**JGEM-SFES**

# 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)
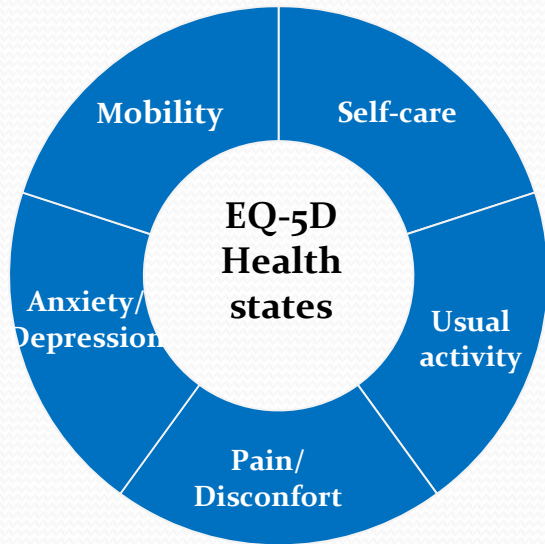  - To illustrate how to use mapping

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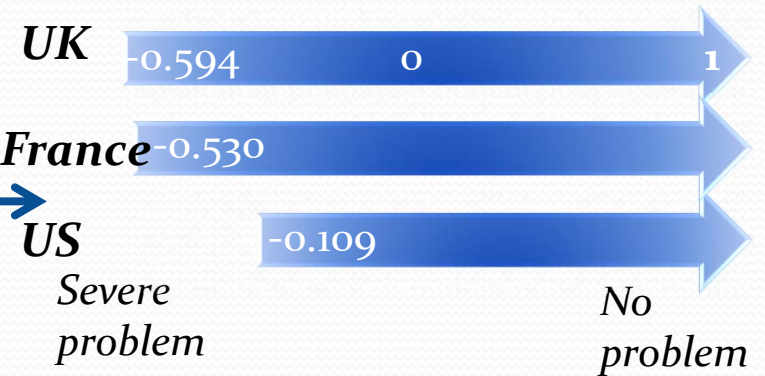
1. EQ-5D 3L/5L
2. SF-36 v2
3. HAQ-DI

# EuroQoL EQ-5D 3L/5L
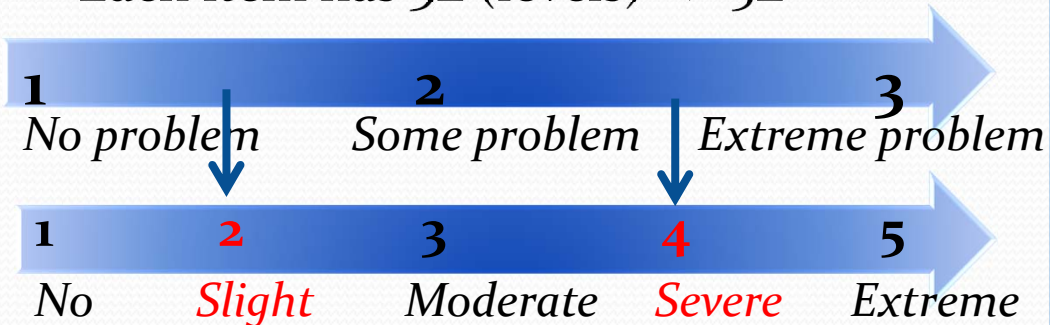
Tariff

A *generic* measure of health

- 5 items for 5 dimensions



Mobility | Self-care
EQ-5D Health states
Anxiety/Depression | Usual activity
Pain/Disconfort

**Scoring**
*Country EQ-5D tariff*

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

| 1 | 2 | 3 |
|---|---|---|
| No problem | Some problem | Extreme problem |

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| No | Slight | Moderate | Severe | Extreme |

- After scoring: Utility index

UK   -0.594   0   1

France   -0.530

US   -0.109

*Severe problem*                    *No problem*

**Possible health states**

$3^5$=243

$5^5$=3125

# Short Form 36 version 2(SF-36 v2) ⚠️

No single global sco

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

**8 domains**

**2 Summary Measures**

Physical Functioning
PF

Role Physical
RP

Bodily Pain
BP

General Health
GH

Vitality
VT

Social Functioning
SF

Role Emotional
RE

Mental Health
MH

**Physical component summary(PCS)**

**Mental component summary (MCS)**
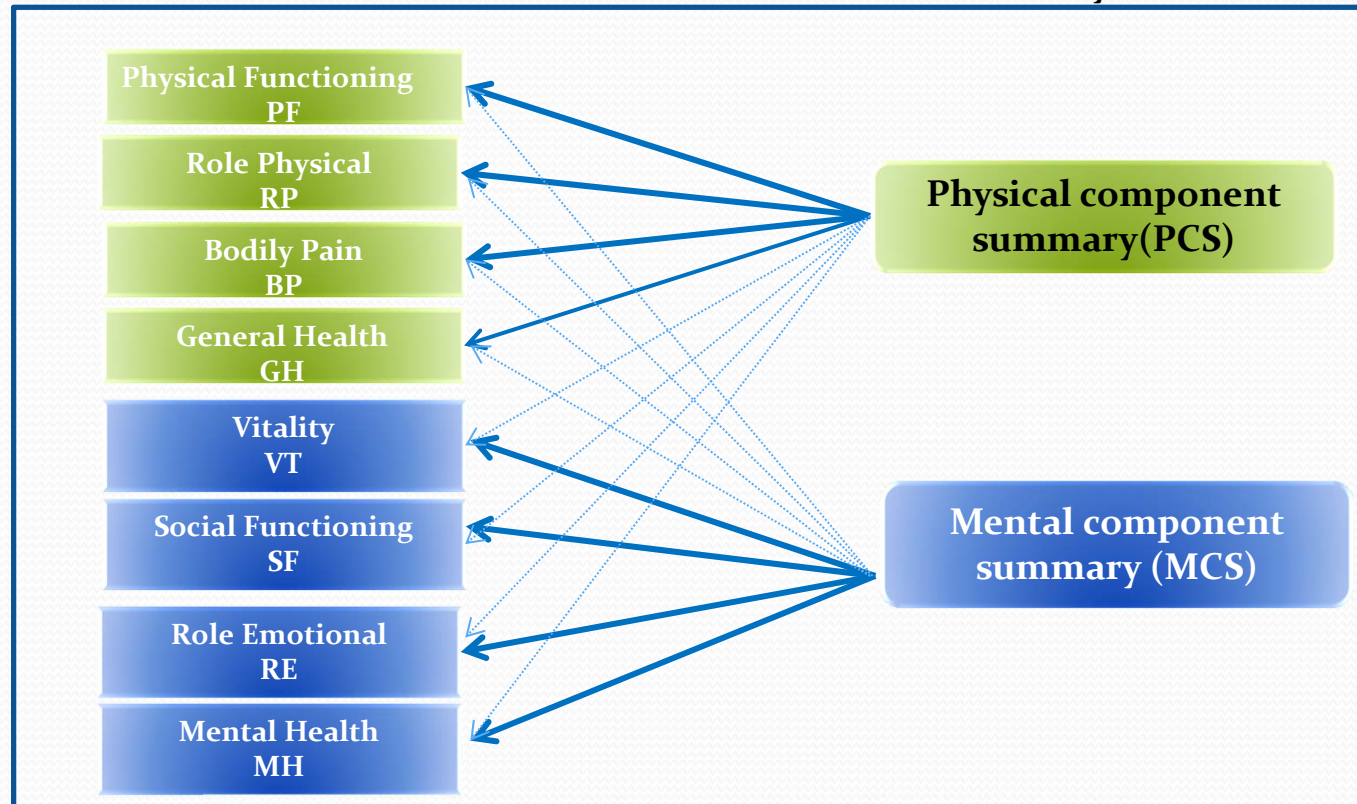
_____:
*contributing* **most** *to the components*

- - - - :
*contributing* **less** *to the components*

Domains Scores

0      50      100

US population norm

Domains & Components Scores
(*T-scores: CI99%~*)

20      50      80

Better QoL

• PRO for the assessment of Rheumatoid Arthritis (RA)

| 8 domains | # Items | HAQ-DI Initial version : 1983 Recent version | PROMIS HAQ (Improved HAQ) |
|---|---|---|---|
| Dressing & Grooming | 2 | | |
| Arising | 2 | | |
| Eating | 3 | | |
| Walking | 2 | 4 Levels 0, 1, 2, 3 | 5 Levels 0, 1, 2, 3, 4 |
| Hygiene | 3 | | |
| Reach | 2 | | |
| Grip | 3 | | |
| Activities | 3 | | |
| Total score | 20 | 0-3 | 0-100 |

$\sum$8items/20 x25
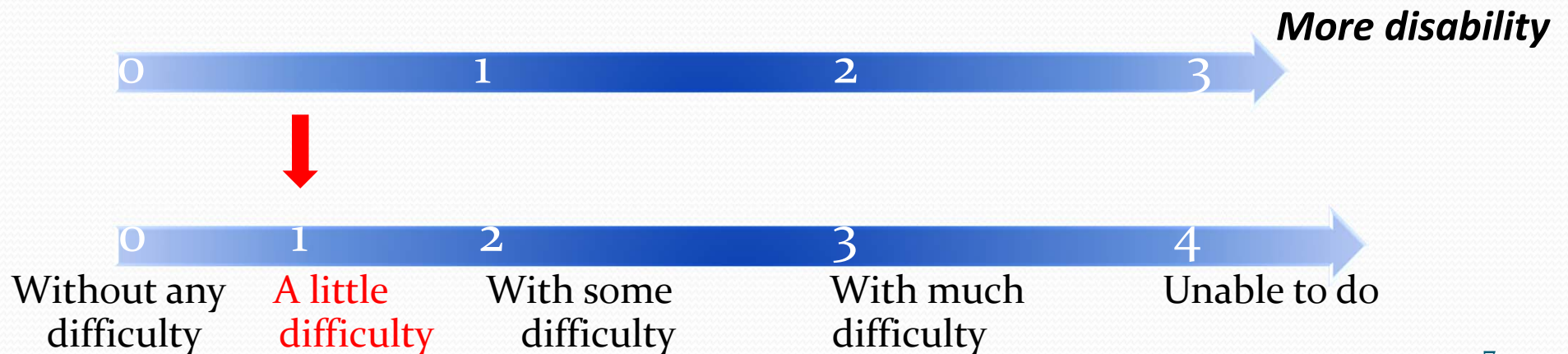
*More disability*

| 0 | 1 | 2 | 3 |
|---|---|---|---|

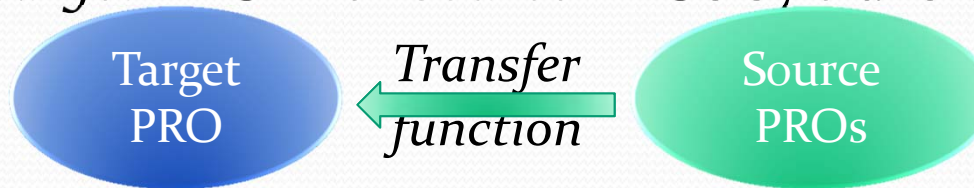| 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Without any difficulty | A little difficulty | With some difficulty | With much difficulty | Unable to do |

7

# II. Mapping techniques

1. Definition
2. Mapping process of EQ-5D based Utility
   - Step1: Estimation Sample
   - Step2: Transfer Function Building
   - Step3: Utility Approximation on Target Sample
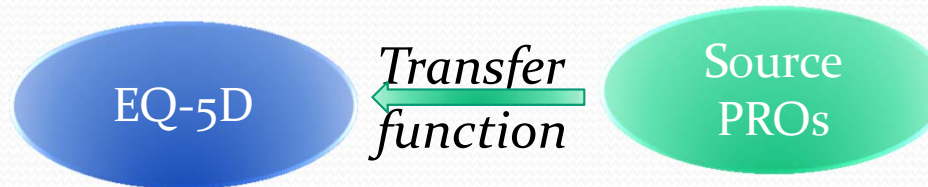3. When Mapping?

