Clinical trial optimization of efficacy studies in slowly progressive diseases

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CONTEXT

- ❑ **Treatments in slow progressive diseases can have both symptomatic and/or disease-modifying effects.**
- ❑ **Symptomatic effects are quickly apparent, so can be shown in short clinical trials.**
- ❑ **Disease-modifying effects are more difficult to show, requiring longer study duration.**
- ❑ **Delayed start or washout designs may improve study power, but are difficult to implement (ethical concerns).**
- ❑ **Due to high variability of disease progression, a high dropout and a high variability on reported disease scores, a high number of patients is required.**
- ❑ **Clinical Trial Simulation can help to quantify the probability of a successful trial (PoS), and can optimize trial design to maximize the probability to reject a suboptimal compound, or demonstrate efficacy of a good compound.**

MODEL

A literature Parkinson Disease model [1] was implemented in Simulo to simulate UPDRS score in a Phase II proof of concept trial.

disease modifying drug effect — Symptomatic drug effect — time profile

Disease progression rate — time profile

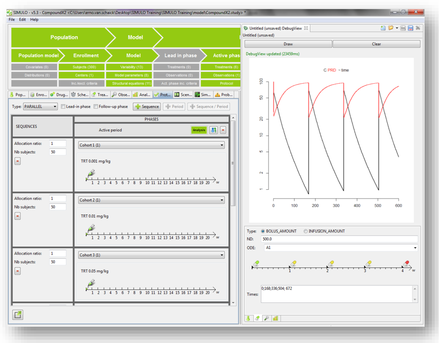
$$\frac{dDP(t)}{dt} = \alpha + \beta_{slope} Ce(t) \qquad E_0(t) = \beta_{offset} Ce(t)$$

$$S(t) = S_0 + DP(t) + E_{plac}(t) + E_0(t)$$

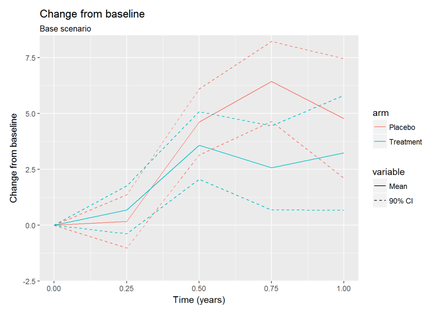
TRIAL DESIGN

Parameter	Assumption
Subjects	150 per arm
Treatment arms	Placebo and active (1:1)
Observation schedule	Every 3 months
Study duration	1 year
Treatment effect	Slow the disease by 50% No symptomatic effect

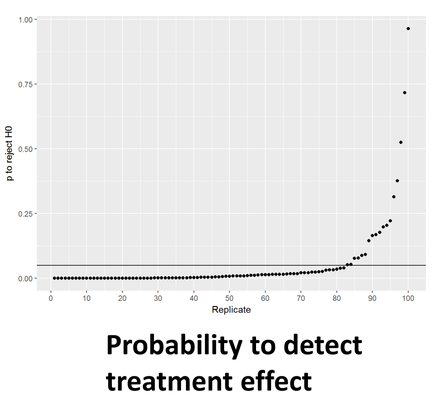
METHODS



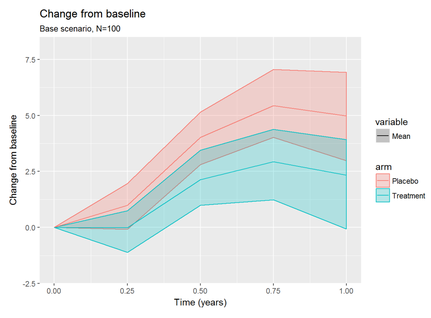
Simulate 300 subjects in N=100 trials



Single trial summary statistics



Probability to detect treatment effect



Confidence interval on mean across N=100 trials

Simulations performed using Simulo clinical trial simulator (www.exprimo.com/simulo)

KEY RESULTS

Scenario	Parameters (*)			Answer or decision
Base Design	Base 49/79/91/74			**Study has sufficient power.**
Study design				
Subjects	100 36/65/70/51	150 49/79/91/74	200 52/82/91/69	150 subjects is adequate 200 subjects does not improve PoS
Observation schedule	Q6m 45/72/68/57	Q3m 49/79/91/74	Q1w 47/46/84/76	No improvement when sampling often
Study robustness				
Treatment effect	None 5/15/20/13	Half 23/46/53/41	Base 49/79/91/74	Model-based analysis detects a treatment effect within the noise
Delay in effect	No delay 49/79/91/74	2m 38/67/76/66	4m 26/52/52/51	Shortens the study duration
Dropout	Normal 49/79/91/74	Double 29/64/80/71		Model-based analysis is robust
Disease progression	Naive 49/79/91/74	MOABi treated (DP=8/yr) 56/76/84/56		No difference, except on disease progression
Placebo K_{ON}	Base 49/79/91/74	Twice as slow 46/82/85/65		No influence, except on disease progression
Placebo P_{MAX}	Base 49/79/91/74	Double 48/83/89/65		No influence, except on disease progression

