Utilizing the items from the MDS-UPDRS score to increase drug effect detection power in de novo idiopathic Parkinson's disease patients

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PAGE meeting
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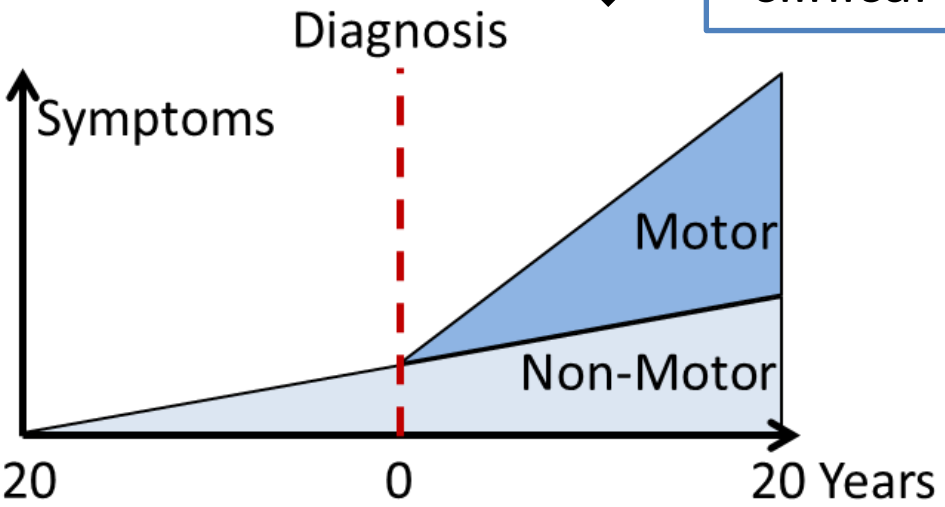
Parkinson's disease (PD)

[1] Parkinson's disease foundation
[2] Kalia L *et al.*, The Lancet. 2015
[3] Vu T *et al.*, Br J Clin Pharmacol. 2012

Causes of the disease uncertain[1]

High number of failed clinical trials

Complex disease progression[2-3]



Heterogeneous clinical assessment

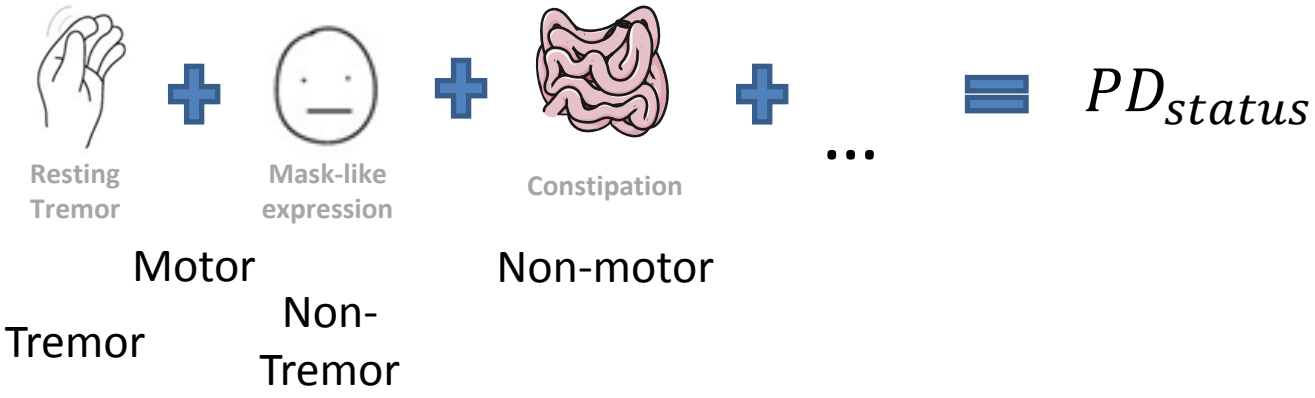
MDS-UPDRS*
- 59 Items
- Composite score:

Non-motor Motor

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

PD clinical trials

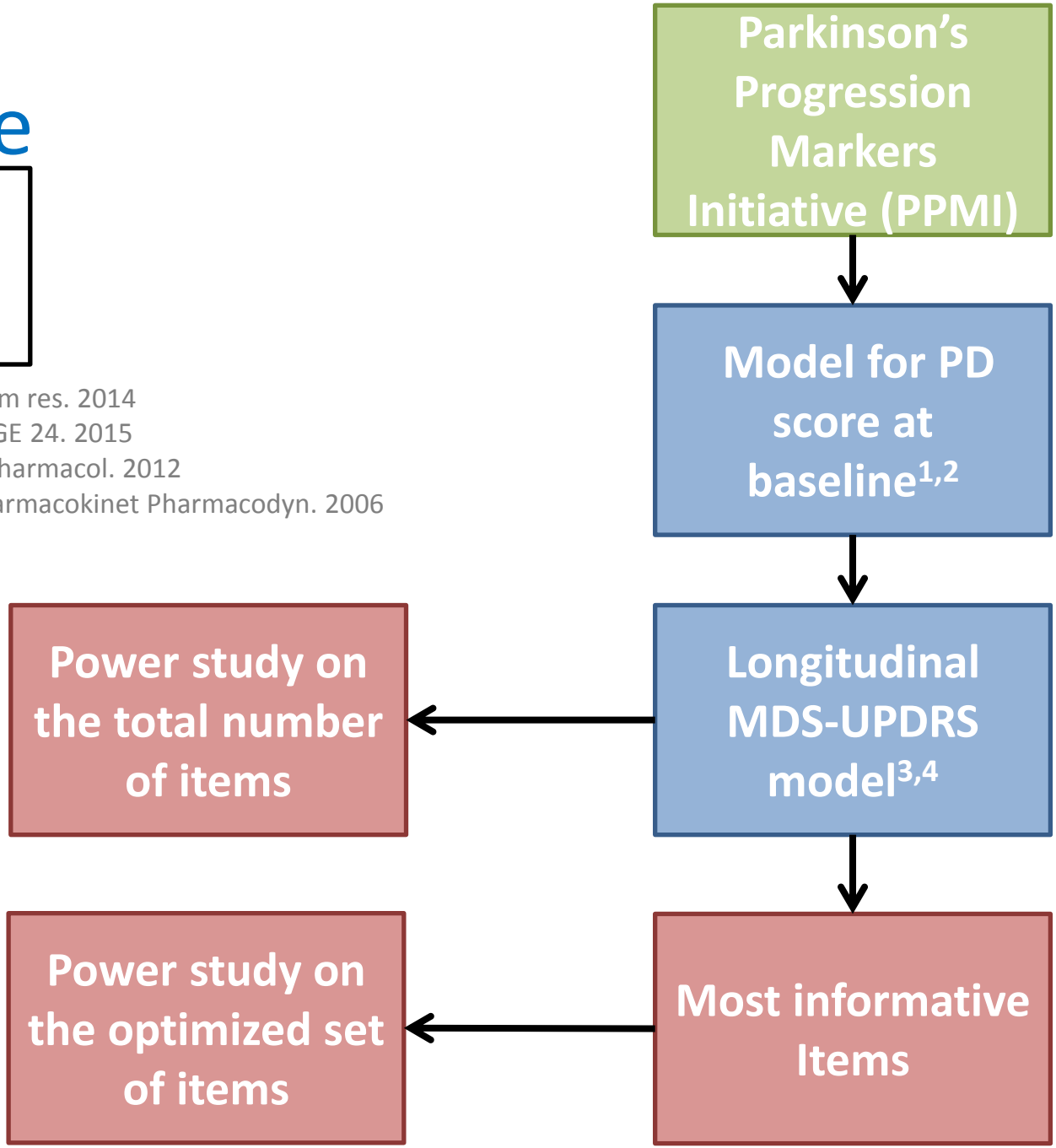
- Primary outcome measure:
  - Change from baseline to end of trial in total MDS-UPDRS score