# Definition

- Mapping

  To link a *target* PRO with *source* PROs by transfer function

  Target PRO ← *Transfer function* ← Source PROs

- Mapping onto EQ-5D

  EQ-5D ← *Transfer function* ← Source PROs

- Double mapping

  EQ-5D ← *Transfer function* ← Intermediary PROs ← *Transfer function* ← Source PROs

# Predictive model building vs Mapping

Objective

**Predictive model building**

Good forecast

**Mapping**

Good approximation

# Mapping Process of EQ-5D based Utility

**Stept 1**
Estimation Sample

**Step 2**
Transfer Function Building

**Step3**
Utility Approximation on Target sample

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

- Similar as Predictive Model Building
- But different

- Target PRO: EQ-5D
- Source PRO(s)
- CROs
- Demographic characteristics
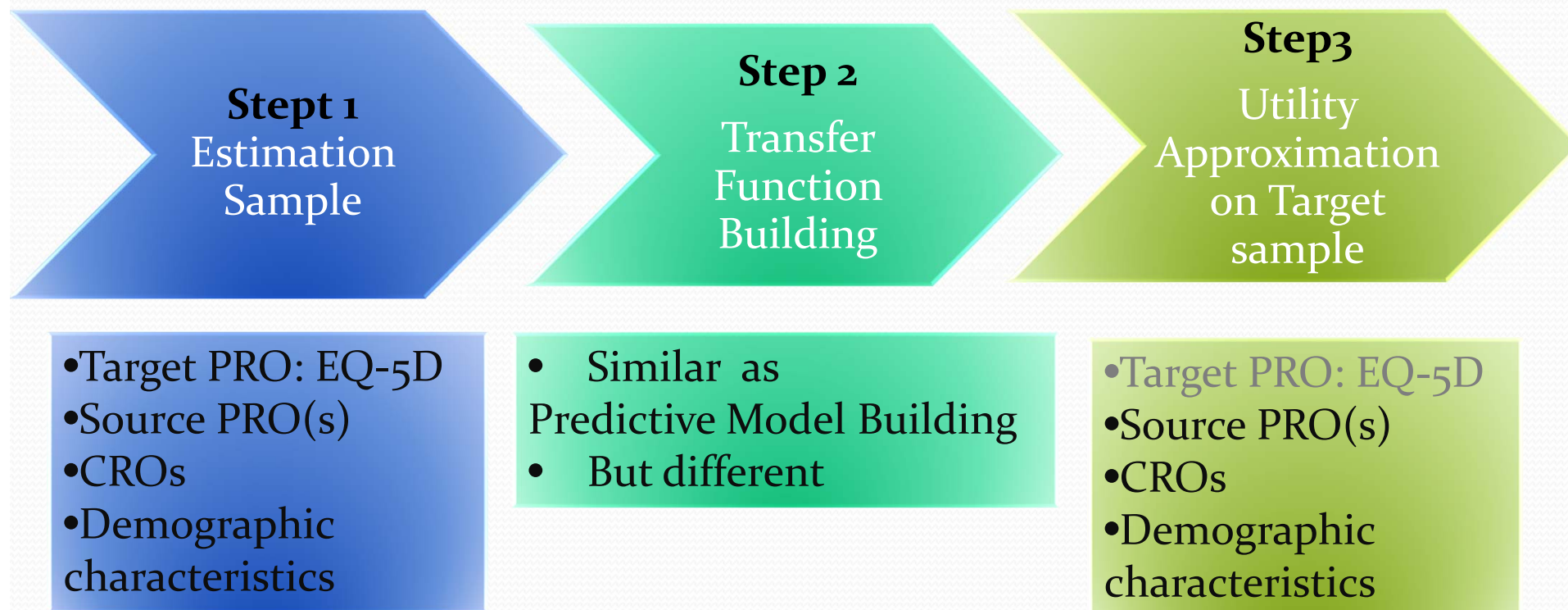
*CROs: Clinical Reported Outcomes*

# Step 1: Estimation Sample

## Similarity



Estimation Sample

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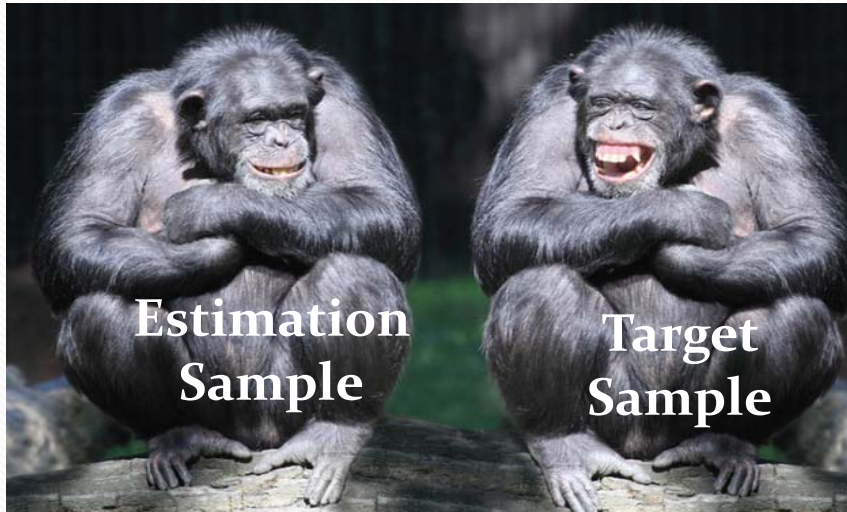
PROs/CROs selected in function have impact on EQ-5D
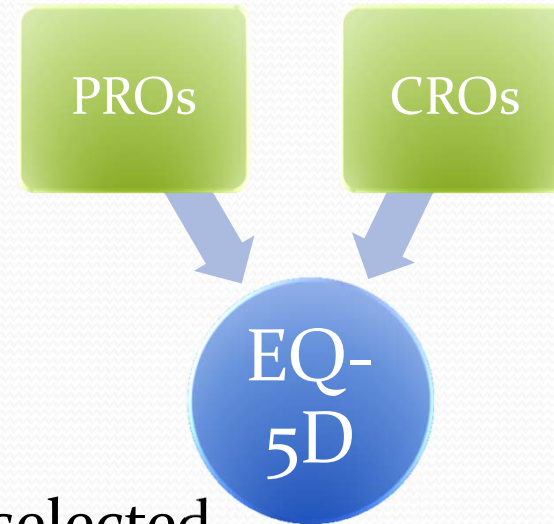


PROs

CROs

EQ-5D

## Overlapping Distributions of selected PROs/CROs in two samples



f(Estimation sample PROs)    f(Target sample PROs)

PROs

*Example: Influence Diagram of Rheumatoid Arthritis QoL and Symptoms*

Mapping                                    TMT HUYNH
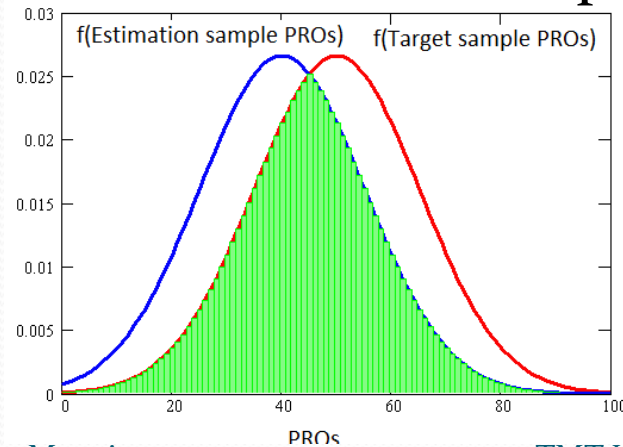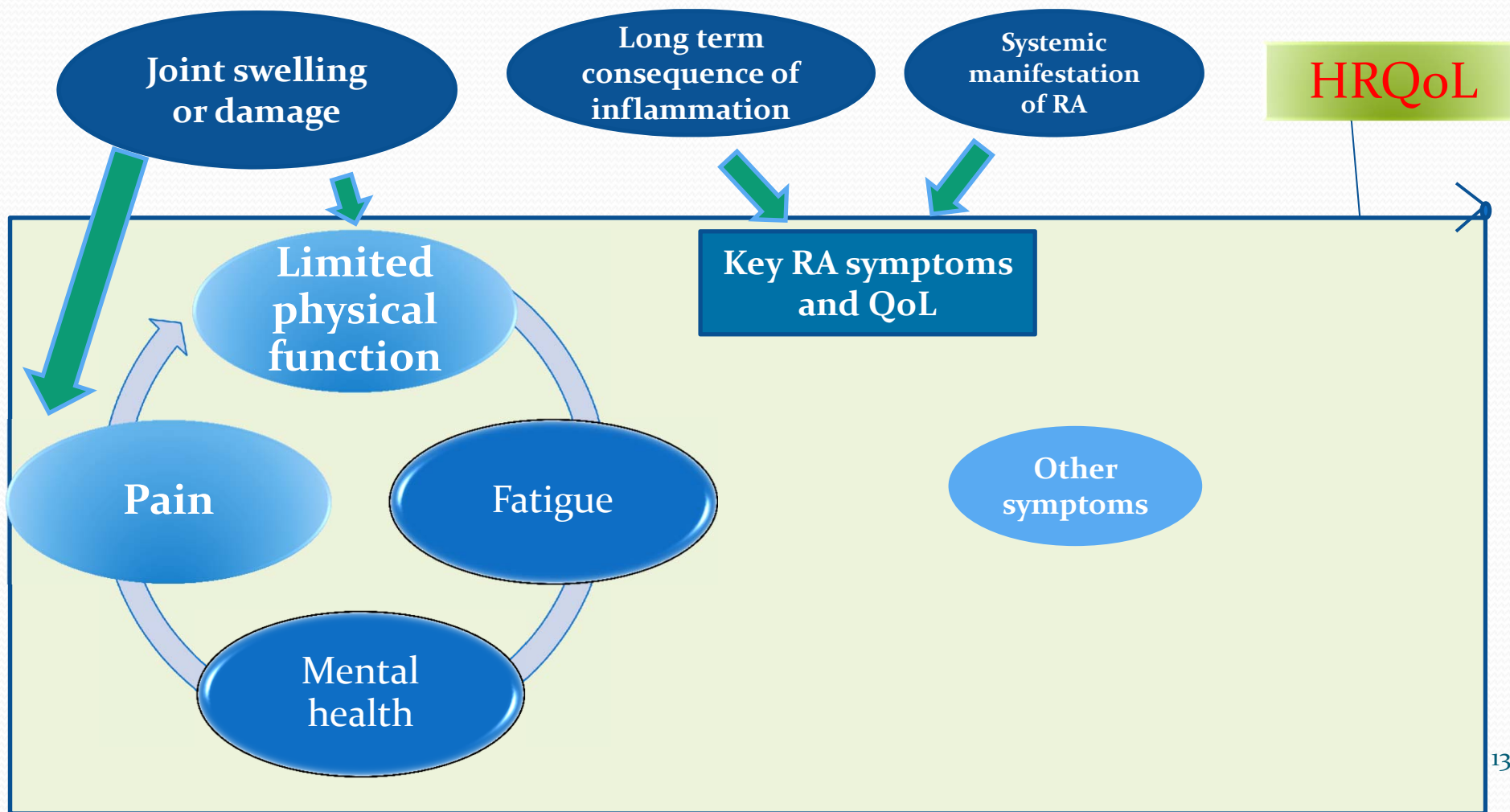
# Mapping Process of EQ-5D based Utility
## Step 1: Estimation Sample