*: PoS reported as W/X/Y/Z (%), with W = probability to reject H0 with t-test, X = probability to reject H0 using MMRM method, Y = probability to reject H0 using model-based analysis, Z = probability to detect significant disease-modifying effect using model-based analysis
(1): For this case, low PoS signifies low probability of false positive

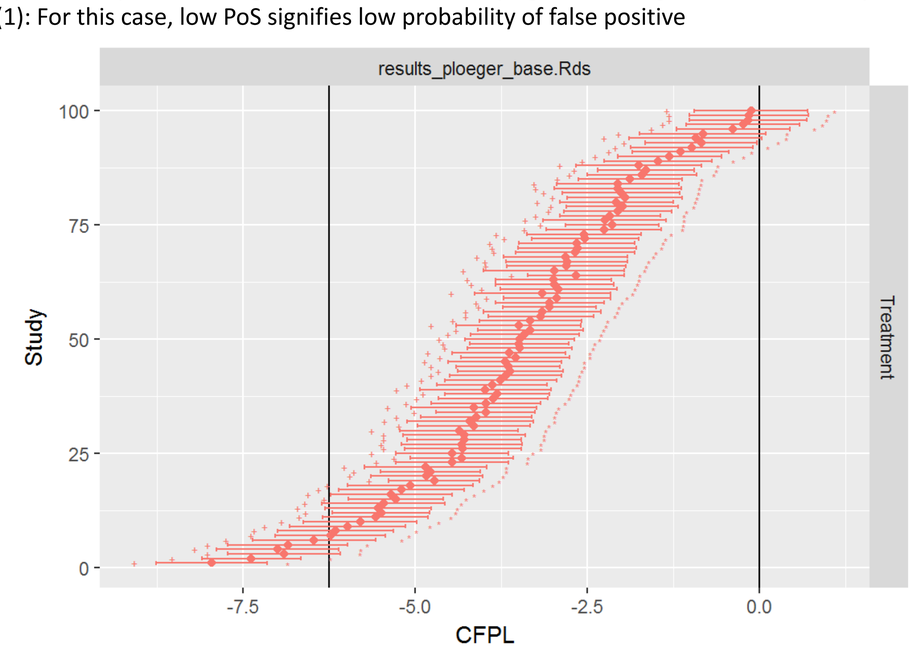


Figure: Overview of placebo-corrected Change from Baseline at endpoint, imputed using model-based analysis. The true treatment effect of -50% is almost never detected.

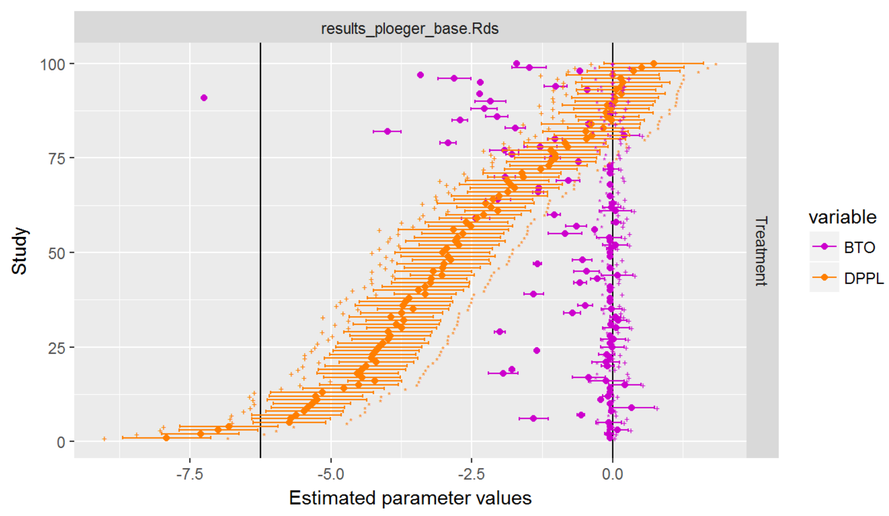


Figure: Overview of possible trial results after model-based analysis. Model-based analysis may detect a symptomatic effect (BTO) in some trials.

CONCLUSIONS

- ❑ **Disease-modifying effects can be detected using model-based analysis, provided the sample size is high enough.**
- ❑ **Model-based analysis increases probability of success for clinical trials in Slowly Progressive Diseases.**
- ❑ **Clinical Trial Simulation is an essential tool when designing Proof of Concept studies for internal decision-making.**

[1] Ploeger, Berend Arnold, and Nicholas HG Holford. "Washout and delayed start designs for identifying disease modifying effects in slowly progressive diseases using disease progression analysis." *Pharmaceutical statistics* 8.3 (2009): 225-238.