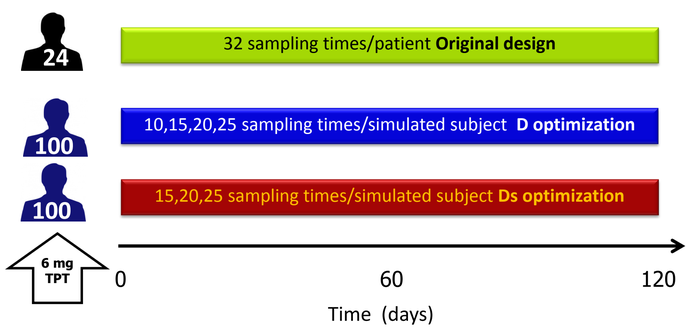


Figure 1. Mechanistic-based pharmacodynamic model of triptorelin effect on testosterone levels after prolonged administration.

Pharmacokinetic parameters	Typical value Estimate	BSV %CV
CL/F (L.day)	41.04	-
V_C/F(L)	11.6	26
F_1	0.26	42
F_2 [b]	0.74	-
B	0.815	-
k_A (day^{-1})	0.068	23
k_B (day^{-1})	7.51 x 10^{-5}	-
Lag time$_2$(day)	1.57	-
Residual [sd,(ng/mL)]	0.26	-
PK/PD parameters		
$TST_{(0)}$ (ng.mL^{-1})	3.68	28
k_D (ng.mL^{-1})	0.913	-
D_{R_50}	0.0289	35
k_{D_R} (day^{-1})	0.202	34
k_{in} (ng·mL^{-1} ·days^{-1})	0.039	31
k_{D_TST} (days^{-1})	0.492	-
AGN	0.386	-
Residual [sd,(ng/mL)]	0.40	-

Estimates are listed with their corresponding coefficient of variation (CV(%); β, Derived parameter from Weibul function, [b], F2 = 1-F1,

Optimal design



- PK/PD model implemented in PopED [2]
- Optimization performed using the D and Ds optimality criteria. For the later, only the PD parameters were considered interesting.
- Modified Fedorov Exchange algorithm with a grid of one sample per day and no replicates was used for the optimization.

In order to compare designs the efficiency was computed as:

$$D_{Eff} = \left(\frac{|FIM(\vec{x_1}, \vec{\Theta})|}{|FIM(\vec{x_2}, \vec{\Theta})|}\right)^{1/p}$$

Where *FIM* is the Fisher information matrix, $\vec{x_1}$ and $\vec{x_2}$ are two different designs, and $\vec{\Theta}$ are the model parameter values and *p* are the number of parameters in the designs.

Results

Comparable coefficients of variations as for the original design were obtained with 62.5 % optimal samples. Similarly, to achieve 100% efficiency only 10 samples with optimal time were needed. Focusing on the PD parameters using Ds optimality permitted a reduction to 87.5 % of the initial number of samples while maintaining 100% efficiency.

Fisher information Matrix

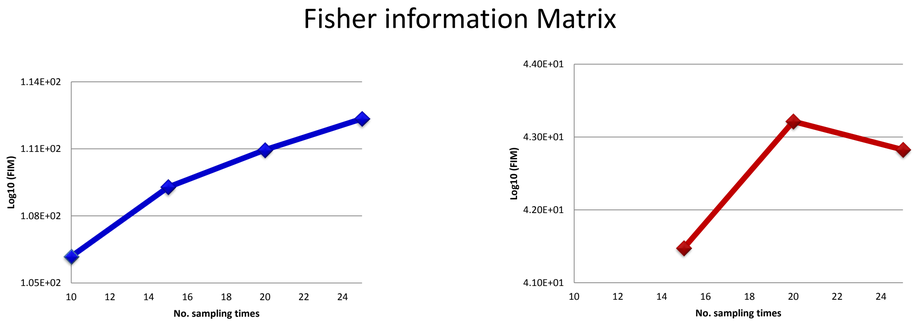


Figure 2. Fisher information matrix plotted on log10 scale vs number of sampling times obtained from D optimization approach (left panel, blue color) and Ds optimization approach (right panel, red color).

