Item Response Models for Translation in CNS disorders

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Composite endpoints

Alzheimer’s Disease

Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog)

Tasks

Word-based

Rater assessed

Sum

Task

Non-motor experiences

Motor experiences

Motor examinations

Complications

Parkinson’s Disease

Movement Disorder Society - Unified Parkinson's disease rating scale (MDS-UPDRS)

Non-motor experiences

Motor experiences

Motor examinations

Complications

Sum

Decision Tree

Models describe change in composite endpoints over time

Multiple Sclerosis

Kurtzke Expanded Disability Status Scale (EDSS)

Bowl&Bladder

Brainstem

Mental

Pyramidal

Cerebellar

Sensory

Visual

Ambulation&Aid

Decisions
Composite endpoints & pharmacometric modeling

**Alzheimer’s Disease**
Alzheimer’s Disease Assessment Scale - Cognition (ADAS-Cog)

**Parkinson’s Disease**
Movement Disorder Society - Unified Parkinson’s disease rating scale (MDS-UPDRS)

**Multiple Sclerosis**
Kurtzke Expanded Disability Status Scale (EDSS)

- Assessment
- Assessment
- Assessment

Why use Item Response Models?
Avoid problems with total score analysis
Provide information and opportunities not available with total score analysis

Standard analysis based on total score
Item Response Theory (IRT) - Concept

As a parent: what do you assume about your kid if it scored the maximal score?

“My daughter is good in doing this math exam”

“My daughter is a math genius”
Item Response Theory (IRT) - Concept

Number of Kids

Mathematical Ability

Low High
Item Response Theory (IRT) - Concept

Item Characteristic Curve (ICC)

Probability to be Right

Low
High
Mathematical Ability

Points 0 1
Item Response Theory (IRT) - Concept

• From intuition:
  
  • Scores are interpreted as measure of ability
  
  • Mathematical ability can’t be observed and is clearly hypothetical
  
  • Exam itself is of no particular interest, but acts a surrogate measure for ability

IRT formalizes this intuition
Item Response Theory (IRT) - Concept

\[ 3x^2 + 3x + 5 = 0 \]

\[ \int 3x \, dx = 3y \]

\[ \frac{dy}{dx} = 3y \]

\[ P(\text{SUCCESS}) \]

\[ P(\text{SUCCESS}) \]

Mathematical Ability

[Graph showing the relationship between mathematical ability and the probability of success with correct and wrong responses.]
Item Response Theory (IRT) - Concept

\[ 3x^2 + 3x + 5 = 0 \]

\[ \int_{0}^{1} 3x \, dx \]

\[ \frac{dy}{dx} = 3y \]

7 June 2012

“Name the date”

“Draw a circle”

“Make a fist”
ICCs in a near-perfect composite scale

![Graph showing 11 curves representing P(Fail) against Disability]
ICCs ADAS-Cog construction

Alzheimer’s Disease
ADAS-Cog
Construction

Failure Probability

“Cube”

“Circle”

Cognitive Disability
IRT & Pharmacometric Modeling

Pharmacometric Disease Progression Model

Natural History  Drug Effect  Covariates

Score

Pharmacometric DP IRT Model

Natural History  Drug Effect  Covariates

Disease State

Score

IRT Model

Disease State

Score

Item 1  Item 2  Item 3  ...
Example: Alzheimer’s Disease

- Utilize data from public or in-house clinical trial databases
- Study influence of patient population & assessment variant independent from another

Reference:
Ueckert et al. Pharm Res 31(2013)
Example: Multiple Sclerosis (2)

1\textsuperscript{st} generation model

- Natural History
- Drug Effect

\rightarrow

Disability

\rightarrow

EDSS

2\textsuperscript{nd} generation model

- Cladribine

\rightarrow

ALC

\rightarrow

EDSS IRT Disability

\rightarrow

BoD

References:
Novakovic et al. AAPSJ (2016)
Novakovic et al PAGE (2017)
Sample size assessment