- 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

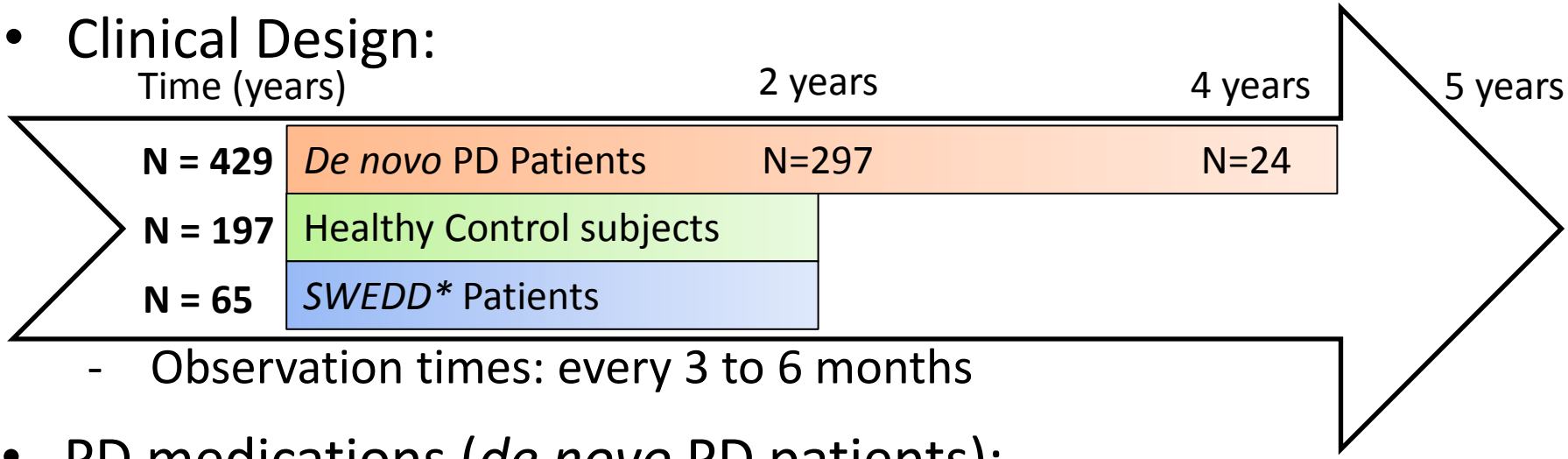


[1] Ueckert S *et al.*, Pharm res. 2014
[2] Gottipati G *et al.*, PAGE 24. 2015
[3] Vu T *et al.*, Br J Clin Pharmacol. 2012
[4] Holford N *et al.*, J Pharmacokinet Pharmacodyn. 2006

PPMI Clinical Data[1]

