Mapping Patient Reported Outcomes onto EQ-5D

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AIXIAL

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Summary

I. PROs Description
   • EQ-5D 3L/5L
   • SF-36v2
   • HAQ-DI

II. Mapping Techniques
   1. Definition
   2. Mapping Process of EQ-5D based utility
   3. When Mapping?
Context and Objective

• Context
  • Quality-adjusted life-years (QALYs) are widely used as an outcome for the economic assessment
  • EQ-5D based utility is preferred by NICE for economic evaluation (2008) but not commonly used in clinical trials
  • Other generic or specific Patient Reported Outcomes (PROs) are used in clinical trials,

• Solution
  • Mapping PROs onto EQ-5D based utility

• Objective
  • To provide an overview of mapping techniques used in Health Technology Assessment (HTA)
  • To illustrate how to use mapping
I. PROs Description

1. EQ-5D 3L/5L
2. SF-36 v2
3. HAQ-DI
EuroQoL EQ-5D 3L/5L

A generic measure of health
- 5 items for 5 dimensions

- Each item has 3L (levels) => 5L

**Scoring**
Country EQ-5D tariff

**Possible health states**

<table>
<thead>
<tr>
<th>UK</th>
<th>0.594</th>
<th>0</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>0.530</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>-0.109</td>
<td>No problem</td>
<td></td>
</tr>
</tbody>
</table>

After scoring: Utility index

Possible health states

3^5=243
5^5=3125
Short Form 36 version 2 (SF-36 v2)

A multi-purpose, short-form health survey with 36 questions:

8 domains

- Physical Functioning (PF)
- Role Physical (RP)
- Bodily Pain (BP)
- General Health (GH)
- Vitality (VT)
- Social Functioning (SF)
- Role Emotional (RE)
- Mental Health (MH)

2 Summary Measures

- Physical component summary (PCS)
- Mental component summary (MCS)

Domains Scores

- US population norm

Domains & Components Scores

- (T-scores: CI99%~)

Better QoL

No single global score
**Health Assessment Questionnaire Disease Index (HAQ-DI)**

- **PRO for the assessment of Rheumatoid Arthritis (RA)**

<table>
<thead>
<tr>
<th>8 domains</th>
<th># Items</th>
<th>HAQ-DI Initial version: 1983 Recent version</th>
<th>PROMIS HAQ (Improved HAQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing &amp; Grooming</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arising</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eating</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>2</td>
<td>4 Levels 0, 1, 2, 3</td>
<td></td>
</tr>
<tr>
<td>Hygiene</td>
<td>3</td>
<td>5 Levels 0, 1, 2, 3, 4</td>
<td></td>
</tr>
<tr>
<td>Reach</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activities</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>20</td>
<td>0-3</td>
<td>0-100</td>
</tr>
</tbody>
</table>

\[ \sum 8 \text{items/20} \times 25 \]

**More disability**

- Without any difficulty
- A little difficulty
- With some difficulty
- With much difficulty
- Unable to do
II. Mapping techniques

1. Definition

2. Mapping process of EQ-5D based Utility
   - Step 1: Estimation Sample
   - Step 2: Transfer Function Building
   - Step 3: Utility Approximation on Target Sample

3. When Mapping?
Definition

- Mapping
  To link a target PRO with source PROs by transfer function

- Mapping onto EQ-5D

- Double mapping
Predictive model building vs Mapping

Objective

Predictive model building
Good forecast

Mapping
Good approximation
Mapping Process of EQ-5D based Utility

**Step 1**
**Estimation Sample**
- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics

**Step 2**
**Transfer Function Building**
- Similar as Predictive Model Building
- But different

**Step 3**
**Utility Approximation on Target sample**
- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics

CROs: Clinical Reported Outcomes
Step 1: Estimation Sample

Similarity

PROs/CROs selected in function have impact on EQ-5D

PROs
CROs

EQ-5D

Overlapping Distributions of selected PROs/CROs in two samples
Mapping Process of EQ-5D based Utility
Step 1: Estimation Sample
Example: Influence Diagram of Rheumatoid Arthritis QoL and Symptoms

Joint swelling or damage
Long term consequence of inflammation
Systemic manifestation of RA

HRQoL

Limited physical function
Key RA symptoms and QoL

Pain
Fatigue
Mental health
Other symptoms
Mapping Process of EQ-5D based Utility

Step 1: Estimation Sample

*Example: From Influence Diagram of Rheumatoid Arthritis QoL and Symptoms To Economic Modelling*
Mapping Process of EQ-5D based Utility

**Step 1**
Estimation Sample

- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics

**Step 2**
Transfer Function Building

- Similar as Predictive Model Building
- But different

**Step 3**
Utility Approximation on Target Sample

- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics
Mapping Process of EQ-5D based Utility

Step 2: Transfer Function Building

1. PROs & Variables Selection
2. Model Type Choice
3. Model Performance & Validation
4. Uncertainty Study
Step 2: Transfer Function Building

1. PROs & Variables Selection

\[ EQ-5D = f(\text{Source PROs, X}) \]

**Target PRO**
- EQ-5D index \([-0.594; 1]^*\)
- EQ-5D dimension levels 1, 2, 3 or \(1,2,3,4,5\)

**Source PROs, X**
- Generic or Condition-specific PROs:
  - Overall, domains, item scores, interaction terms
  - Item-level dummies
- CROs
- Socio demographic variables

* Prior clinical knowledge (ex: Influence diagram)
  - Statistical methods: Correlation, distribution...