Expected increase in sample size needed for 80% power with total score over IRT

**Parkinson’s Disease**
MDS-UPDRS +31%

**Patient Reported Outcome**
FACT-B +35%

**Alzheimer’s Disease**
ADAS-Cog +33%

**References:**
Schindler et al, PAGE (2016)
Ueckert et al. Pharm Res 31 (2013)
Item information

Reduced tests options:
- Screening
- Trial conduct with limited tests
- Trial conduct with individualized dynamic testing
  - tests administered to maximize information with few items
  - items can be selected to minimize learning effects
  - tests can be administered more frequently (device-based)
Example: Schizophrenia

Reference:
Krekels et al. CPT:PSP (2017)
Example: Parkinson’s Disease

+ Possibility to characterize and identify different drug effects for different components of the assessment

\[ D_v(t) = D^0_v + \alpha_v \cdot t + S_v(t) \]

\[ S_{Motor}(t) = E^0_M + \beta_M \cdot (1 - e^{-k_{eq} \cdot t_d}) \]

\[ S_{Tremor}(t) = E^0_T + \beta_T \cdot t_d \]

\[ S_{N-motor}(t) = E^0_{NM} \]

+ Possibility to maximize power to detect drug effect by choosing subset

References:
Buatois et al. PAGE 25 (2016) Abstr 5865
Example: Parkinson’s Disease (2)

+ Model links established (UPDRS) and novel endpoint (MDS-UPDRS)
  + Leverage historic data
  + Comparison with older compounds
  + Joint framework for complete disease severity range

+ Also done in AD for MMSE (often used for screening & diagnosis) & ADAS-cog (regulatory accepted endpoint)
  + Utilize all collected data
  + Leverage clinical routine data
  + Predict clinical endpoint from screening

References:
Gottipati et al. AAPSJ(2017)
Gottipati et al. PAGE 25 (2016) Abstr 5990
Jönsson et al PAGE (2017) Abstr 7236
Parkinson’s Disease

• Parkinson Progression Markers Initiative (PPMI) Database:

De Novo Parkinson’s Disease Subjects

(n = 423)
Diagnosed ≤ 2 years
Not taking any medications for Parkinson’s disease

Subjects With Scans Without Evidence of Dopaminergic Deficit (SWEDD)

(n = 64)
Consented as Parkinson’s patients
<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
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<td>33</td>
<td>7</td>
<td>80</td>
</tr>
<tr>
<td>SWEDD</td>
<td>29</td>
<td>6</td>
<td>109</td>
</tr>
</tbody>
</table>
IRM-based diagnosis
IRT – challenges

• IRT analysis complex
  – Increasing community experience

• IRT model data demanding
  – #Items and #Observations can’t be too low
  – Literature models can be used for ICC

• IRT model assumption dependent
  – Assumptions can be assessed through diagnostics

• Software limitations for IRT analysis
  – NONMEM/STAN flexible but offer few built-in facilitations
  – SAS/R has useful functions but restrictive in model scope
Analyze

Plan

Outlook

Leverage more existing data (across compounds, populations, endpoints)
Select more specific patient populations
Choose more informative endpoints

POC

Infer with higher power
Understand with increased detail

Design more precisely (for regulatory accepted endpoint)
Decide with increased confidence

Phase III

Pharmacometric IRT Model
Interim analysis

Final analysis

Enroll & run

Inclusion criteria component
Dynamic selection of tasks during trial

Interim analysis

Futility analysis
Adaptive design (drop arm, revision of sample size)

Final analysis

E-R analysis
Benefit-risk
Disease-modifying effect
Biomarker validation

Outlook

Phase III

Pharmacometric IRT Model
Conclusions

- Composite assessment data is complex
- Simplification results in loss of information
- IRT allows to capture data complexity
- Combination with pharmacometric modeling yields
  - Higher sensitivity and flexibility to detect drug effect
  - Integrated framework to link different endpoints and populations
  - More precise and versatile trial design
  - ...