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

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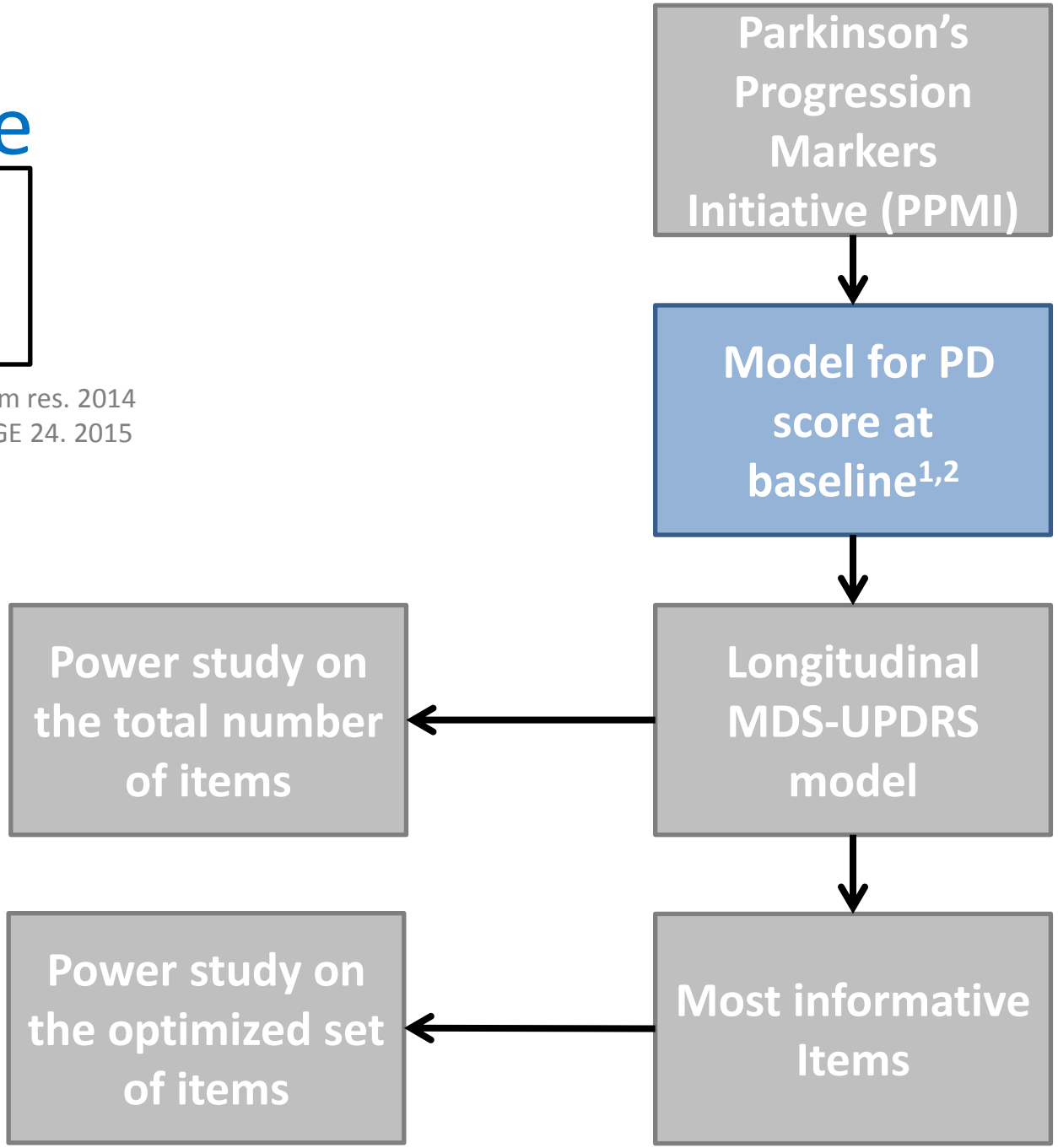
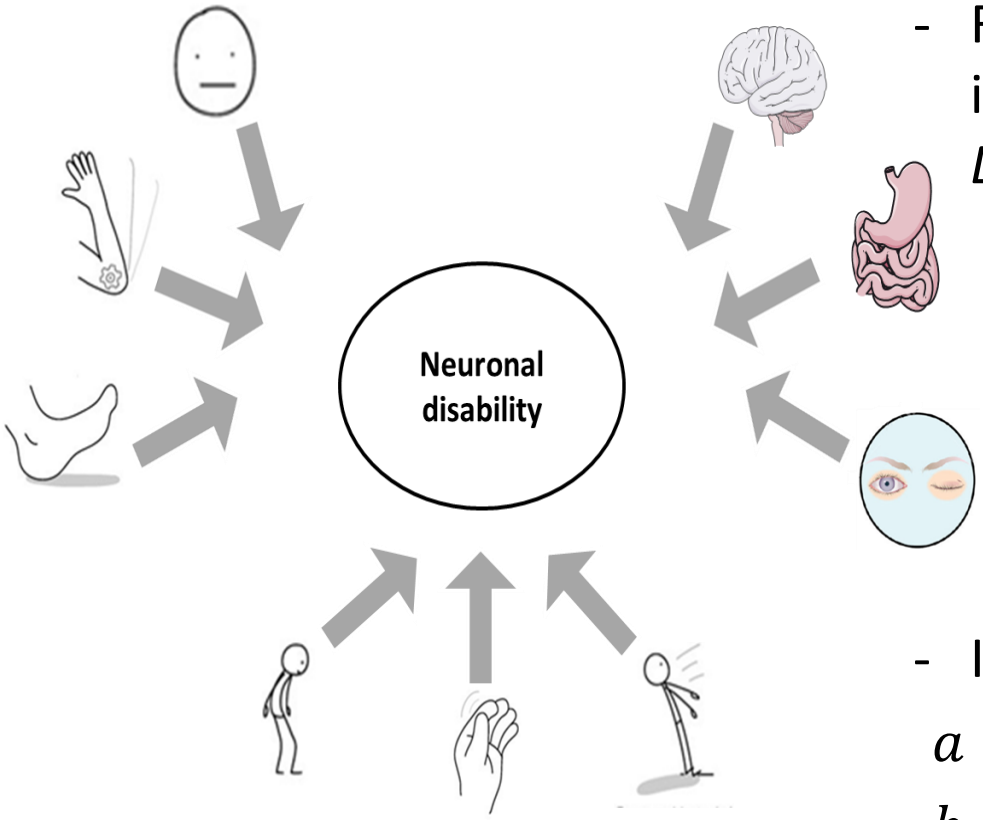


