Optimizing trial designs for distinguishing short (symptomatic) and long-term (protective) treatment effects from natural disease progression

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Introduction
The onset of the treatment effect in slowly progressive diseases, such as Parkinson's and Alzheimer's might either be short and reversible or long and persisting after stopping treatment. Reversible short-term effects are referred to as 'symptomatic' while long-term effects are referred to as 'protective' or 'disease modifying' [1].

For estimating the actual treatment effect it is essential to distinguish the time course of treatment effects from those due to natural disease progression. Therefore, changes in clinical status over time in untreated patients should be taken into consideration in the analysis of clinical trials in slowly progressing diseases [1]. In addition, the trial design should be able to distinguish short-term and long-term treatment effects from natural disease progression.

When (mixed effects) disease progression modeling is applied to analyze the change in disease status over time the designs should give unbiased and precise estimation of the effect sizes. This can be evaluated using clinical trial simulation in which the simulated trial outcome is analyzed with the disease progression model repetitively to estimate bias (i.e. the relative difference from the true value) and imprecision (standard deviation of the bias).

Although NONMEM serves as a well established and flexible tool for this, the computational work might limit the number of scenarios that can be evaluated. Optimizing the determinant of the Fisher information matrix, using WinPOPT [2], is a less computationally intensive alternative. As this approach only provides insight into imprecision and not in bias we explored the use of WinPOPT to select trial designs for evaluation in NONMEM. For this purpose we compared the imprecision estimates of WinPOPT and NONMEM.

Aim
To compare the efficiency of different trial designs (parallel group, washout and delayed start) in describing the effect of drug treatment in slowly progressive diseases, using WinPOPT and NONMEM.

Methods
*Disease progression models assuming linear disease progression in untreated patients, a transient placebo effect and a combined symptomatic and disease modifying treatment effect were implemented in WinPOPT and NONMEM. The placebo effect was estimated using literature data and the overall treatment effect was comparable to that of delayed [2] (6% per year) assuming that 50% is due to a symptomatic effect with a delayed onset of 14 or 30 days and the other 50% is due to a immediate disease modifying effect. The Fisher information matrix criterion reported by WinPOPT was used for comparison of the designs. If the criterion ratio between design A and design B is greater than 1 then design A is more efficient compared to design B.

The number of treatment groups was optimized for the delayed start and wash-out design and for the wash-out design the length of the wash-out period was optimized.

In the NONMEM analysis 100 datasets were simulated and subsequently analysed using the same disease progression model with the FOCE interaction method (NONMEM VI version 1.2).

Models
Combined symptomatic and disease modifying effect

\[ S(t) = S_0 + E_0(t) + DP(t) + E_{\alpha\beta}(t) \]

Placebo effect

\[ E_0(t) = \beta_0 + \alpha \times e^{-\gamma t} \]

Symptomatic effect

\[ E_0(t) = \beta_0 + \alpha \times (t - t_{\text{onset}}) + Ce(t) \]

Disease modifying effect

\[ DP(t) = \beta_0 + \beta_{\alpha\beta} \times \text{DoseRate} \]

\[ t_{\text{onset}} = \begin{cases} 0 & \text{_Delayed start} \\ t_{\text{Teq}} & \text{Wash-out} \end{cases} \]

Design assumptions
- Treatment groups: placebo and 1 – 3 active groups
- Sample size: 500 per group (or 1000 in total)
- Observations: 11 per subject
- Trial duration: 16.6 months
- Delayed start: 6 months
- Washout: 1 – 5 months

Results

**Fisher information criterion and imprecision of treatment effect estimated with delayed start (DS) or parallel group designs either with (WO) or without (PO) washout. A criterion ratio greater than 1 reflects a more efficient design**

Table: Design assumptions (WinPOPT vs. NONMEM)

<table>
<thead>
<tr>
<th>Design</th>
<th>Groups</th>
<th>Active</th>
<th>Washout</th>
<th>Criterion</th>
<th>Ratio</th>
<th>Imprecision</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2 0; 1 mg/day</td>
<td>13.6 3</td>
<td>0.70 1.39</td>
<td>90 -122.2 -113.8</td>
<td>0.50 1.00</td>
<td>1.67 0.97</td>
<td></td>
</tr>
<tr>
<td>DS 2 0; 1 mg/day</td>
<td>16.6 6</td>
<td>2.05 2.11</td>
<td>90 -201.6 -208.2</td>
<td>0.70 1.39</td>
<td>1.72 1.78</td>
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</tr>
<tr>
<td>WO 2 0; 1 mg/day</td>
<td>15.6 1</td>
<td>2.01 0.98</td>
<td>90 -48.1 -27.3</td>
<td>0.50 1.00</td>
<td>1.67 0.97</td>
<td></td>
</tr>
<tr>
<td>DS 2 0; 1 mg/day</td>
<td>16.6 3</td>
<td>2.01 0.98</td>
<td>90 -44.2 -19.0</td>
<td>0.70 1.39</td>
<td>1.72 1.78</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- The number of treatment groups has a minimal effect on the efficiency.
- A wash-out period of 3 months is optimal in the wash-out design for a drug with a fast symptomatic effect.
- A delayed start design is more efficient in estimating the effect size of drug treatment compared to a parallel group design with or without wash-out.
- The NONMEM standard error is over-predicted by WinPOPT for all evaluated designs. This over-prediction is greater for the wash-out design and for a drug with a slow onset symptomatic effect.