* Using UK tariff
Step 2: Transfer Function Building
2. Model Type

Study of EQ-5D utility distribution

- Multimodal nature of the distribution

This very reason explains linear regression performing poorly.

Source: Hernandez, 2013

US National Data Bank for Rheumatic Diseases (NDB). (n = 100,398 observations)
Step 2: Transfer Function Building

2. Model Type: Target PRO

\[ \text{EQ-5D} = f(\text{Source PROs, } X) \]

**EQ-5D Index**

- [-0.549; 1]*
  - OLS Regression
  - Mixture model
  - PLS regression approach
  - Latent variables

**EQ-5D dimension levels**

- 1, 2, 3 or 1, 2, 3, 4, 5
  - Multinormal logistic regressions
  - PLS discriminant analysis
    - 5 dimensions levels on latent variables
  - Canonical analysis

**Warnings:**

- PROs version

- OLS: Ordinary Least Squares
- PLS: Partial Least Squares

- Using UK tariff
Step 2: Transfer Function Building

3. Model Performance and Validation

Using Similar criteria and techniques as predictive modeling:

- Goodness of fit: \( \text{adjusted } R^2, \text{AIC, BIC} \)
- Prediction power: \( \text{RMSE} \)
- Comparing with existing mapping
- Estimation sample: \( \text{learning vs testing samples} \)
- Ideally, external sample similar to the target sample
Step 2: Transfer Function Building

4. Uncertainty Study

Why?
Multiple sources of errors
- Heterogeneity in measure of utility index
- Target vs Source measures
- Estimation

How?
Uncertainty study
- Change EQ-5D tariff
- Multiple possible transfer functions for sensitivity analysis
- Bootstrap
  - Precision of estimation and values

Double mapping
- More error and uncertainty around the mapped EQ-5D utility
- the uncertainty should be fully accounted for within economic analysis
Step 2: Transfer Function Building
Some Examples

- Mapping SF36 (12) onto EQ-5D
- Mapping HAQ-DI onto EQ-5D
Step 2: Transfer Function Building

Example: Mapping SF-36/12 onto EQ-5D-3L

<table>
<thead>
<tr>
<th>Target PRO</th>
<th>Model Type</th>
<th>Source PRO</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-3L Dimension levels</td>
<td>5 Mutinomial logistic regression model for 5 EQ-5D dimension</td>
<td>SF-12: PCS, MCS</td>
<td>Gray 2006</td>
</tr>
<tr>
<td>EQ-5D-3L Utility Index</td>
<td>Linear Regression 2 Components + 2 Components^2 + 1 interaction</td>
<td>SF-12: PCS, MCS</td>
<td>Francks 2004</td>
</tr>
<tr>
<td></td>
<td>Linear Regression 8 domains + (8 domains^2) + (28 interactions)</td>
<td>SF-36</td>
<td>Brazier 2009</td>
</tr>
</tbody>
</table>
Step 2: Mapping algorithm building

Example: Mapping SF-36 onto EQ-5D-3L (Brazier 2009)

- **Model 1**
  \[ f(8 \text{ domains}) \]

- **Model 2**
  \[ f(8 \text{ domains}, 8 \text{ domain}^2) \]

- **Model 3**
  \[ f(8 \text{ domains}, 8 \text{ domain}^2, 28 \text{ interactions}) \]

EQ-5D Utility Index = [0;1]

Domain transformation: [0;1]
Step 2: Building Transfer function

Example: Mapping SF-36 onto EQ-5D-3L (Brazier 2009)

<table>
<thead>
<tr>
<th>8 domains</th>
<th>Estimated coefficients (GLM: Model 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Domains</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>BP</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>PF</td>
</tr>
<tr>
<td>Mental Health</td>
<td>MH</td>
</tr>
<tr>
<td>General Health</td>
<td>GH</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>SF</td>
</tr>
<tr>
<td><strong>Role-Physical</strong></td>
<td>RP</td>
</tr>
<tr>
<td><strong>Vitality</strong></td>
<td>VT</td>
</tr>
<tr>
<td><strong>Role-Emotional</strong></td>
<td>RE</td>
</tr>
</tbody>
</table>

VT, RP and RE did not significantly effect the EQ-5D index,
### Step2: Transfer Function Building