[1] Ueckert S *et al.*, Pharm res. 2014
[2] Gottipati G *et al.*, PAGE 24. 2015

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

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

$$P(Y_{ij} = k) = P(Y_{ij} >= k) - P(Y_{ij} >= k+1)$$

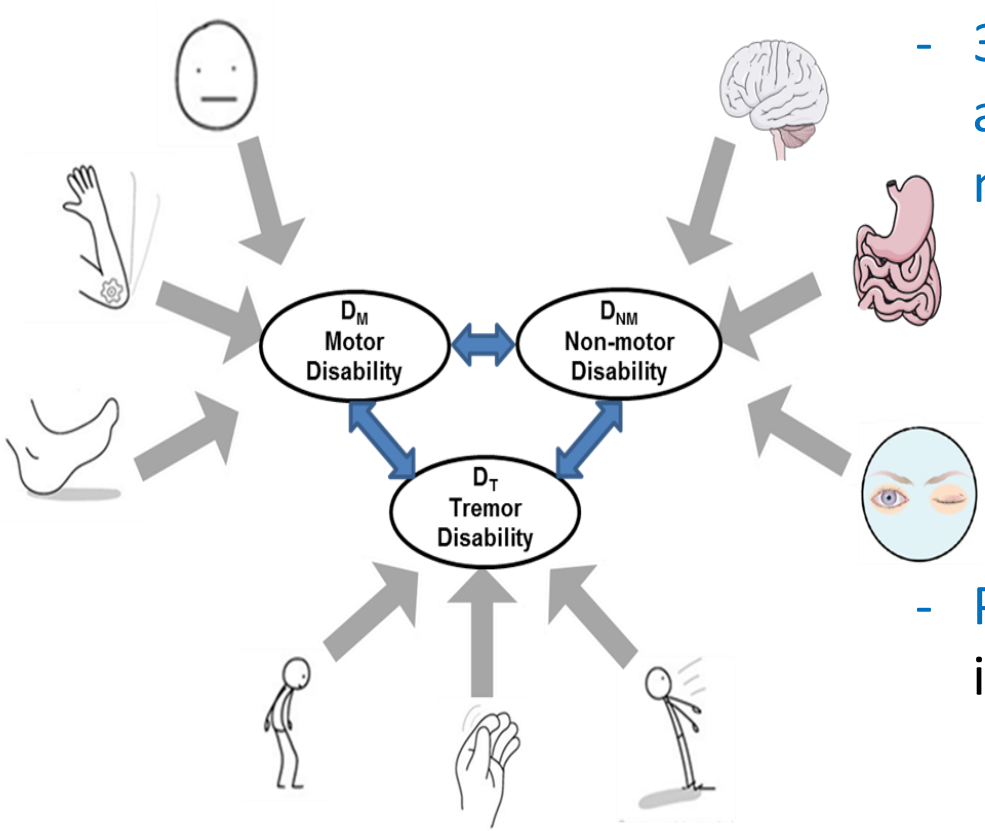
- Item specific parameters:

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%

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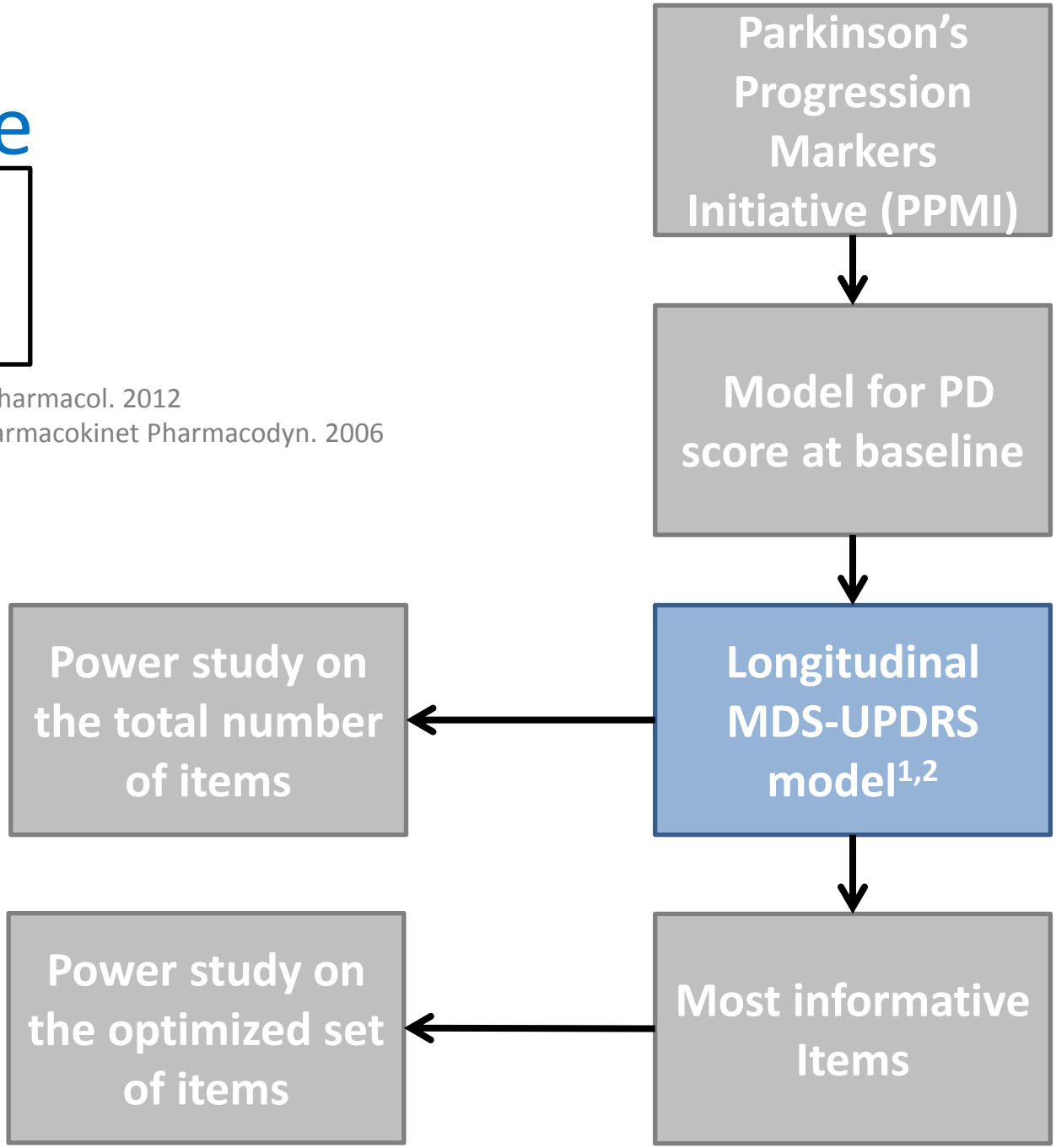


