Utilizing the items from the MDS-UPDRS score to increase drug effect detection power in de novo idiopathic Parkinson's disease patients
Simon Buatois\textsuperscript{1,3}, Sylvie Retout\textsuperscript{1}, Nicolas Frey\textsuperscript{1}, Sebastian Ueckert\textsuperscript{2,3}

\textit{PAGE meeting 06/10/16}

1. pRED, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland
2. Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
3. IAME, UMR 1137, INSERM, F-75018 Paris, France
Parkinson’s disease (PD)

Causes of the disease uncertain[1]

Complex disease progression[2-3]

High number of failed clinical trials

Heterogeneous clinical assessment

MDS-UPDRS*
- 59 Items
- Composite score:
  - Non-motor
  - Motor

*Movement Disorder Society- Unified Parkinson’s Disease Rating Scale

[1] Parkinson’s disease foundation
PD clinical trials

- Primary outcome measure:
  - Change from baseline to end of trial in total MDS-UPDRS score

- Questions:
  - Could the power of detecting a drug effect be increased by changing:
    - **Outcome**: Analyzing a subset of the scale (most informative items) for a known drug effect?
    - **Analysis method**: Integrating the whole available items information using item response theory (IRT)?
Outline

Database Modelling Simulation


Parkinson’s Progression Markers Initiative (PPMI)

Model for PD score at baseline

Longitudinal MDS-UPDRS model

Most informative Items

Power study on the total number of items

Power study on the optimized set of items
PPMI Clinical Data

Ongoing study

- **Clinical Design:**
  - Observation times: every 3 to 6 months
  - **PD medications** (*de novo* PD patients):
    - At baseline all patients are treatment-naïve
    - PD medications may be initiated at any time
    - At 9 months more than 50% of patients were taking PD medications
      - L-dopa or dopamine agonists

---

[1] www.ppmi-info.org/data

*Subjects Without Evidence of Dopaminergic deficit*
Outline

Database
Modelling
Simulation


Model for PD score at baseline\(^1,2\)

Power study on the total number of items

Longitudinal MDS-UPDRS model

Most informative Items

Power study on the optimized set of items
Item Response Theory – IRT

• Methods:
  - Each item of the MDS-UPDRS is a surrogate measure of the neuronal disability
  - Relate the probability of the score $k$ in each item $j$ to an hidden variable $D$ for a patient $i$

Ordered categorical model

\[
P(Y_{ij} \geq k) = \frac{e^{a_j(D_i - b_{j,k})}}{1 + e^{a_j(D_i - b_{j,k})}}
\]

\[
P(Y_{ij} = k) = P(Y_{ij} > = k) - P(Y_{ij} > = k+1)
\]

- Item specific parameters:
  $a$ power of discrimination
  $b$ difficulty
Item Response Theory – IRT

• Results:

  - 3 correlated hidden variables $D_v$ accurately capture the composite nature of the MDS-UPDRS score:
    - Motor disability ($D_M$)
    - Non-Motor disability ($D_{NM}$)
    - Tremor disability ($D_T$)

  - Precise estimation for most of the item-specific parameters
    - RSE below 30%
Outline

Database
Modelling
Simulation

Power study on the total number of items

Power study on the optimized set of items

Model for PD score at baseline

Longitudinal MDS-UPDRS model\textsuperscript{1,2}

Most informative Items

Parkinson’s Progression Markers Initiative (PPMI)

Longitudinal MDS-UPDRS model

\[ D_{v,i}(t) = D_{v,i}^0 + \alpha_{v,i} \cdot t + S_{v,i}(t) \]

\[ S_{M,i}(t) = E_{M,i}^0 + \beta_{M,i} \cdot (1 - e^{-k_{eq} \cdot t_d}) \]
\[ S_{T,i}(t) = E_{T,i}^0 + \beta_{T,i} \cdot t_d \]
\[ S_{NM,i}(t) = E_{NM,i}^0 \]

\[ E^0 = \text{Symptomatic effect} \]
\[ k_{eq} = \text{Rate constant} \]
\[ \beta = \text{Symptomatic increase} \]
\[ t_d = \text{Time since start of drug} \]

Mean disease progression rate (unit/item/year)
Outline

Database
Modelling
Simulation

- Model for PD score at baseline
- Longitudinal MDS-UPDRS model
- Power study on the total number of items
- Power study on the optimized set of items
- Most informative Items
Clinical Trial Simulations (CTS)

• Model
  - Longitudinal MDS-UPDRS model
  - Hypothetical disease modifying drug effect:
    - **Scenario 1:** 50% reduction of the rate of disease progression (DP)
    - **Scenario 2:** 50, 30 and 20% reduction of the DP for respectively the motor, tremor and non-motor items

• Design
  - Placebo versus treatment arm
  - Observation times: 0 and 6 months
  - Population: de novo PD patients
  - Number of subjects: range from 0-600 patients
Select the most informative items

• **Methods:**
  - **Approach:** Compute the score difference $\Delta_c$ between placebo $S1$ and treatment $S2$ arms under the total number of combination $C$ of items and each scenario at end of trial
  - **Optimal combination of items:** $\text{argmax}_{c}(P(\Delta_c > 0))$
  - **Limiting factor:** $C (>10^{15}$ combinations) $\Rightarrow$ Greedy algorithm$^1$
    ▶ Heuristic to approximate the optimal set
    ▶ Corresponds to the forward approach in covariate selection

S1 and S2 were approximated by $N_{S1}(\mu_1, \sigma_1)$ and $N_{S2}(\mu_2, \sigma_2)$:
For each combination of items
  ▶ $\mu \cong \Sigma_j \bar{y}_j$
  ▶ $\sigma \cong$ variance for the sum of correlated variables

[1] Cormen T et al., 2009
Select the most informative items

Scenario 1:
Drug effect = 50% reduction
For all items

Scenario 2:
Drug effect = 50, 30 and 20 % reduction for M, T & NM items

Optimized set: 40 items

Optimized set: 34 items
Power to detect a drug effect

- Methods:
  - End of trial comparison
  - Power was computed using parametric power estimation (PPE) for the 2 scenarios and under different conditions:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Summary score</th>
<th>IRT model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>t-test/MMRM</td>
<td>LRT</td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Total number of items</td>
<td>Optimized set of items</td>
</tr>
</tbody>
</table>

Power to detect a drug effect

Scenario 1:
Drug effect = 50% reduction
For all items

Scenario 2:
Drug effect = 50, 30 and 20% reduction for M, T & NM items

\[ \Delta_1 = 13\% \]
\[ \Delta_2 = 31\% \]
\[ \Delta = 31\% \]
Power to detect a drug effect

Scenario 1:
Drug effect = 50% reduction
For all items

Scenario 2:
Drug effect = 50, 30 and 20% reduction for M, T & NM items

Expected drug effect = 20% M, 30% T and 60% NM
Conclusion

• **Adequate description** of the data at both item and total score level using **longitudinal three hidden variables IRT based modelling.**

• **Selection of the most informative items** of the MDS-UPDRS may be used to **increase power** of a summary score analysis. However, it requires an **accurate assumption of drug effect prior to the analysis.**

• **IRT analysis based** on all collected data items **increase the power** compared to the summary score analysis **without** the need for an **a priori selection** of the most informative items and is the **recommended approach.**
Acknowledgements

Inserm Colleagues:

Roche Colleagues: