Composite Clinical Score Assessment through Item Response Theory-Based Pharmacometric Modeling

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Enhance Understanding of Treatment Response for Diseases with Composite Endpoints

- Composite Clinical Score Assessment through Item Response Theory Based Pharmacometric Modeling
- Other
  - 7:30 AM-8:00 AM May 17, 2016
  - Sheraton Boston Hotel - Back Bay Ballroom AB
Pharmacometric modeling

- Complex data
  - Hierarchical (Study, center, subject)
  - Longitudinal (hours – years)
  - Heterogeneous (different doses, clinical centers, patient groups, …)
  - Potentially sparse (esp. later phases of development)
- “Assumption rich” models (e.g., taking biology into account)

Largely increased probability to detect drug effects (power)

Reference:
Karlsson et al., “Comparisons of Analysis Methods for Proof-of-Concept Trials.”
Composite endpoints & pharmacometric modeling

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

Tasks

Word-based

Rater assessed

Sum

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

Non-motor experiences

Motor experiences

Motor examinations

Complications

Sum

Multiple Sclerosis
Kurtzke Expanded Disability Status Scale (EDSS)

Bowel & Bladder

Brainstem

Mental

Pyramidal

Cerebellar

Sensory

Visual

Ambulation & Aid

Decision Tree

Models describe change of score over time
Composite endpoints & pharmacometric modeling

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

**Parkinson’s Disease**
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**Multiple Sclerosis**
Kurtzke Expanded Disability Status Scale (EDSS)

What information is lost?
Plus/minus one point always the same meaning?
What if parts of the assessment are missing?
How do scores at boundaries (0 & max) behave?

**Alternative?**
Success of group testing of military recruits greatly increased interest in multiple choice tests

College Entrance Examination Board dropped essay based test in 1942

Theory laid out by Lazarsfeld, Lord and Birnbaum (based on several advances in statistics & psychometrics)

Important tool in psychometrics

Used to analyze & design several important high-stakes examinations:

- Graduate Management Admission Test (GMAT) with > 200,000 examinees annually
- Graduate Record Examination (GRE) used at most American graduate schools

Reference:
Bock, “A Brief History of Item Theory Response.”
IRT & Pharmacometric Modeling

Pharmacometric Disease Progression Model
- Natural History
- Drug Effect
- Covariates

Score

IRT Model
- Disease State
- Score
- Item 1
- Item 2
- Item 3
- ...

Pharmacometric DP IRT Model
- Natural History
- Drug Effect
- Covariates

Disease State

Score
- Item 1
- Item 2
- Item 3
- ...

UPPSALA UNIVERSITET
Example: Alzheimer’s Disease

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

Natural History

Cognitive Disability

ADAS-cog

Population/Treatment specific

Assessment specific

e.g. “make a fist”
“draw a circle”,…

Reference:
Ueckert et al. Pharm Res 31(8)
**Example: Multiple Sclerosis**

- Increased power to detect drug effect
- Possibility to better understand endpoint, e.g., use optimal design to find most informative items

**References:**
- Kalezic et al. PAGE 22 (2013) Abstr 2903
- Kalezic et al. PAGE 23 (2014) Abstr 3262
- Kalezic et al. Manuscript submitted
Example: Schizophrenia

- Possibility to characterize different disease components in joint model

\[ DS_{ij} = DS_{\text{base},i} - P_{\text{max},i} \cdot (1 - e^{-\ln(2)/t_{1/2}t_j}) \]

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{\text{max}} )</td>
<td>0.789</td>
<td>0.352</td>
<td>0.450</td>
</tr>
<tr>
<td>( t_{1/2} ) (days)</td>
<td>18.1</td>
<td>18.1</td>
<td>18.1</td>
</tr>
<tr>
<td>( \text{corr}(DS-P_{\text{max}}) )</td>
<td>-0.157</td>
<td>-0.114</td>
<td>0</td>
</tr>
</tbody>
</table>

References:
Krekels et al. PAGE 22 (2013) Abstr 2894
Krekels et al. PAGE 23 (2014) Abstr 3262
Example: Parkinson’s Disease

- Possibility to characterize and identify different drug effects for different components of the assessment:
  \[
  D_v(t) = D_v^0 + \alpha_v \cdot t + S_v(t)
  \]
  \[
  S_{Motor}(t) = E_M^0 + \beta_M \cdot (1 - e^{-k_{eq}t_d})
  \]
  \[
  S_{Tremor}(t) = E_T^0 + \beta_T \cdot t_d
  \]
  \[
  S_{Non-motor}(t) = E_{nm}^0
  \]

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

References:
Buatois et al. PAGE 25 (2016) Abstr 5865 ➔ Upcoming oral
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. PAGE 25 (2016) Abstr 5990
<table>
<thead>
<tr>
<th>Therap. area</th>
<th>Endpoint</th>
<th>Objectives</th>
<th>References</th>
</tr>
</thead>
</table>
| Oncology    | Patient reported outcome (PRO), e.g. “I have lack of energy”, “I am bothered by side effects” | • Understand patient/endpoint relationships  
• Understand endpoint evolution | Schindler et al. ACOP 2015  
Schindler et al. WCOP 2016  
Upcoming Oral |
| Neurology   | Neuro Psychiatric Index (NPI), e.g. hallucinations, agitation | • Identify common patterns between component evolution | Ueckert et al. ACOP 2015 |
| Analgesia   | Multiple pain measures for newborns, e.g. Premature Infant Pain Profile | • Assess the efficacy of morphine in preterm neonates | Välitalo et al. PAGE PAGE 24 (2015) Abstr 3388 |
| Neurology   | Amyotrophic Lateral Sclerosis (ALS) Functional Rating Scale (ALSFRS), e.g. swallowing, handwriting | • Characterize ALS disease progression | Johansson et al. PAGE 24 (2015) Abstr 3585 |
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
  - More precise and versatile trial design
  - …
Pharmacometric IRT Model

Analyze

Plan

POC

Phase III

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

Infer with much higher power
Understand with increased detail

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

Outlook
Thanks to

• Content & input
  – Elke Krekels, UU (now Leiden University)
  – Emilie Schindler, UU
  – Gopichand Gottipati, UU
  – Ana Kalezic, UU
  – Simon Buatois, University Paris Diderot/Roche
  – Mats Karlsson, UU

• Travel support: AAPS & UU

• Listening: YOU