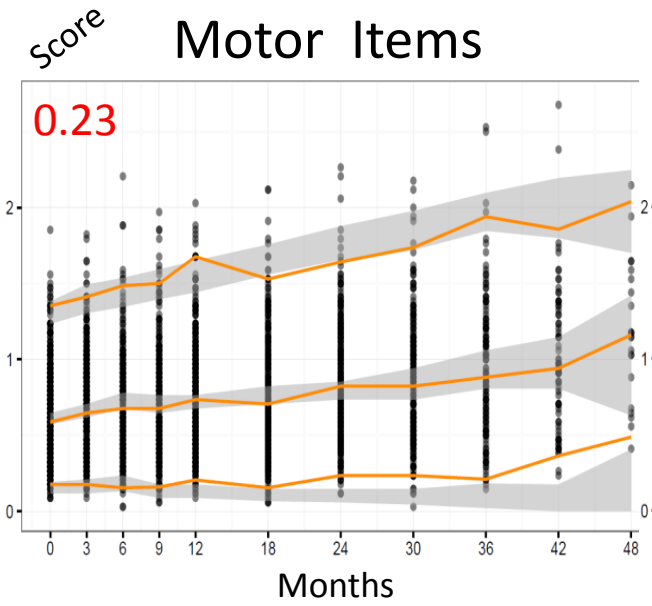
[1] Vu T *et al.*, Br J Clin Pharmacol. 2012
[2] Holford N *et al.*, J Pharmacokinet Pharmacodyn. 2006

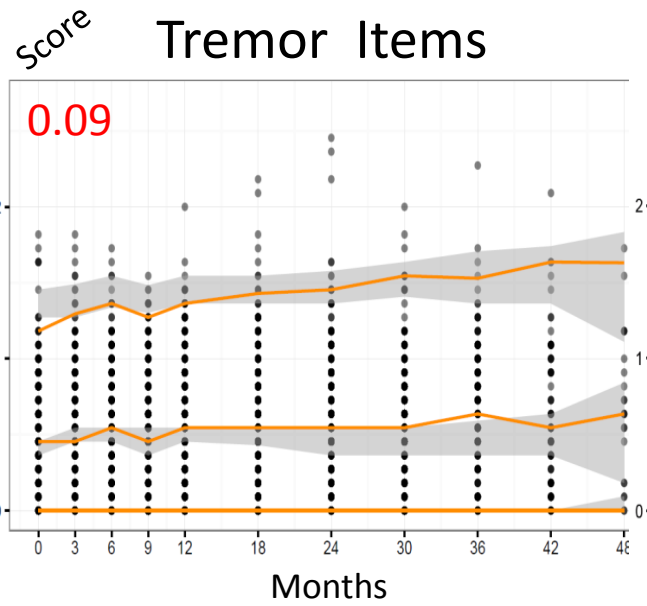
Longitudinal MDS-UPDRS model

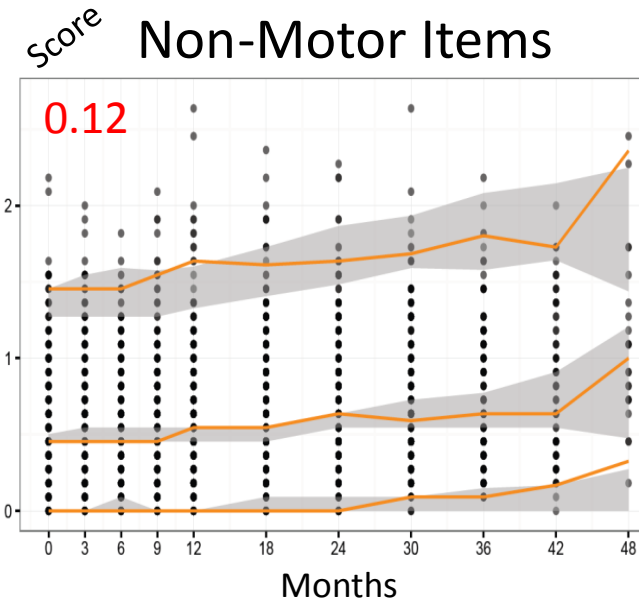
$$D_{v,i}(t) = \underbrace{D^0_{v,i}}_{\text{Baseline}} + \underbrace{\alpha_{v,i} \cdot t}_{\text{Disease progression}} + \underbrace{S_{v,i}(t)}_{\text{Drug effect}}$$

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

E^0 = Symptomatic effect
k_{eq} = Rate constant
β = Symptomatic increase
t_d = Time since start of drug







Mean disease progression rate (unit/item/year)

Outline

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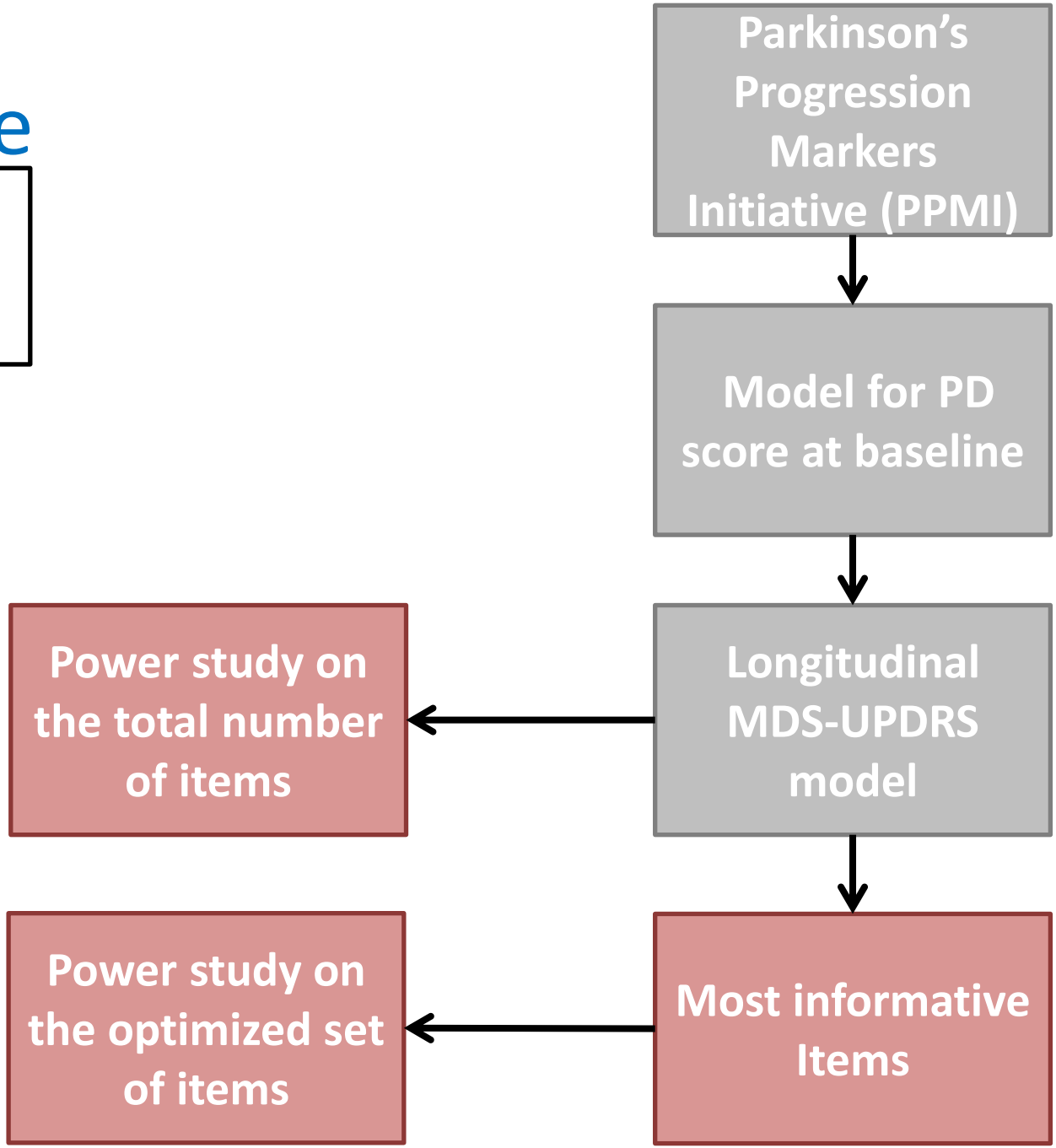