*Example: From Influence Diagram of Rheumatoid Arthritis QoL and Symptoms*
*To Economic Modelling*

# Mapping Process of EQ-5D based Utility

| Stept 1 Estimation Sample | Step 2 Transfer Function Building | Step3 Utility Approximation on Target sample |
|---|---|---|
| •Target PRO: EQ-5D<br>•Source PRO(s)<br>•CROs<br>•Demographic characteristics | • Similar as Predictive Model Building<br>• But different | •Target PRO: EQ-5D<br>•Source PRO(s)<br>•CROs<br>•Demographic characteristics |
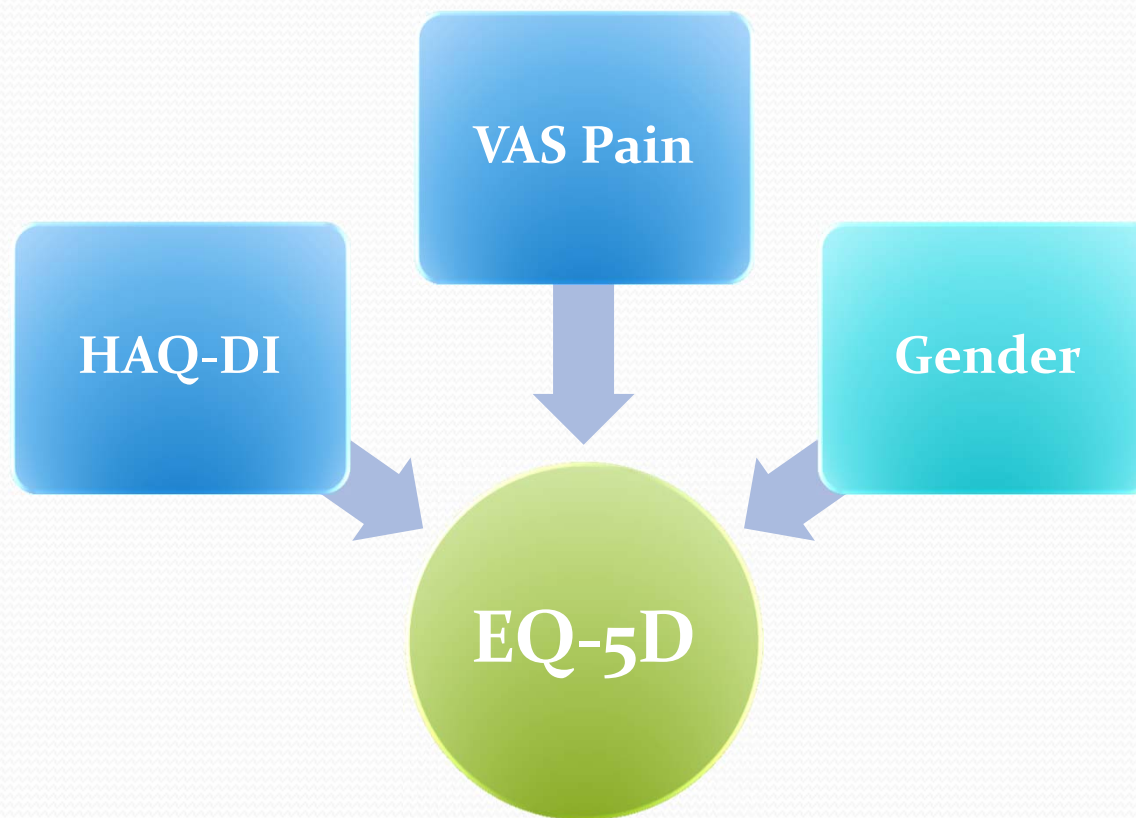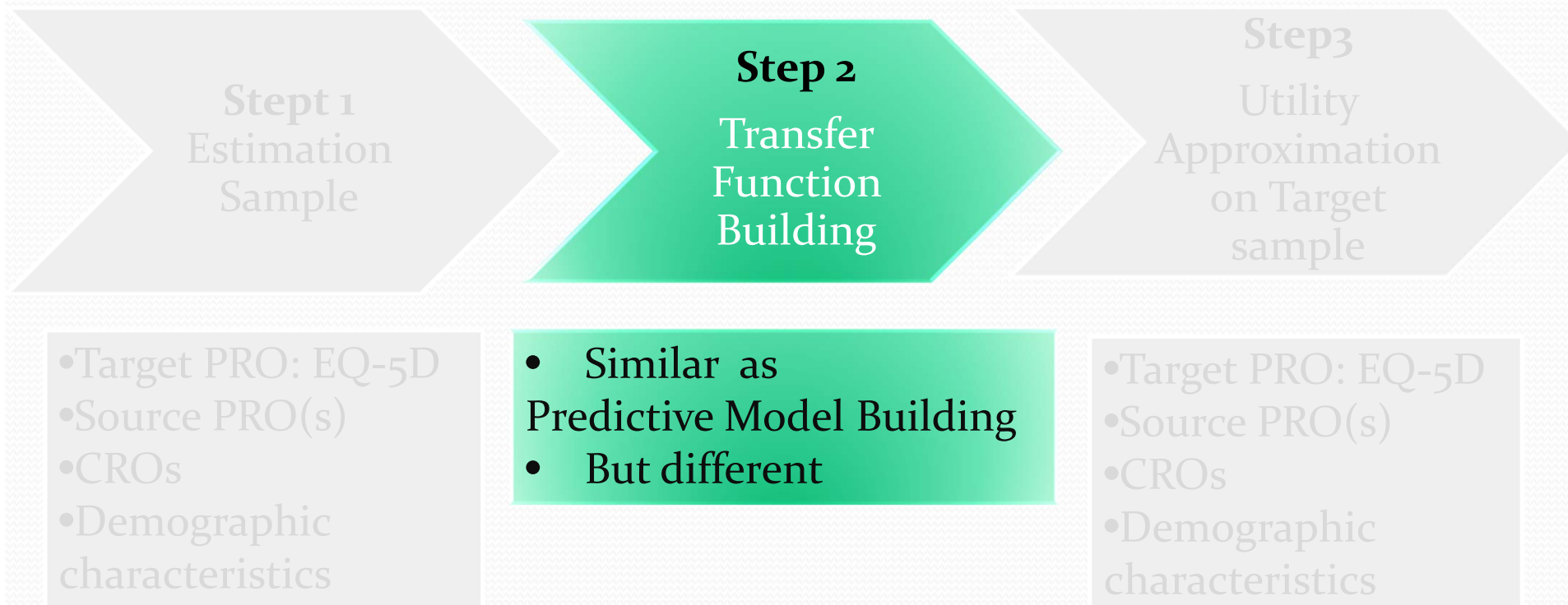
# Mapping Process of EQ-5D based Utility
## Step2: Transfer Function Building
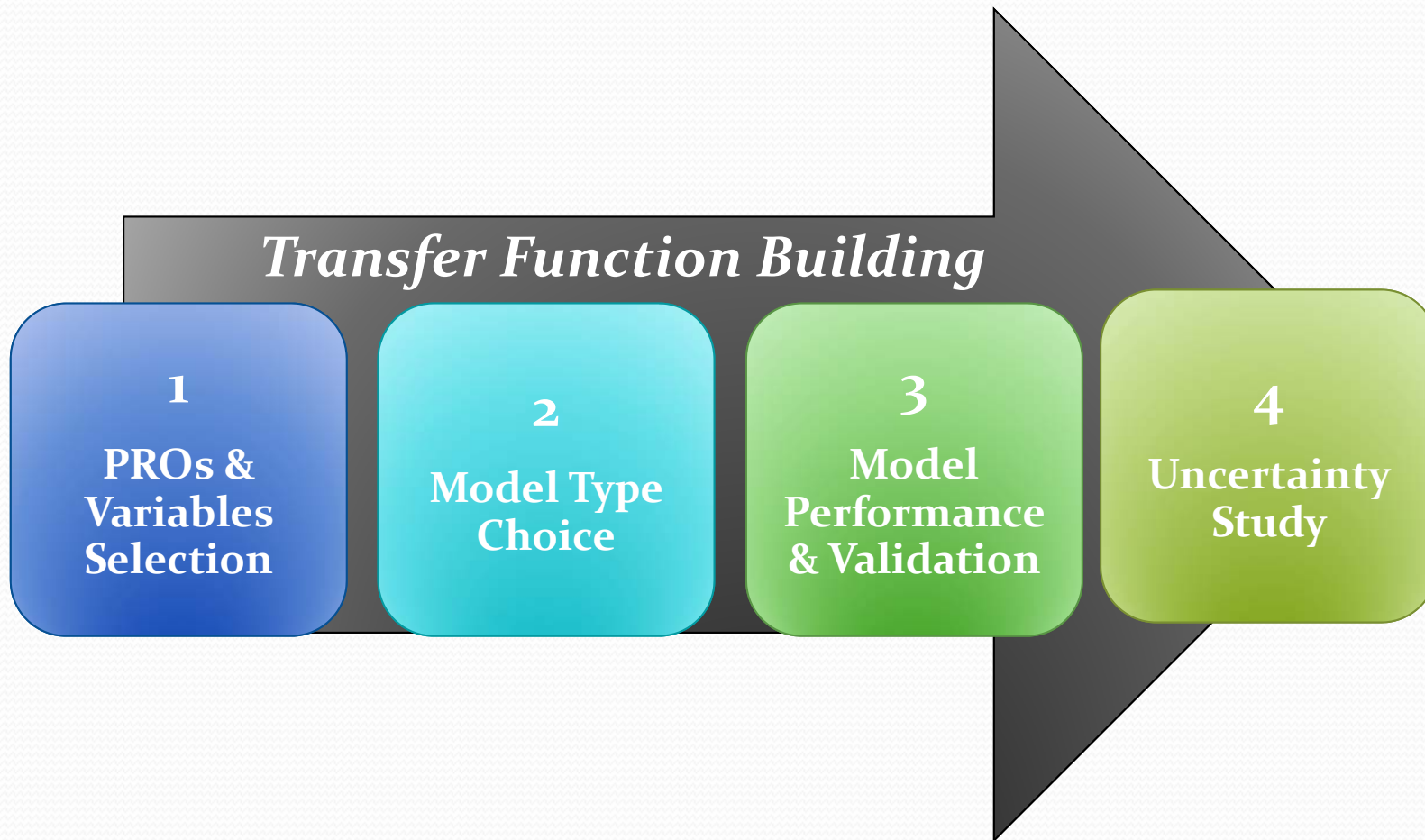
**Transfer Function Building**