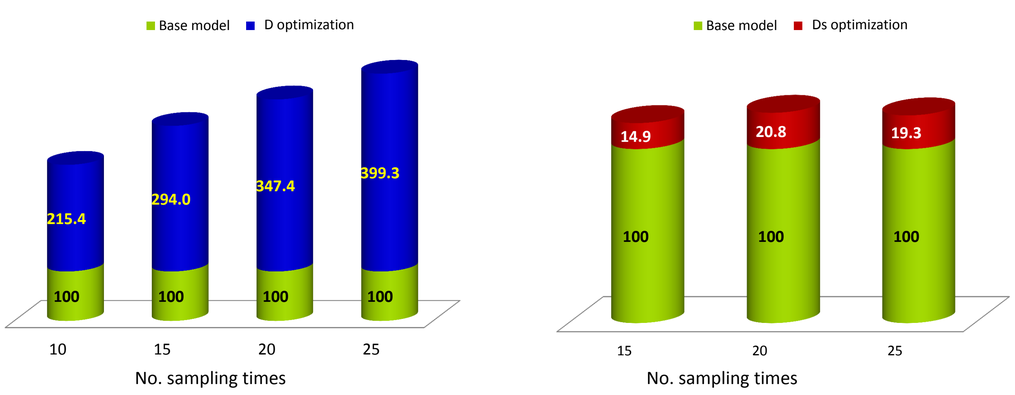


Figure 3. Ratio of efficiency from D and Ds optimization approaches. Values are expressed as percentages.

Coefficient of variation per parameter

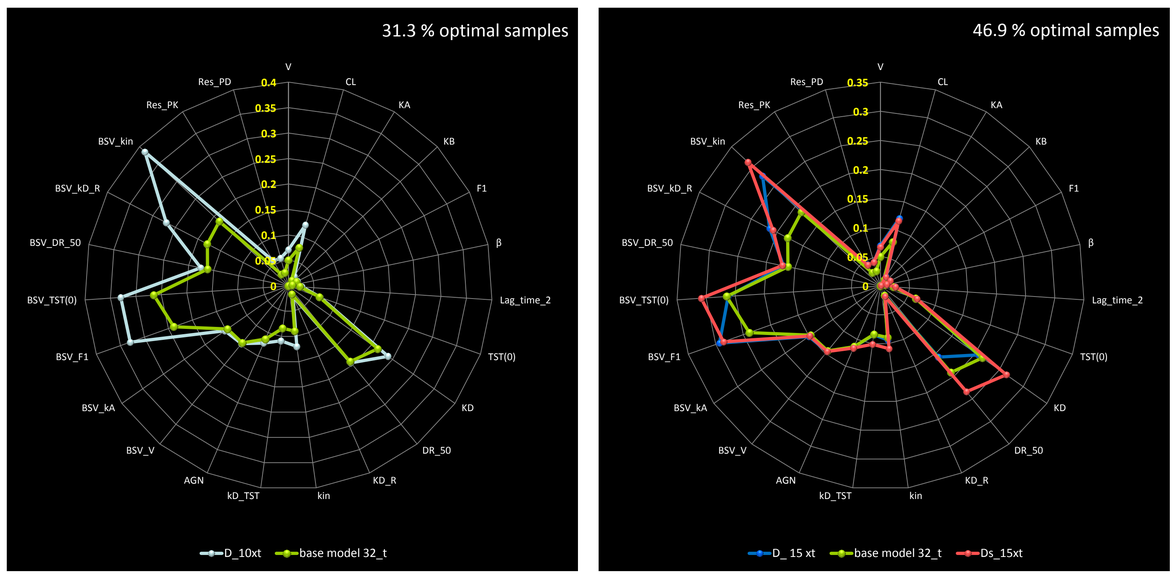
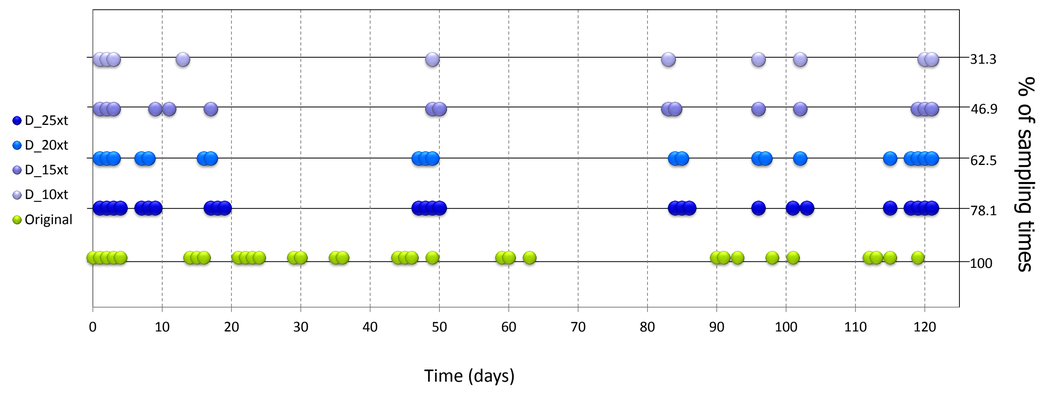