Clinical Trial Simulations (CTS)

- 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 Δ_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**: $\underset{c}{\operatorname{argmax}}(P(\Delta_c > 0))$
  - **Limiting factor**: C (>10^{15} combinations) ➔ Greedy algorithm[1]
    - ➢Heuristic to approximate the optimal set
    - ➢Corresponds to the forward approach in covariate selection

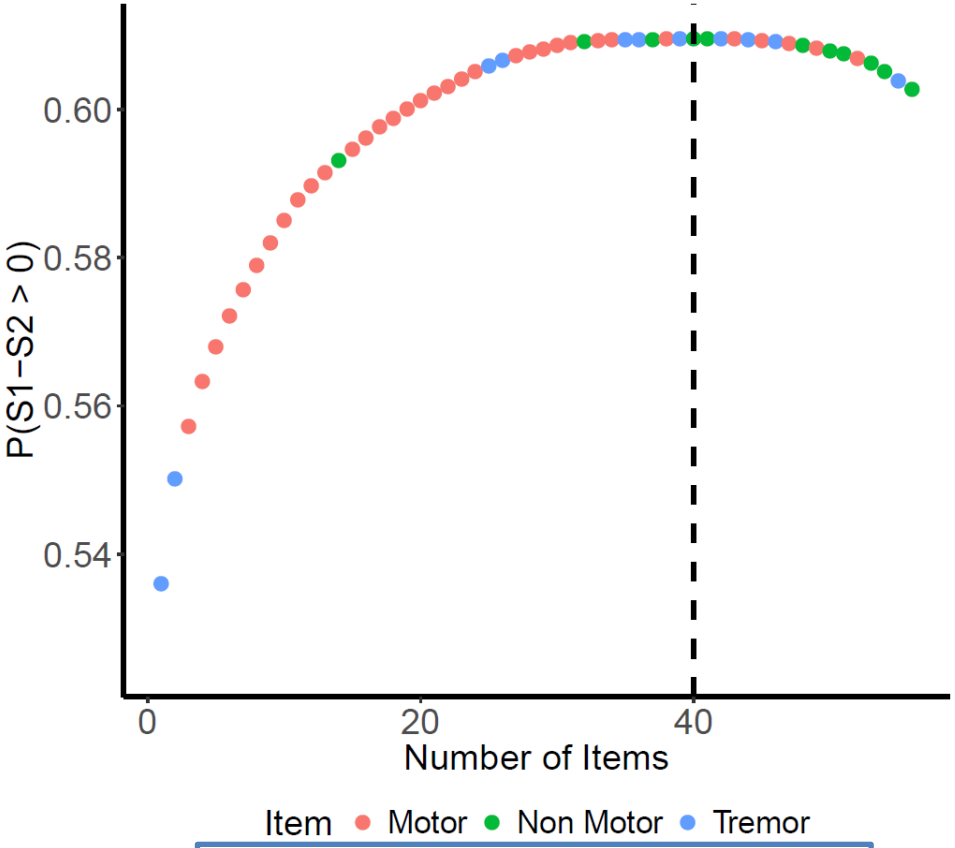
S1 and S2 were approximated by $N_{S1}(\mu_1,\sigma_1)$ and $N_{S2}(\mu_2,\sigma_2)$:
For each combination of items

- ➢$\mu \cong \sum_j \bar{y}_j$
- ➢$\sigma \cong$ variance for the sum of correlated variables