**1**
PROs & Variables Selection

**2**
Model Type Choice

**3**
Model Performance & Validation

**4**
Uncertainty Study

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

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

**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

*\* Using UK tariff*

## 2. Model Type
### Study of EQ-5D utility distribution

**Not normal distribution**

- Multimodal nature of the distribution

Under Hypothesis of

*Normal distri bution*
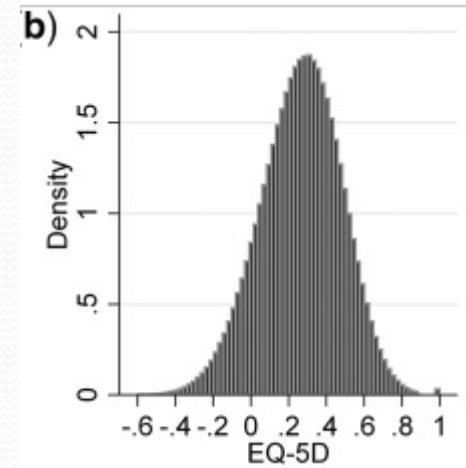
*Mixture of distributions*
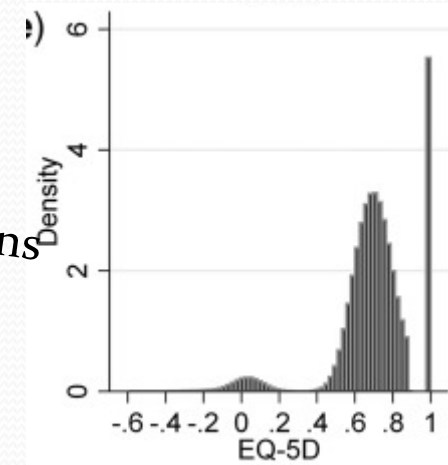
- This very reason explains linear regression performing poorly,

# Step2: Transfer Function Building
# 2. Model Type: Target PRO

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

**EQ-5D Index**

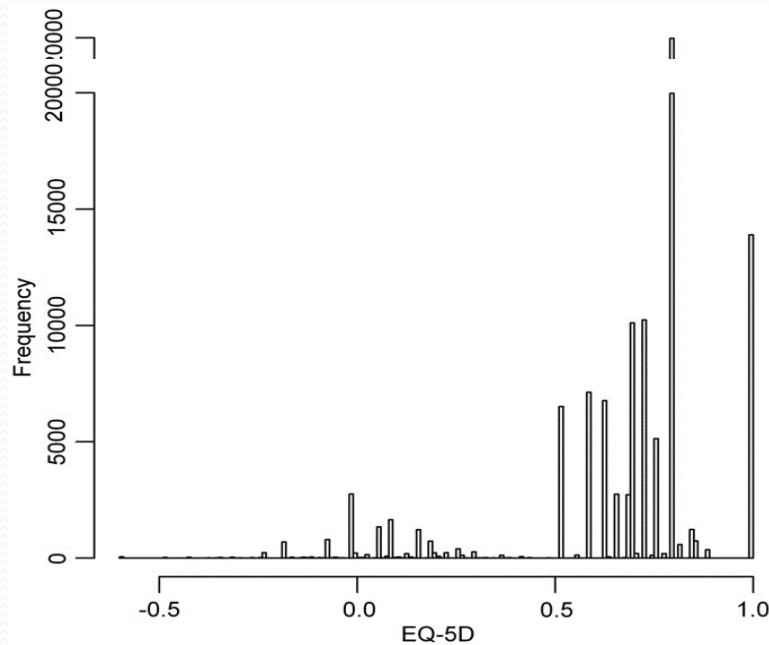**[-0.549; 1]***

- OLS Regression

- Mixture model

- PLS regression approach
  *Latent variables*

**EQ-5D dimension levels**

**1, 2,3 or 1,2,3,4,5**

- Multinormial logistic regressions

- PLS discriminant analysis
  *5 dimensions levels on latent variables*

- Canonical analysis
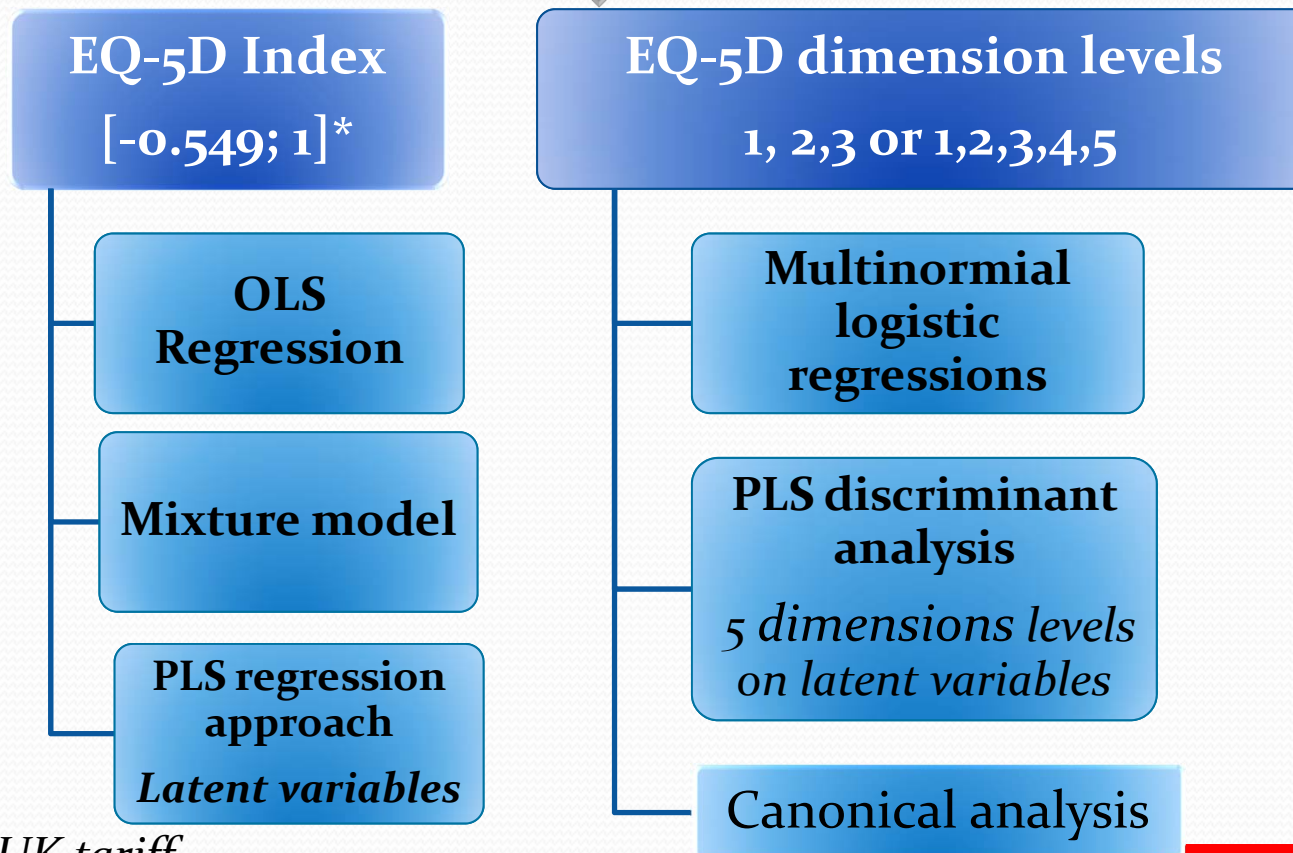
- *Using UK tariff*
- *OLS: Ordinary Least Squares*
- *PLS: Partial Least Squares*

Warnings: PROs version

19

# Step2: Transfer Function Building
# 3. Model Performance and Validation

Using Similar  criteria and techniques as predictive modeling:

**Model Performance** → **Validation**

**Model Performance:**

Goodness of fit
*ajusted R², AIC, BIC*

Prediction
power: *RMSE*

Comparing with
existing mapping

**Validation:**

Estimation
sample
*learning vs testing
samples*

Ideally, external
sample similar to
the target sample
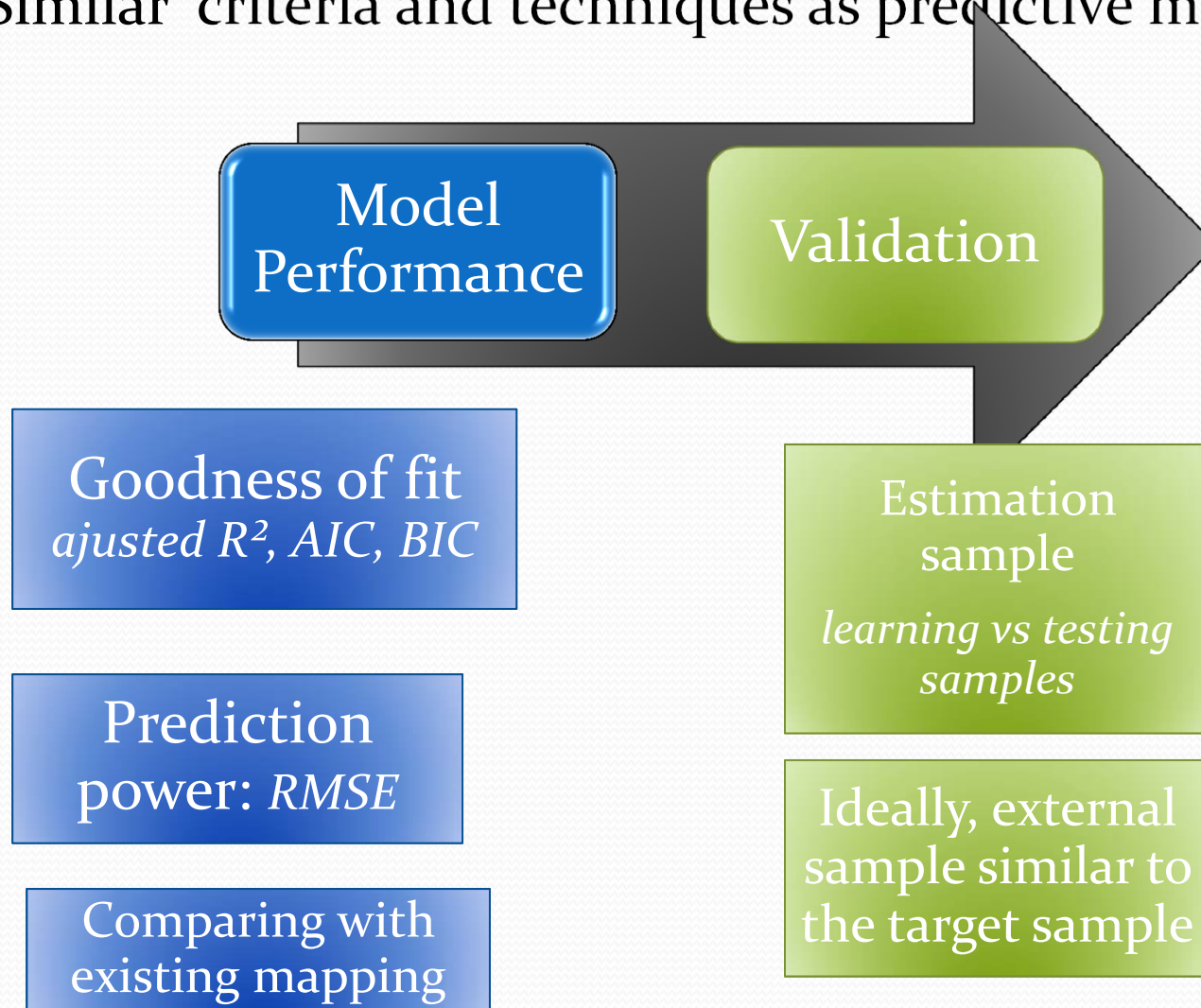
# Step2: Transfer Function Building
## 4. Uncertainty Study