Figure 4. Variability per parameter estimated reported as coefficient of variation and plotted on yellow scale, D and Ds optimality design at same schedule times (xt) 10,15,20 and 25 are plotted *vs* base model of 32 sampling times (t).

Optimal sampling schedule D optimality criteria



Optimal sampling schedule Ds optimality criteria

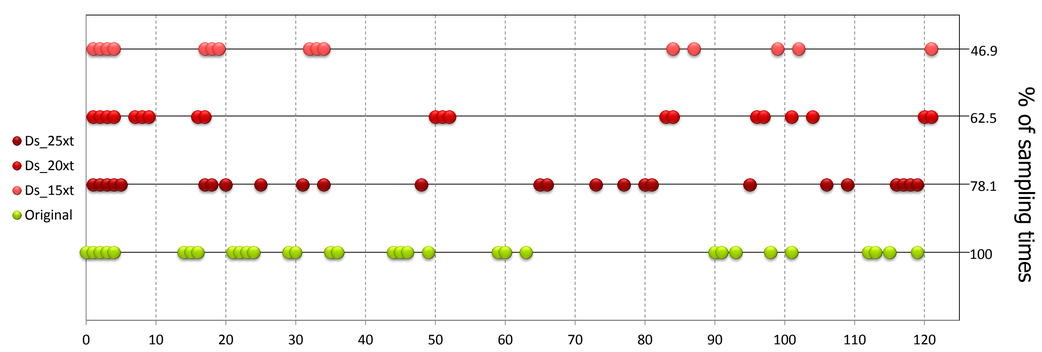


Figure 5. PK and PD sampling times were optimized simultaneously. PK and PD data observation is acquired at the same sampling time. Different number of sampling times (10,15,20,25) were optimized and plotted with original design (32 sampling times)

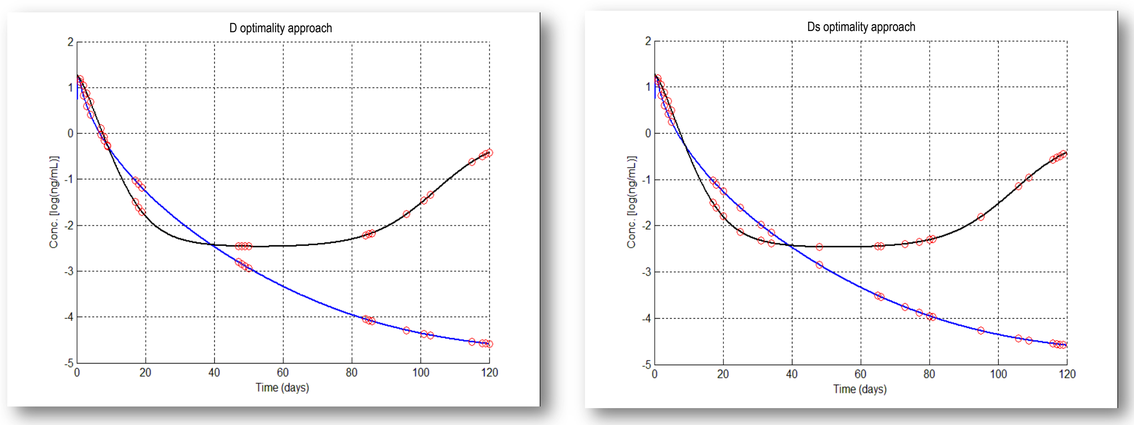


Figure 6. Plotted results of optimization approaches. Blue line represents typical PK profile of triptoreline, black line represents typical profile of testosterone. Red empty circles represent PK and PD optimized sampling times.

Conclusions

Using optimal design theory the number of samples in a long term sustained release trial could be substantially reduced, lowering both costs and patient burden..

Bibliography

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[2] Foracchia M, Hooker A, Vicini P, Ruggeri A. POPED, a software for optimal experiment design in population kinetics. Computer Methods and Programs in Biomedicine. 2004 Apr;74(1):29-46