[1] Cormen T *et al.*, 2009

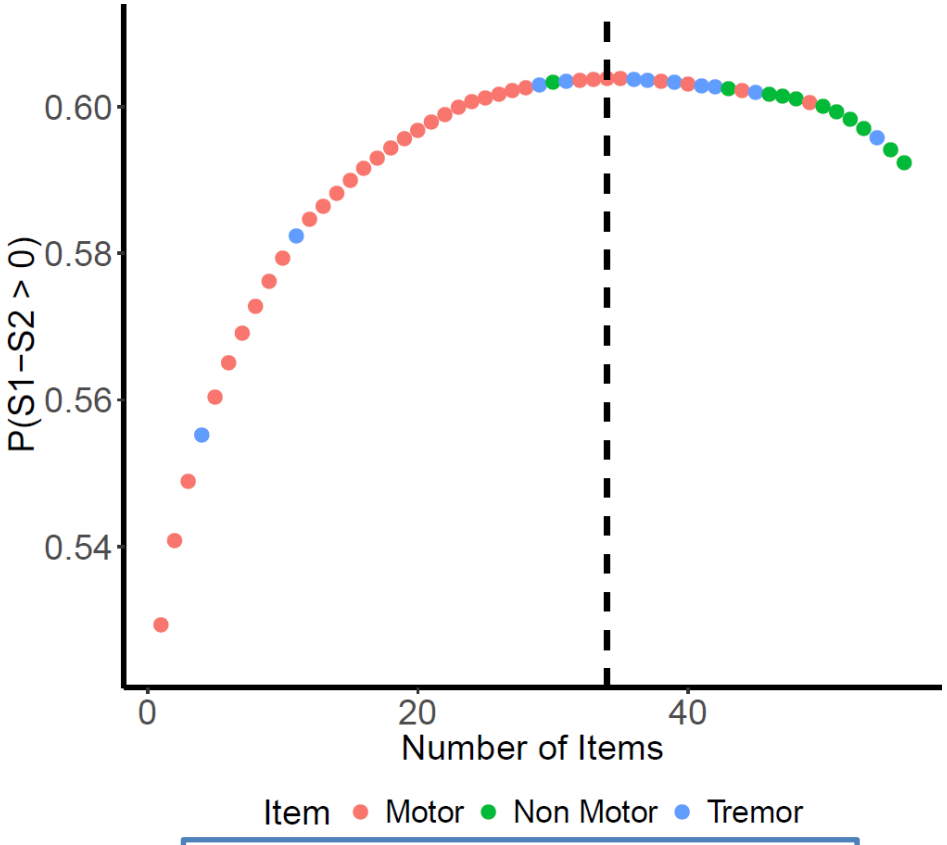
Select the most informative items

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



Optimized set: 40 items

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



Optimized set: 34 items

Power to detect a drug effect

- Methods:
  - End of trial comparison
  - Power was computed using parametric power estimation[1] (PPE) for the 2 scenarios and under different conditions:

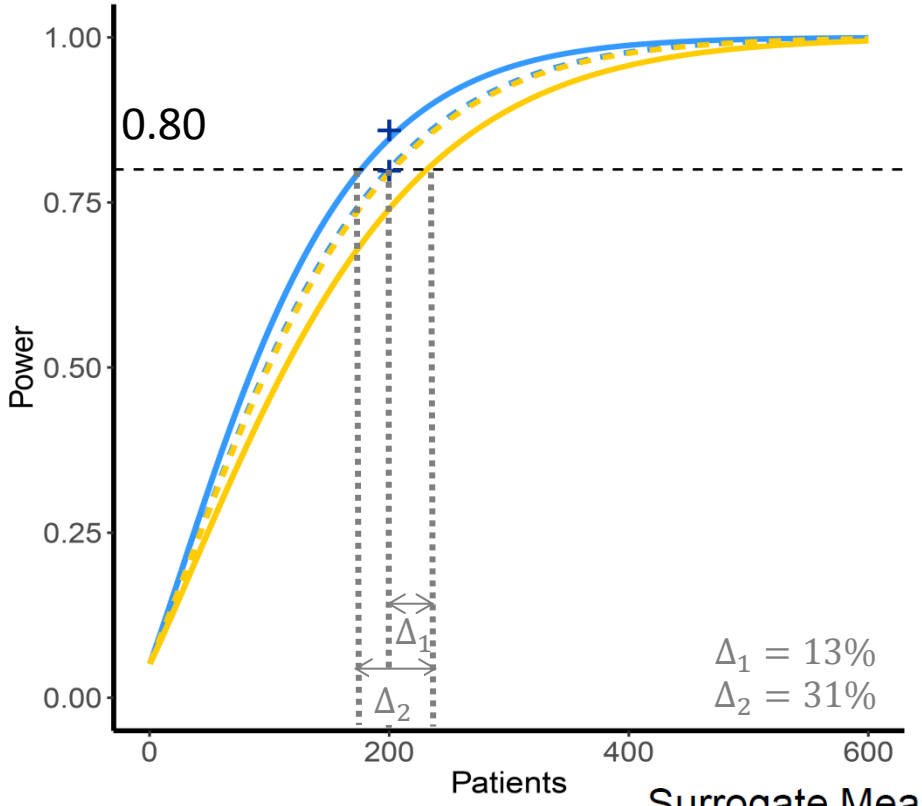
Analysis	Summary score	IRT model
Test	t-test/MMRM	LRT
Outcome measure	Total number of items Optimized set of items	

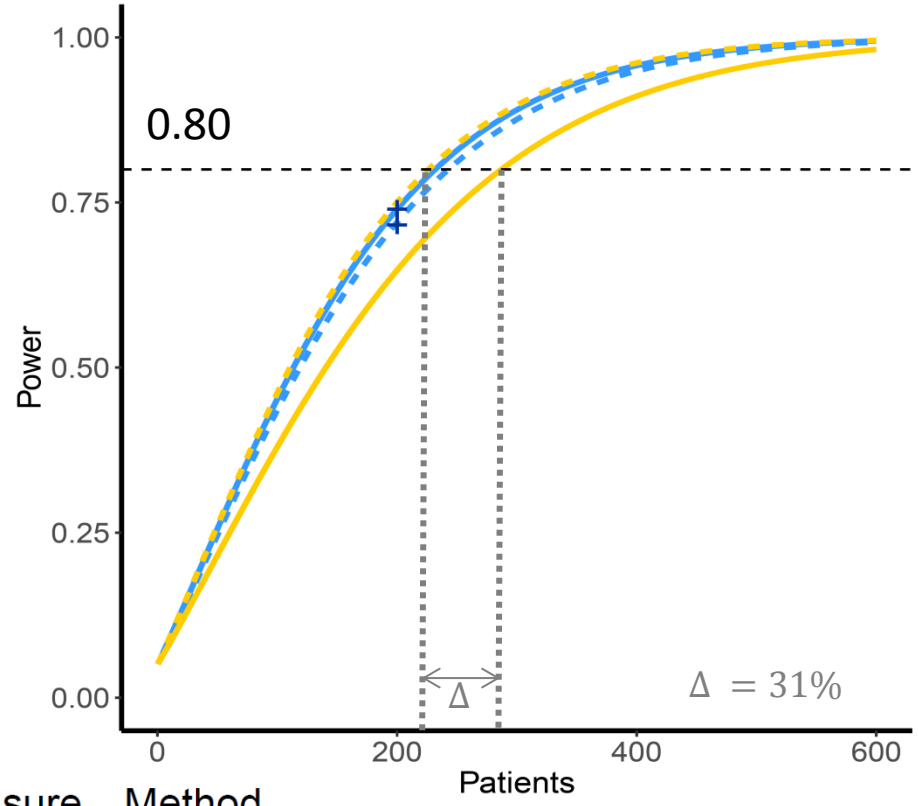
[1] Ueckert S *et al.*, J Pharmacokinet Pharmacodyn. 2016