### 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

# Step2: Transfer Function Building
# Some Examples

- Mapping SF36 (12) onto EQ-5D
- Mapping HAQ-DI onto EQ-5D

# Step2: Transfer Function Building
# Example: Mapping SF-36/12 onto EQ-5D-3L

**EQ-5D** ← *Transfer function* — **SF36/12**

| Target PRO | Model Type | Source PRO | Author |
|---|---|---|---|
| EQ-5D-3L Dimension levels | 5 Mutinomial logistic regression model *for 5 EQ-5D dimension* | SF-12: PCS, MCS | Gray 2006 |
| EQ-5D-3L Utility Index | Linear Regression 2 Components+ 2 Components$^2$+1 interaction | SF-12: PCS, MCS | Francks 2004 |
| | Linear Regression 8 domains+ (8 domains $^2$)+ (28 interactions) | SF-36 | Brazier 2009 |

# Step2: Mapping algorithm building
Example: Mapping SF-36 onto EQ-5D-3L *(Brazier 2009)*

EQ-5D Utility Index =

$f(8\ domains)$
**Model1**

$f(8\ domains,\ 8\ domain^2)$
**Model2**

$f(8\ domains,\ 8\ domain^2,\ 28\ interactions)$
**Model3**
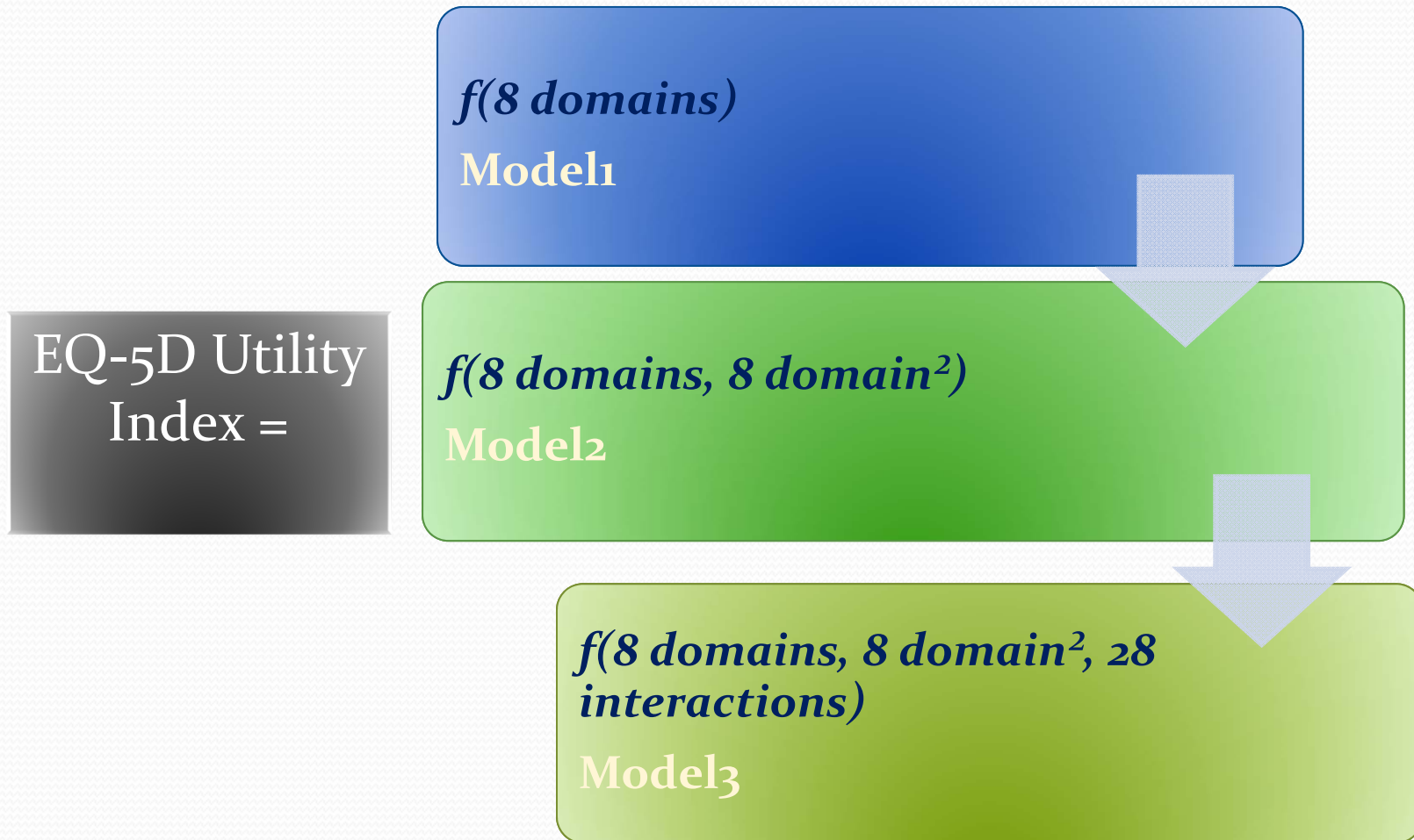
*Domain transformation: [0;1]*

# Step2: Building Transfer function
## Example: Mapping SF-36 onto EQ-5D-3L *(Brazier 2009)*

| 8 domains | | Estimated coefficients (GLM: Model 3) | | |
|---|---|---|---|---|
| | | Domains | Domains$^2$ | Interaction |
| Bodily Pain | BP | 0.715* | -0.330 * | |
| Physical Functioning | PF | 0.559* | -0.227* | |
| Mental Health | MH | 0.483* | -0.242* | |
| General Health | GH | 0.407* | 0.032 | |
| Social Functioning | SF | 0.293* | -0.163* | |
| **Role-Physical** | RP | -0.146* | 0.001 | |
| **Vitality** | VT | 0.017 | -0.012 | |
| **Role-Emotional** | RE | 0.067* | 0.034 | |
| $\sum coef$ (ins+Mental domains) | | | | |

**PCS**

**MCS**

VT, RP and RE did not significantly effect the EQ-5D index,

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PF × RP | 0.022 | | | | | | | | | | | | |
| PF × BP | -0.032 | RP × BP | 0.019 | | | | | | | | | | |
| PF × GH | 0.073 | RP × GH | 0.068* | BP × GH | -0.217* | | | | | | | | |
| PF × VIT | -0.132* | RP × VIT | 0.050 | BP × VIT | -0.002 | GH × VIT | -0.066 | | | | | | |
| PF × SF | -0.023 | RP × SF | 0.067* | BP × SF | 0.055 | GH × SF | -0.157* | VIT × SF | 0.143* | | | | |
| PF × RE | 0.047* | RP × RE | -0.012 | BP × RE | -0.038 | GH × RE | -0.033 | VIT × RE | -0.020 | SF × RE | -0.023 | | |
| PF × MH | -0.014 | RP × MH | 0.022 | BP × MH | 0.131* | GH × MH | -0.084 | VIT × MH | 0.023 | SF × MH | -0.065 | RE × MH | -0.048 |

# Step2: Transfer Function Building
## Example: Mapping HAQ-DI onto EQ-5D in RA

EQ-5D ← *Transfer function* ← HAQ-DI

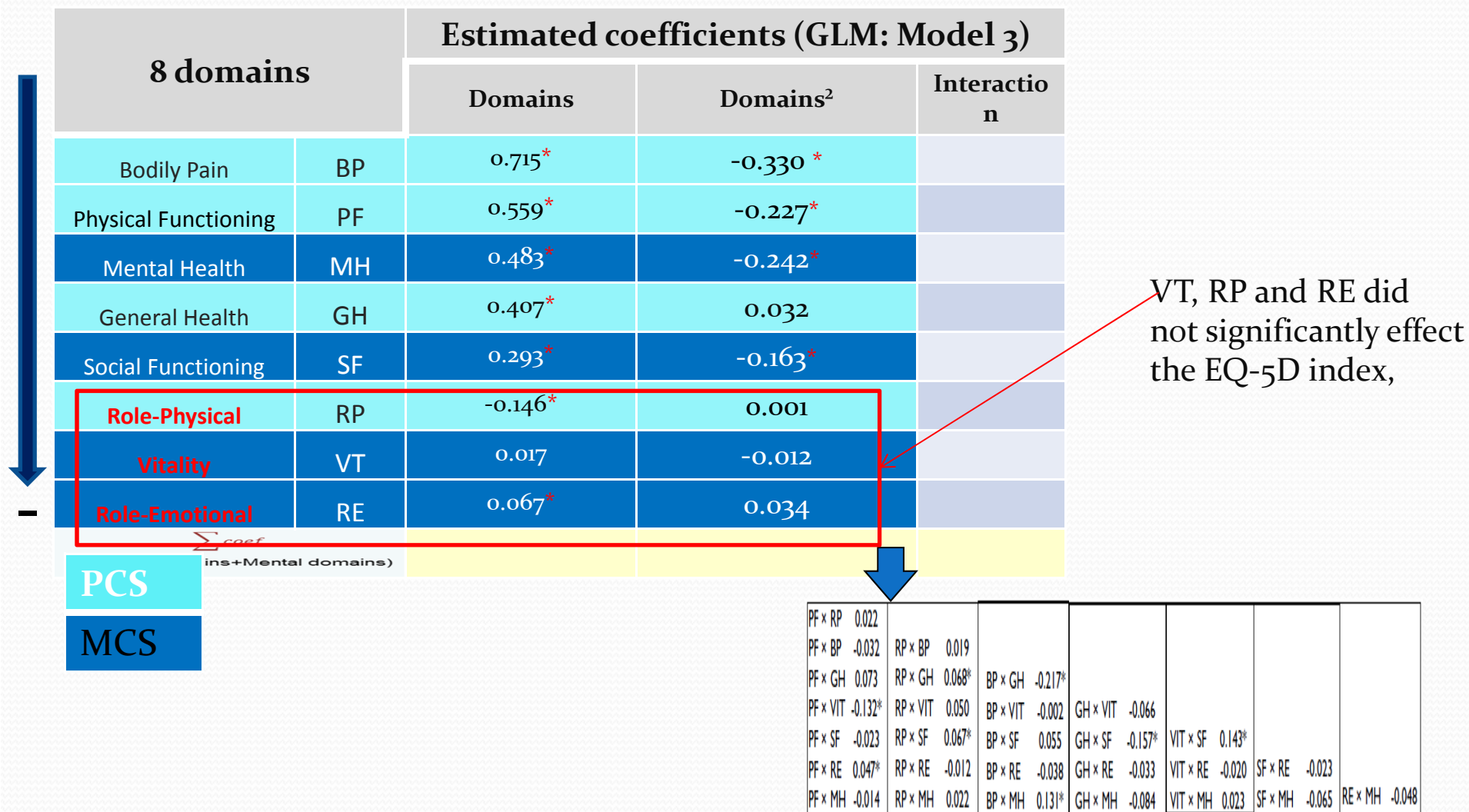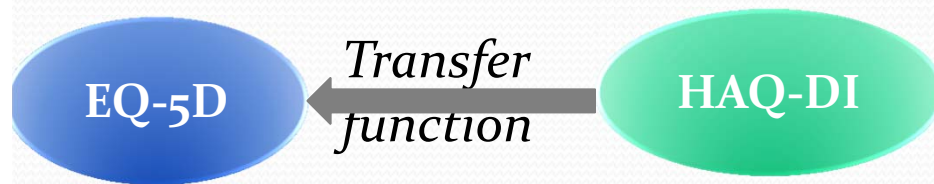| Target PRO | Model Type | Source PROs | Author |
|---|---|---|---|
| EQ-5D-3L Index | Linear regression | HAQ-DI *Dummy Items* | Bansback, 2007 |
| | Linear regression | HAQ-DI and DAS28 | Adams, 2010 |
| | Mixture model | HAQ-DI, VAS pain and age | Hernandez, 2013 |

