Application of Optimal Design for Disease Progression Studies

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Background and Objective

Disease progression (DP) studies are performed to obtain information on the effect of drugs for the long term prognosis on a disease. The aim of this study is to demonstrate an application of optimal design optimizing period lengths (delayed start, treatment, wash-out) for DP studies. Additionally, to characterize drug effects across different mechanisms and magnitudes allowing model discrimination through uncertainty on parameter values and the expectation of the determinant (ED).

Methods

- 3 linear drug effect models (protective (P), symptomatic (S) and protective+symptomatic (PS)) were used in combination with a linear natural history model
- Model parameters:

Baseline natural history	S_0=100
Slope natural history	α_0 = 2
Baseline symptomatic effect	S_s = 90
Slope protective effect	α_p = 0.2
Between subject variability on all fixed effect parameters (CV%)	30%
Parameter uncertainty on α_0 (mean, var)	N(2, 0.1)
σ^2_{add}	10
σ^2_{prop}	22%

- Optimization on: (I) start and stop time of the treatment during the study and (II) simultaneously[1] on period lengths and sampling times
- Study design: total study length of 12 time units, 13 evenly spread fixed observations times
- Additional study designs: without wash-out periods, with more or less samples or observation time
- Effect differentiation: employing ED-optimality with a uniform distribution from 0-100% of total effect on effect parameters (P or S)
- ED-optimality was performed using PopED v.2. (http://poped.sf.net)
- Simulation (n=1000) and re-estimations using NONMEM VI
- RMSE and ME were calculated for 9 particular effect combinations

Results and Discussion

- Optimal start and stop times for the flexible start and stop time design are shown in Figure 1
- Table 1 shows the number of observations which would fall into the three study periods depending on the optimal start and stop time of treatment
- An efficiency loss of 10-40% on average per parameter was found if no observations were taken during the wash-out period
- Simultaneous optimization on sampling times and treatment period improved the efficiency of the designs by 35-50%
- Relative merits of extending the study length compared to increasing the number of samples per individual are shown in Figure 2

***Table 1**: Optimal design results under the flexible start and stop time design, and designs with no observations during washout.*

Design	Model	Percentage of Observation (%) Before Treatment	During Treatment	After Treatment
Flexible start and stop time design	Protective	0	50	50
	Symptomatic	20	50	30
	Protective + Symptomatic	10	40	50
	Combined Models	10	50	40
No washout observations	Protective	50	50	-
	Symptomatic	10	90	-
	Protective + Symptomatic	50	50	-
	Combined Models	10	90	-

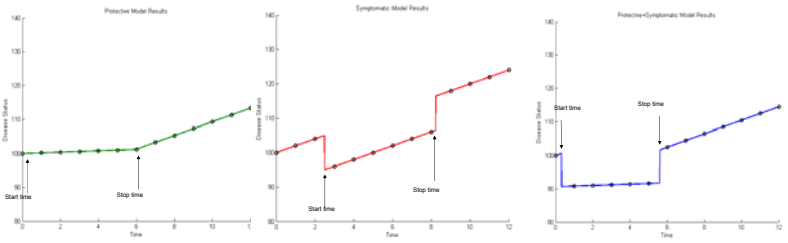

***Figure 1**: Results from optimal designs for different disease progression effect models under the flexible start and stop time design showing start and stop time of treatment as well as sampling times (black dots) during a 12 time units long study.*

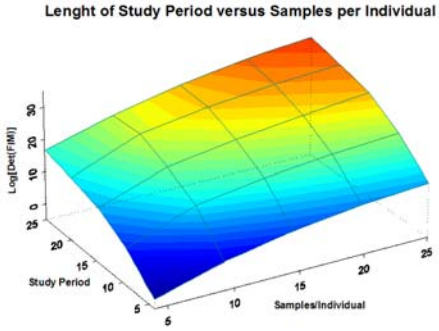

***Figure 2.** The logarithmic determinate of the Fisher information matrix surface versus study length and samples/individual, extrapolated from 24 tested design options for the protective and symptomatic model. The blue areas show low information designs and the red areas high information designs.*

- Design optimized for a uniform distribution of effects (start time = 1.07, stop time = 6.11) showed good performance in comparison with designs optimal for a specific effect (Figure 3)
- Confidence regions spanning large parts of the parameter range made differentiating between some close effects impossible (Figure 4)
- Low bias for all fixed effect parameters under the tested 9 effect combinations can be shown and the RMSE for 92% of the fixed effect parameters was under 20% (Figure 5,6)

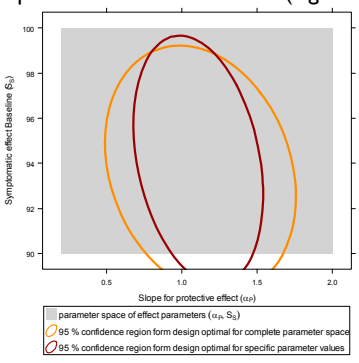

***Figure 3.** Confidence region after optimization for the full effect range (orange) versus optimization on a specific effect (red, here: P50%S50%).*

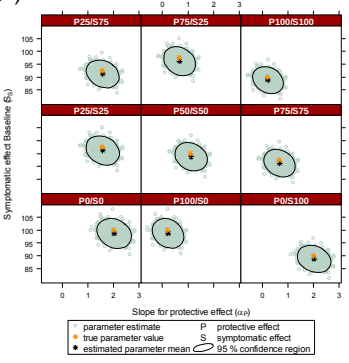

***Figure 4.** 95% Confidence regions after simulations and re-estimation of 9 particular effect combinations from the optimal design optimized for the full effect range.*

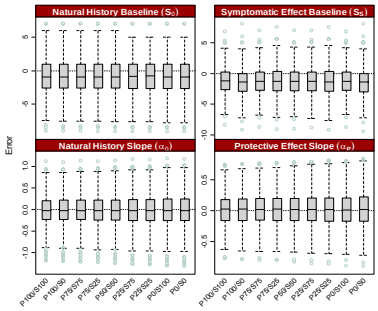

***Figure 5.** Absolute Error shown for the 4 fixed effect parameters under the uniform ED-design (P=rotective effect, S=symptomatic effect)*

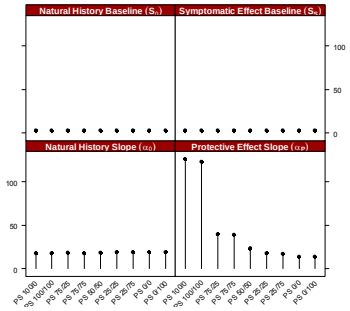

***Figure 6.** Relative mean standard error (RMSE) shown for the 4 fixed effect parameters under the uniform ED-design*

Conclusion

- Results shown in this study illustrate how DP study designs can benefit from formal optimal design analysis
- Additionally we can illustrate how ED-optimality can be used to optimize for a wide range of effects

Reference:

1. Nyberg J, Karlsson MO, Hooker A. Sequential versus simultaneous optimal experimental design on dose and sample times. PAGE 16 (2007) Abstract 1160 [www.page-meeting.org/?abstract=1160].