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





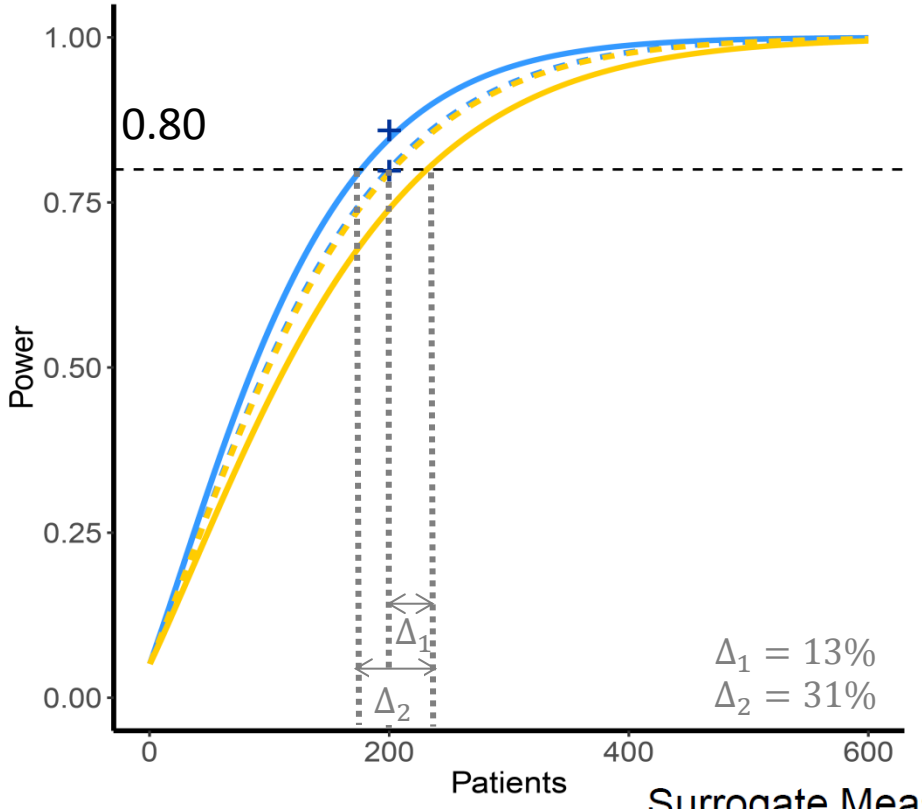
Surrogate Measure
All items
Optimal set

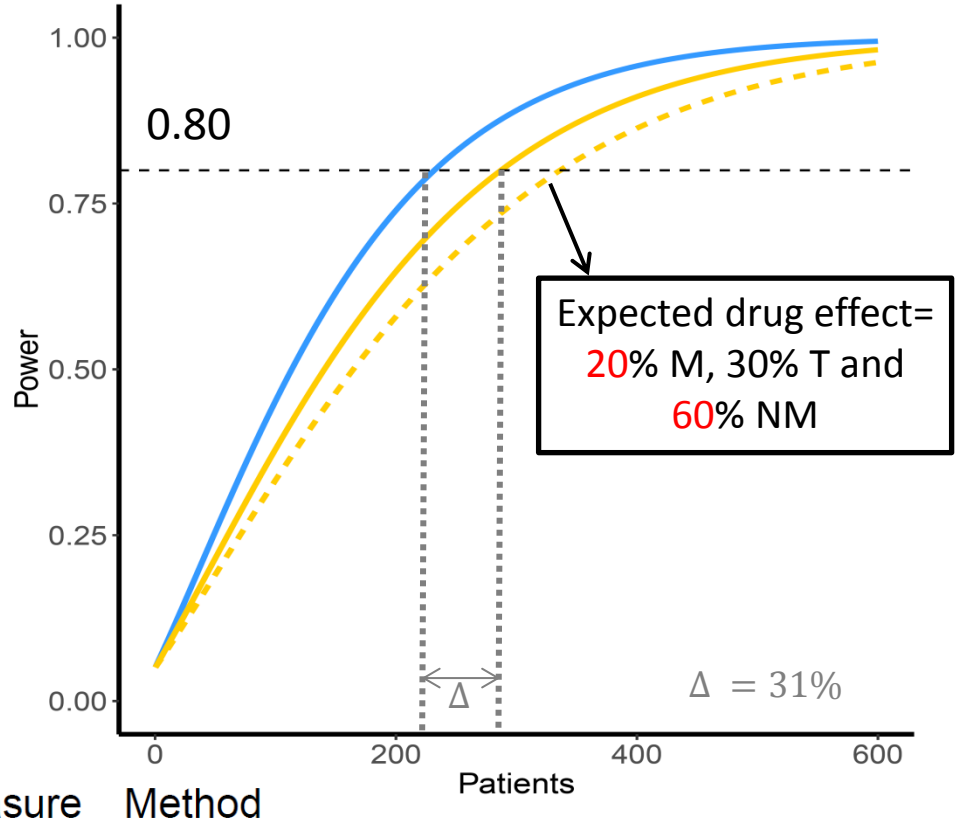
Method
Summary Score
IRT

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





Surrogate Measure
All items
Optimal set

Method
Summary Score
IRT

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

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