| Domain/item | B | SE | P |
|---|---|---|---|
| Dressing and grooming | | | |
| $H_1 = 2$ | −0.15 | 0.04 | < 0.01 |
| Arising | | | |
| $H_4 = 1$ | −0.08 | 0.02 | < 0.01 |
| $H_4 = 2$ | −0.12 | 0.05 | 0.02 |
| $H_4 = 3$ | −0.59 | 0.08 | < 0.01 |
| Eating | | | |
| $H_6 = 2$ | −0.15 | 0.05 | 0.01 |
| $H_7 = 1$ | −0.04 | 0.02 | 0.02 |
| $H_7 = 2$ | −0.08 | 0.03 | 0.01 |
| Walking | | | |
| $H_9 = 2$ | −0.10 | 0.04 | 0.03 |
| $H_9 = 3$ | 0.12 | 0.05 | 0.02 |
| Aids or devices | | | |
| $H_{13} = 2$ | −0.14 | 0.04 | < 0.01 |
| $H_{16} = 1$ | 0.07 | 0.03 | 0.01 |

| Domain/item | B | SE | P |
|---|---|---|---|
| Hygiene | | | |
| $H_{23} = 1$ | −0.05 | 0.02 | < 0.01 |
| $H_{24} = 1$ | −0.05 | 0.02 | 0.01 |
| $H_{24} = 2$ | −0.11 | 0.04 | < 0.01 |
| Reach | | | |
| $H_{26} = 2$ | −0.14 | 0.04 | < 0.01 |
| $H_{26} = 3$ | −0.13 | 0.06 | 0.03 |
| Grip | | | |
| $H_{27} = 2$ | −0.08 | 0.04 | 0.04 |
| $H_{27} = 3$ | −0.20 | 0.07 | < 0.01 |
| $H_{28} = 3$ | | | |
| Activities | | | |
| $H_{30} = 1$ | −0.05 | 0.02 | < 0.01 |
| $H_{31} = 1$ | −0.07 | 0.02 | < 0.01 |
| $H_{31} = 2$ | −0.08 | 0.04 | 0.03 |
| $H_{32} = 3$ | −0.09 | 0.03 | < 0.01 |
| Constant | 0.80 | 0.01 | < 0.01 |

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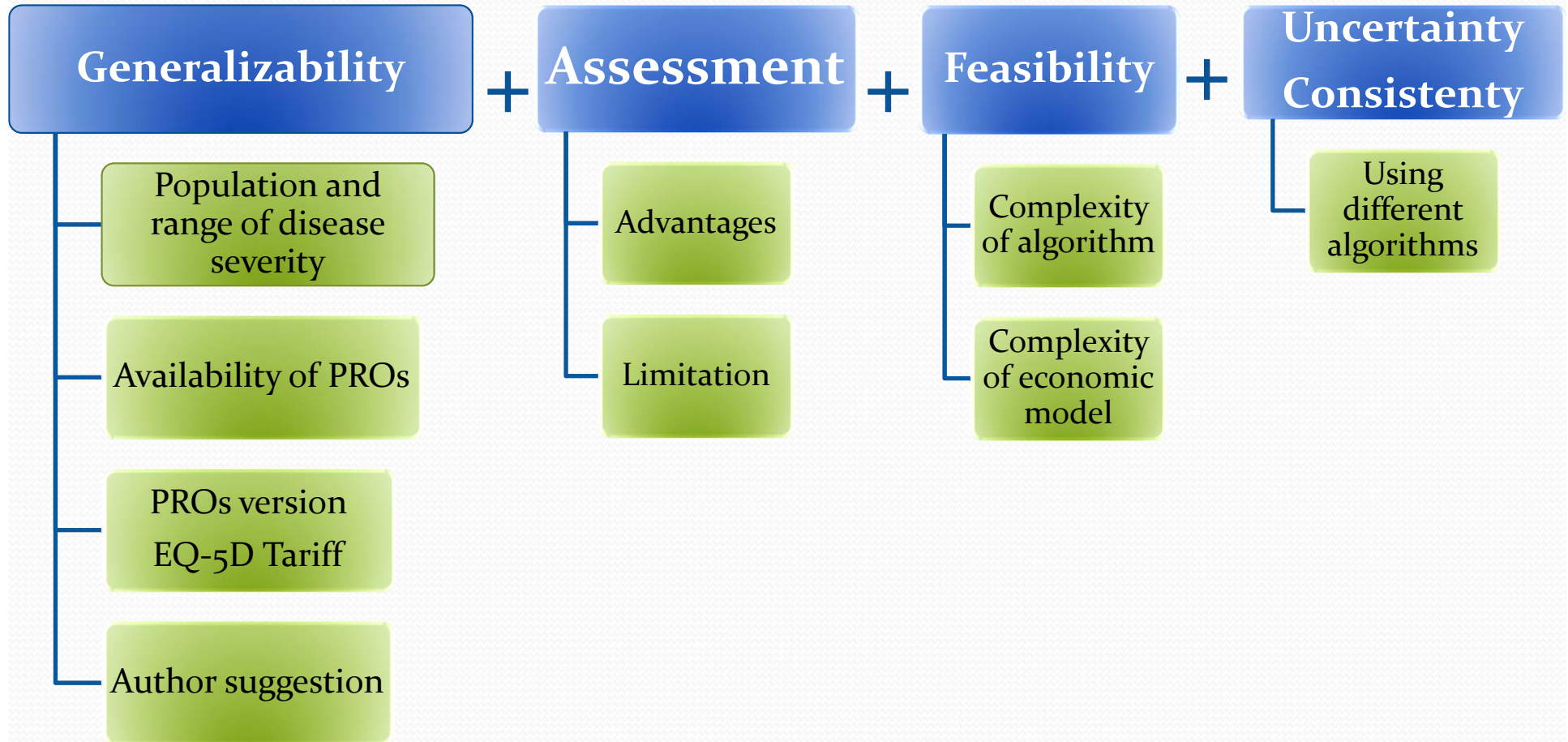
# Mapping Process of EQ-5D based Utility

**Stept 1**

Preparing an Estimation sample

**Step 2**

Transfer function building

**Step3**

Utility Approximation on Target sample

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

•Similar as predictive model building

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

# Step3: 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

# Step3: Utility Approximation on *Target* Sample Using existing Mapping algorithm

**Generalizability** + **Assessment** + **Feasibility** + **Uncertainty Consistenty**

**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 Consistenty**
- Using different algorithms

# Step3: 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**
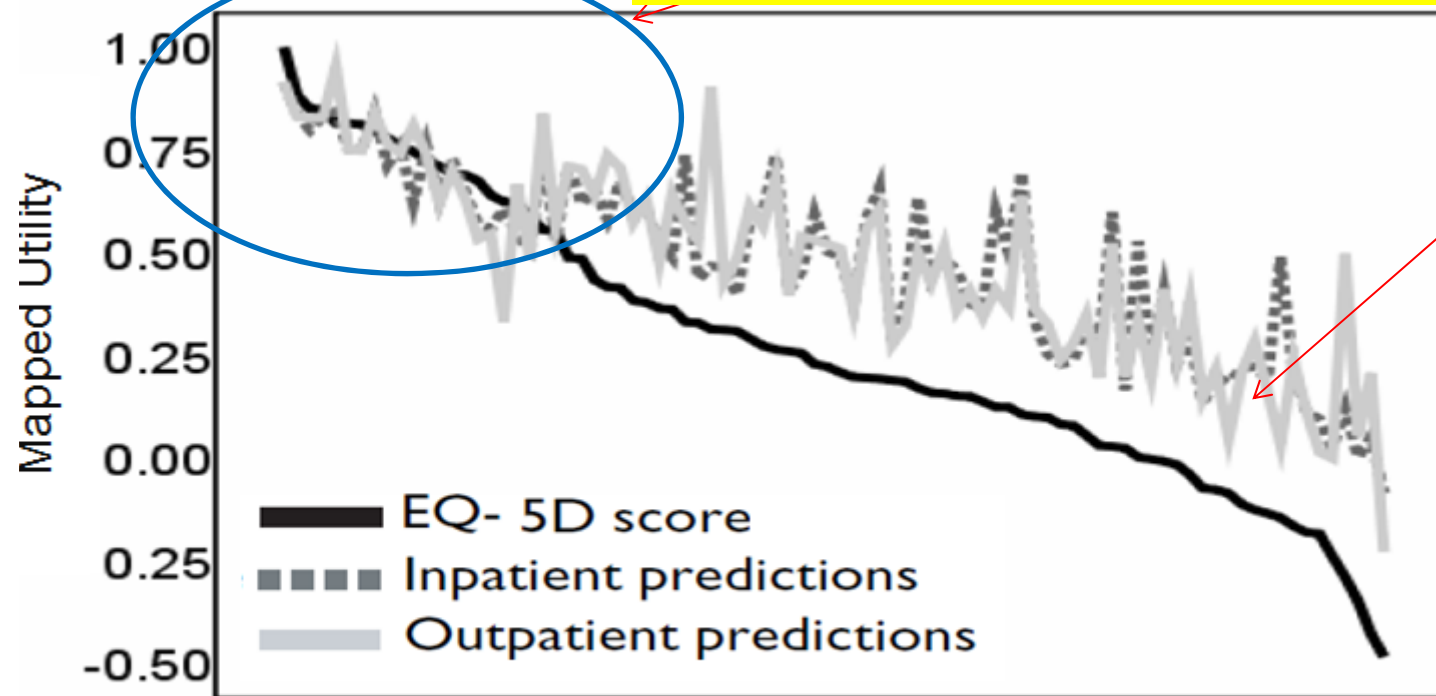
Very reason of Multimodal nature of the EQ-5D distribution?