**Example: Mapping HAQ-DI onto EQ-5D in RA**

<table>
<thead>
<tr>
<th>Target PRO</th>
<th>Model Type</th>
<th>Source PROs</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-5D-3L Index</td>
<td>Linear regression</td>
<td>HAQ-DI <em>Dummy Items</em></td>
<td>Bansback, 2007</td>
</tr>
<tr>
<td>EQ-5D-3L Index</td>
<td>Linear regression</td>
<td>HAQ-DI and DAS28</td>
<td>Adams, 2010</td>
</tr>
<tr>
<td>Mixture model</td>
<td>Mixture model</td>
<td>HAQ-DI, VAS pain and age</td>
<td>Hernandez, 2013</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain/Item</th>
<th>B</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing and grooming</td>
<td>-0.15</td>
<td>0.04</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bathing</td>
<td>-0.08</td>
<td>0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Eating</td>
<td>-0.12</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>Bathing</td>
<td>-0.28</td>
<td>0.06</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Transfer function</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Very complicated to calculate, therefore computationally intensive for an Individual Markov model and might not be feasible.
Mapping Process of EQ-5D based Utility

**Step 1**
Preparing an Estimation sample
- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics

**Step 2**
Transfer function building
- Similar as predictive model building

**Step 3**
Utility Approximation on Target sample
- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics
Step 3: Utility Approximation on Target Sample

**Target sample**

- **Similarity**
  - Target vs Estimation samples

- **Availability**
  - of PROs, variables included in the algorithm

- **Same**
  - PROs version
  - EQ-5D Tariff (Ideal)

**EQ-5D Utility Approximation**

- **Apply at**
  - Mean level
  - Patient level

- **Compare**
  - Mapped vs Direct EQ-5D utility
Step 3: Utility Approximation on Target Sample
Using existing Mapping algorithm

Generalizability
- Population and range of disease severity
- Availability of PROs
  - PROs version
  - EQ-5D Tariff
  - Author suggestion

Assessment
- Advantages
- Limitation

Feasibility
- Complexity of algorithm
- Complexity of economic model

Uncertainty Consistency
- Using different algorithms
Step 3: Utility Approximation on Target Sample
Using existing Mapping algorithm
Example: Mapping SF-36 onto EQ-5D-3L (Brazier 2009)

Model predicts well for milder health state
Mean of 0-100 scaled domains >55

Very reason of Multimodal nature of the EQ-5D distribution?
When Mapping?

- When Mapping
- Example of Mapping HAQ-DI onto EQ-5D
When Mapping?

- Direct utility should be used in parallel for assessment of mapped ones
- Different mapping algorithms should be used for sensitivity analysis
When mapping?
Example: Utility calculation in CE Model for RA

Simplified logical flow for CE Model in RA

<table>
<thead>
<tr>
<th>Health states</th>
<th>Cycle calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st treatment</td>
<td>Assess response to treatment</td>
</tr>
<tr>
<td>#th treatment</td>
<td>Determine if patient stays on treatment or switch to another treatment</td>
</tr>
<tr>
<td>Palliative care</td>
<td>Update HAQ-DI and VAS pain scores</td>
</tr>
<tr>
<td>Death</td>
<td>Update QoL</td>
</tr>
<tr>
<td></td>
<td>Update mortality and costs</td>
</tr>
</tbody>
</table>

(M) Using mapping (HAQ and VAS pain) function to approximate EQ-5D utilities:
Conclusion

- Mapping gives a possibility of utility approximation for economic evaluation
- Mapping should include not only CROs but also PROs to reflect the impact of other effects of treatment that are not captured by CROs.
- Mapping on direct statistical links rather than purely on the opinion of expert
- Following a rigorous mapping process
- Prefering direct utility than mapped one
Thank you for your attention
Bibliography

2. Donna Rowen, John Brazier and Jennifer Roberts: «Mapping SF-36 onto the EQ-5D index: how reliable is the relationship?”. Health and Quality of Life Outcomes, 2009
Back-up
I. PROs description

**SF-36**

**SF-6D based Utility**

- The health state utility index derived from the SF-36 (11 items) or SF-12 (7 items) contain 6 dimensions (6D)
- Index scores = [0.30; 1] represents worst health state to best health state

**EQ-5D based Utility**

| -0.594 | 0 | 0.30 | 1 |

**SF-6D based Utility**
Step 3: Utility Approximation on Target Sample Using existing Mapping algorithm

Example of mapping SF-36 onto EQ-5D-3L (Simulation)
Correlation between SF36, SF-6D & Estimated EQ-5D

Trend of higher correlation between SF-36 and estimated EQ-5D utility than SF-6D utility

Sysmatic distribution for SF-6D but not estimated EQ-5D utility

Pearson Correlation Matrix: n= 989
The Estimated EQ-5D has produced quite different utility values from that of the SF-6D.