- Mapped Utility
- EQ- 5D score
- Inpatient predictions
- Outpatient predictions
- Observed Utility ordered according to severity

# When Mapping?

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

# When Mapping?
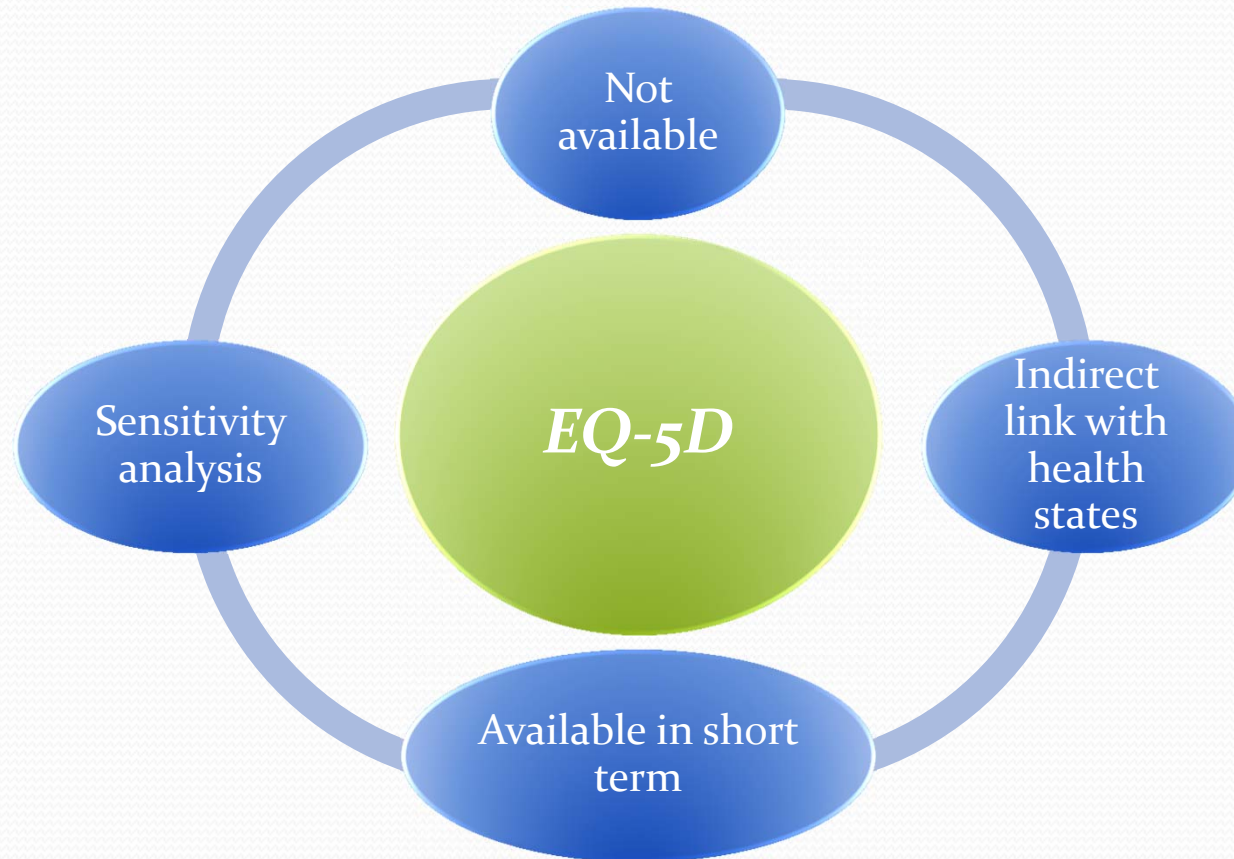


- Direct utility should be used in parallel for assessment of mapped ones
- Different mapping algorithms should be used for sensitivity analysis

# When mapping?
## Example: Utility calculation in CE Model for RA

Simplified logical flow for CE Model in RA

| Health states | Cycle calculation |
|---|---|

1st treatment

Death

#th treatment

Palliative care

Assess response to treatment

Update HAQ-DI and VAS pain scores

(M)

Determine if patient stays on treatment or switch to another treatment

Update QoL
Update mortality and costs
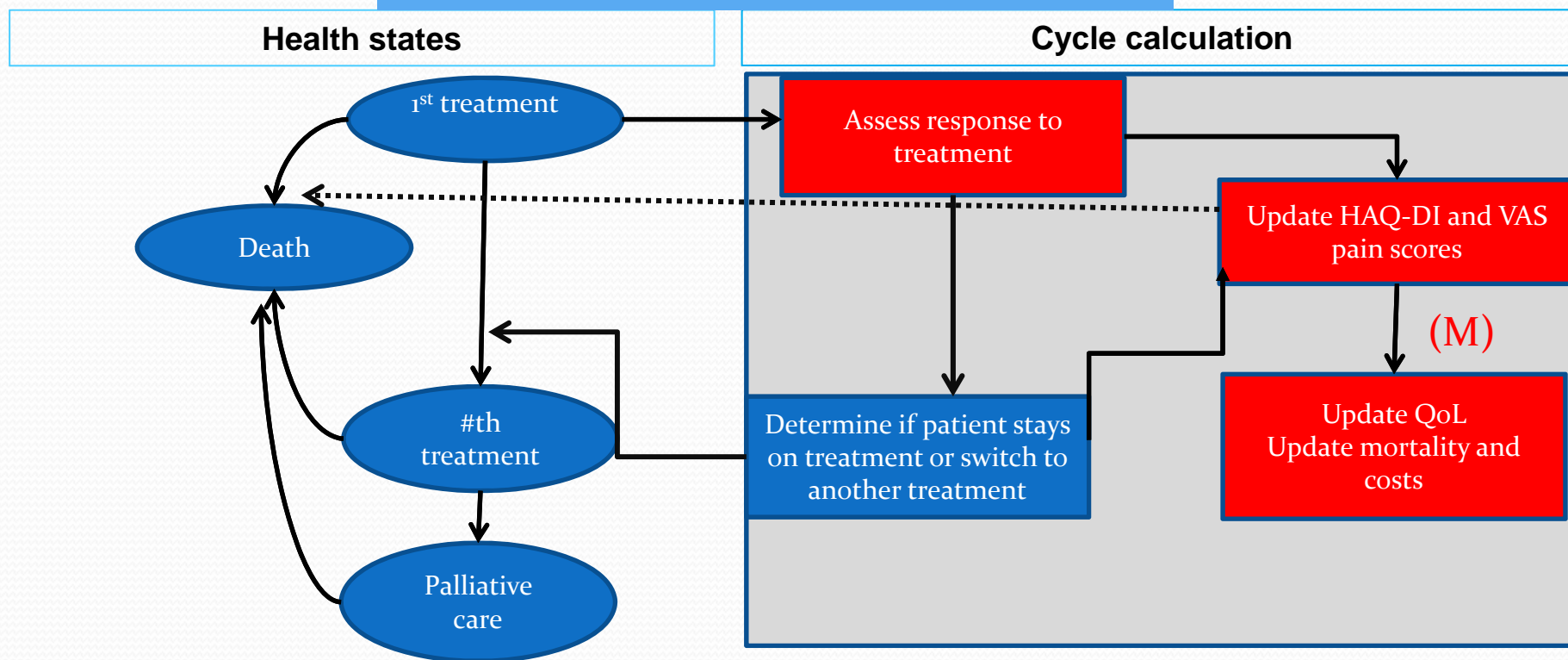
(M) Using mapping (HAQ and VAS pain ) function to approximate EQ-5D utilities:

# Conclusion

- Mapping gives a possiblity 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

1. L. Longworth et al: « *Mapping to Obtain EQ-5D Utility Values for Use in NICE Health Technology Assessments*". Value in Health, 2013

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

3. Franks P, Lubetkin EI, Gold MR, Tancredi DJ, Haomiao J: *"Mapping the SF-12 to the EuroQol EQ-5D Index in a National US Sample"*. Medical Decision Making 2004, 24:247-254.

4. Gray AM, Rivero-Arias O, Clarke PM: *"Estimating the Association between SF-12 Responses and EQ-5D Utility Values by Response Mapping"*. Medical Decision Making 2006, 26:18-294, 24:247-254

5. Hernandez Alava, M., Wailoo, A., Wolfe, F., Michaud, K. "*The relationship between EQ-5D, HAQ and pain in patients with rheumatoid arthritis*". Rheumatology 2013.

6. Bansback, N., Marra, C., Tsuchiya, A., Anis, A., Guh, D., Hammond, T. et al. *Using the health assessment questionnaire to estimate preference-based single indices in patients with rheumatoid arthritis*. Arthritis & Rheumatism-Arthritis Care & Research 2007; 57(6):963-971.

7. Adams R., Walsh C., Veale D., Bresnihan B., Fitzgerald B., Barry M. *Understanding the Relationship between the EQ-5D, SF-6D, HAQ and Disease Activity in Inflammatory Arthritis*. Pharmacoeconomics 2010; 28 (6): 477-487

# 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)
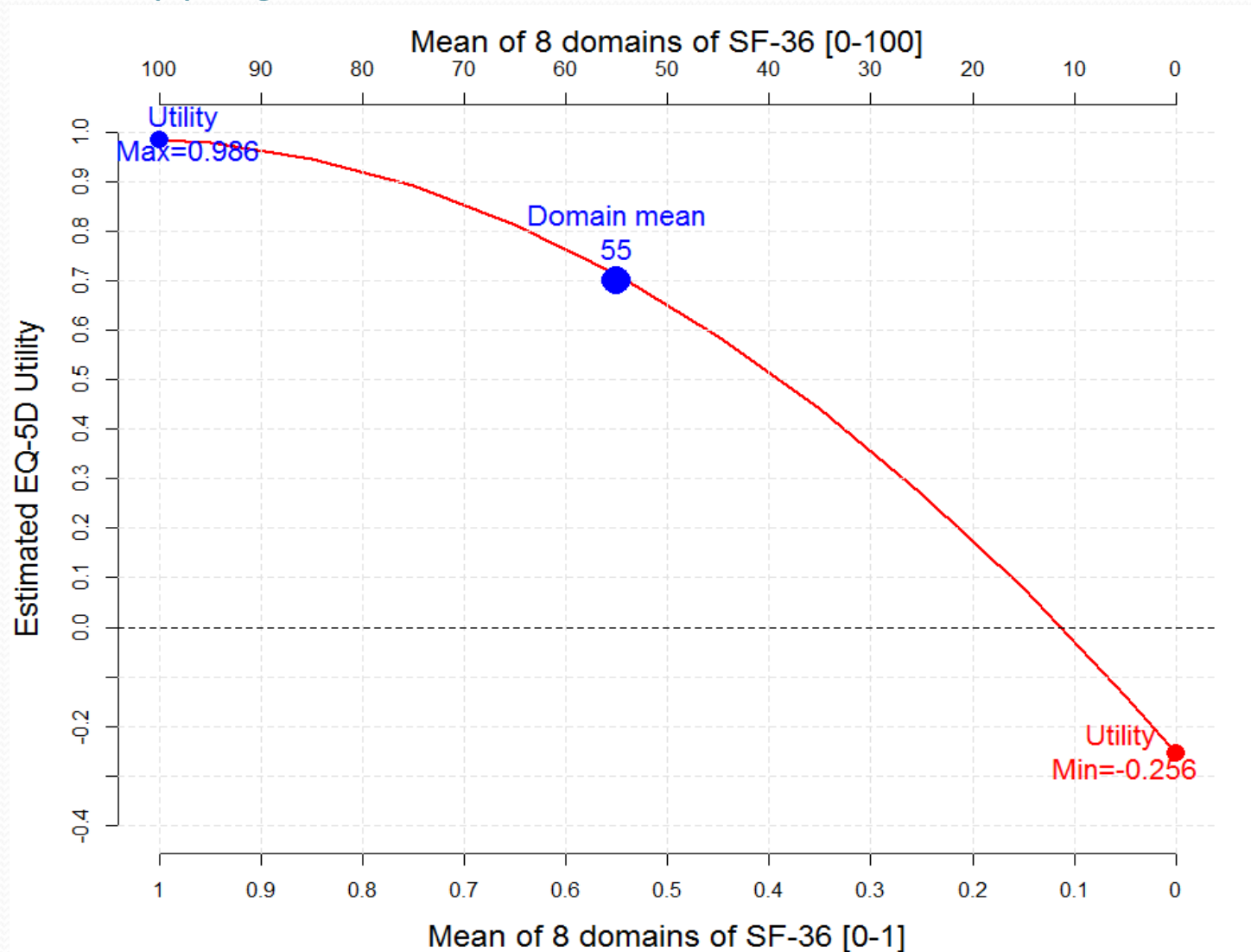- Index scores =[0.30; 1] represents *worst health state* to *best health state*
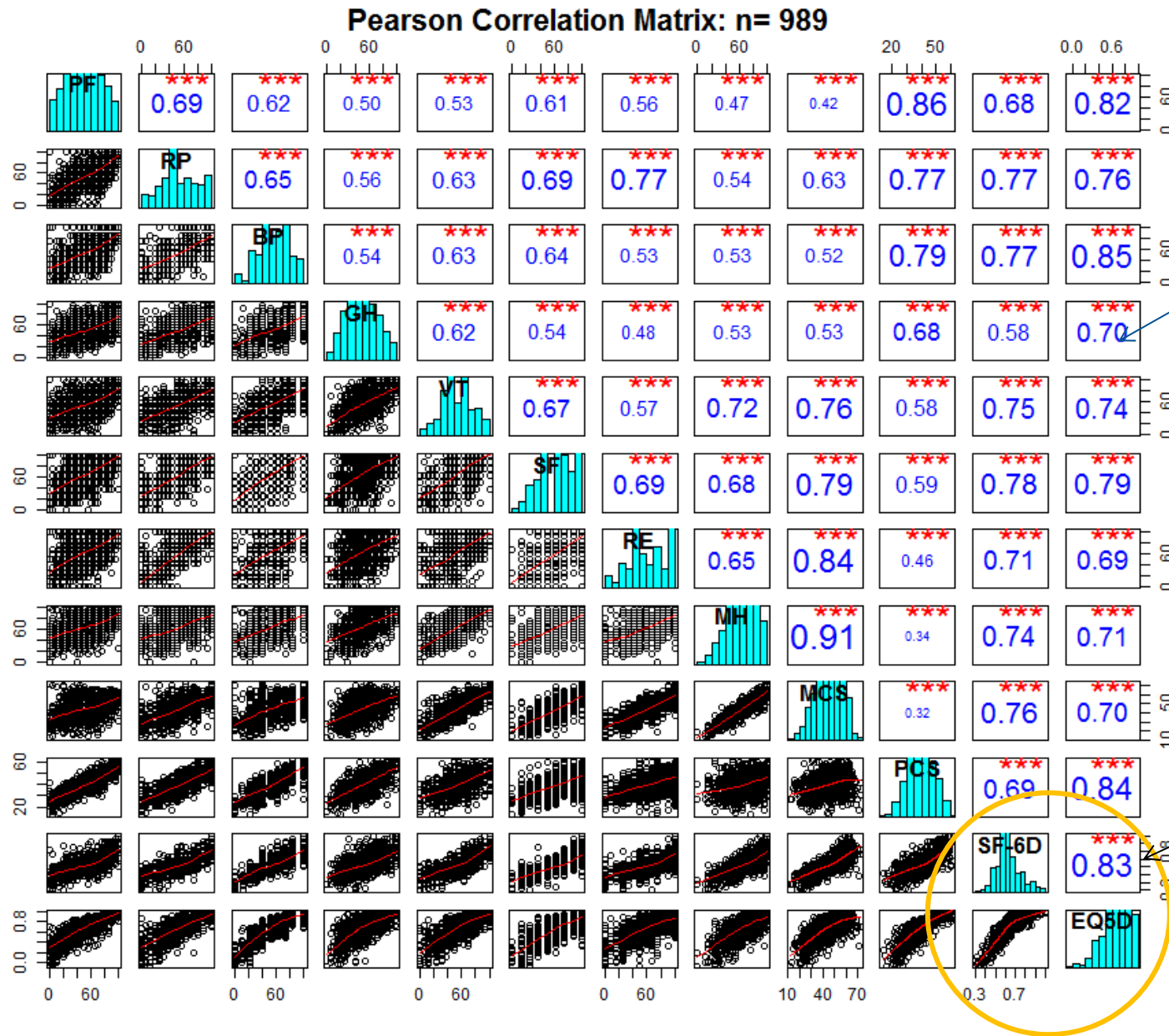
*EQ-5D based Utility*

| -0.594 | 0 | 0.30 | 1 |

*SF-6D based Utility*

# Step3: 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



**Pearson Correlation Matrix: n= 989**

Trend of higher correlation between SF-36 and estimated EQ-5D utility than SF-6D utility
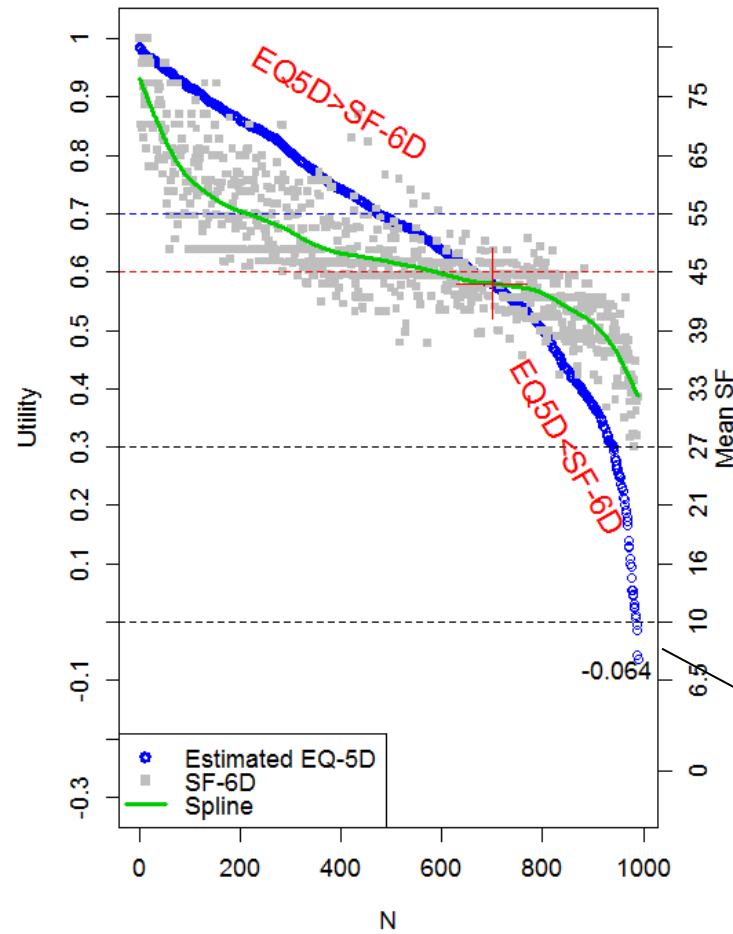
Sysmatric distribution for SF-6D but not estimated EQ-5D

# The Estimated EQ-5D has produced quite different utility values from that of the SF-6D

| Stat | SF-6D | Estimated EQ-5D |
|---|---|---|
| Min | 0.301 | -0.064 |
| q1 | 0.559 | 0.551 |
| Median | 0.616 | 0.692 |
| Mean | 0.631 | 0.670 |
| q3 | 0.691 | 0.839 |
| Max | 1 | 0.987 |
| SD | 0.114 | 0.207 |
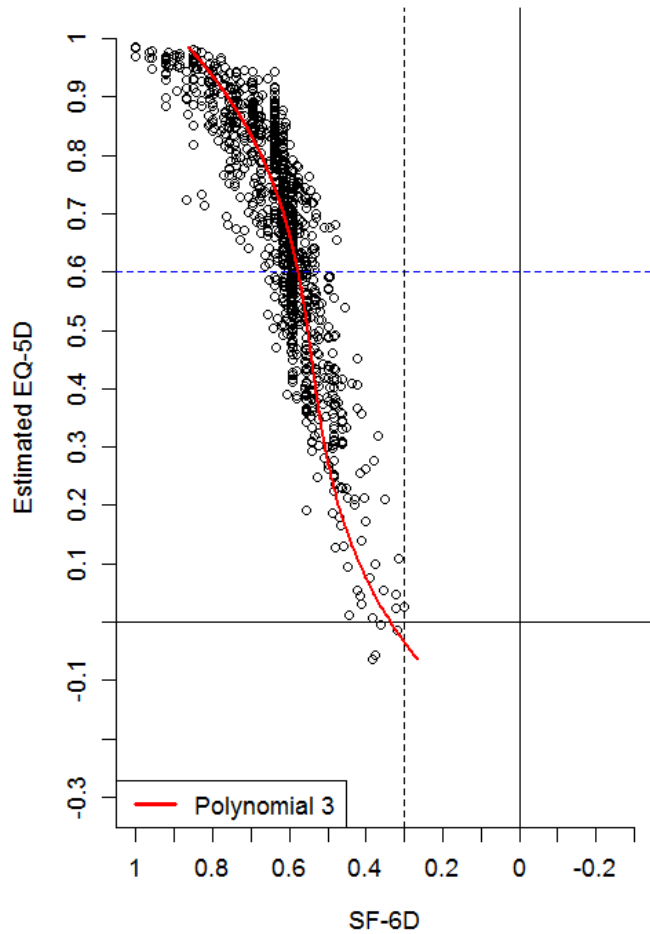


Simulation:
meanSF:8.23
=>EQ-5D=-0.067

*meanSF:  mean of 8 domains of 0-100 scaled SF-36*