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Response mapping to translate health outcomes into the generic health-related quality-of-life instrument EQ-5D: Introducing the mrs2eq and oks2eq commands

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Abstract. Reliable and accurate mapping techniques that translate health-related quality-of-life data into EQ-5D index values are now in demand by researchers conducting economic evaluation of health care technologies. In this article, we present two commands (`mrs2eq` and `oks2eq`) that translate data from two widely used disease-specific instruments into EQ-5D index values and predicted probabilities of being at a particular level on each EQ-5D domain. `mrs2eq` conducts a response mapping approach to transform data from the stroke-specific modified Rankin scale into index values from the generic quality-of-life EQ-5D instrument. `oks2eq` uses a response mapping model to estimate EQ-5D index values based on patients' responses to the Oxford Knee Score.

Keywords: st0305, mrs2eq, oks2eq, response mapping, EQ-5D

1 Introduction

The development of algorithms to translate disease-specific or generic health outcomes into EQ-5D index values has increased considerably over the last decade (Dakin 2013). Reliable and accurate mapping techniques that translate responses or scores on other health-related quality-of-life (HRQoL) instruments into EQ-5D index values are now in demand by researchers conducting economic evaluations of health care technologies. The UK National Institute for Health and Care Excellence (NICE) requests that health outcomes be measured in quality-adjusted life years (QALYs) in the economic evaluations of health care technologies submitted to the institute by sponsors (National

Institute for Health and Care Excellence 2013). Calculation of QALYs requires an HRQoL index (sometimes called "utility" in the literature) on which 0 is death, 1 is full health, and negative values allow for health states considered worse than death. NICE recommends that utility weights to calculate QALYs be derived from the EQ-5D questionnaire; if data from this instrument are not present, then validated mapping algorithms can be used to translate the available information into EQ-5D index values (National Institute for Health and Care Excellence 2013).

The EQ-5D instrument, which is widely used in health economics, is a five-domain generic HRQoL questionnaire with three levels per domain (known as EQ-5D-3L). EQ-5D data can be converted into an index by using a country-specific value set (also called a tariff) (Szende, Oppe, and Devlin 2007). These value sets provide index values for the 243 possible health states of the EQ-5D instrument.[1]

Ideally, when one designs a new prospective clinical study, an HRQoL questionnaire (for example, EQ-5D) that allows QALY calculations should be included in the design. However, often that information is collected from one or more disease-specific or generic questionnaires that cannot be used to calculate QALYs. In this case, a mapping equation or algorithm is needed to obtain index values from the disease-specific or generic instrument data. This is the purpose of the two commands presented in this article.

Mapping studies often use simple regression techniques such as ordinary least squares to directly predict EQ-5D utilities for one country-specific tariff conditional on other HRQoL measures. However, predicting EQ-5D responses on each domain by using indirect or response mapping is gaining popularity (Dakin 2013): it allows for the non-Gaussian distribution of index values and estimates a single mapping algorithm that can be used with any EQ-5D tariff. Calculation of predicted utilities from the output from the five multinomial logistic regression models estimated with response mapping is nontrivial (see the *Methods and formulas* section).

In this article, we introduce two commands to derive EQ-5D index values and domain responses from two widely used disease-specific instruments in the area of stroke and knee replacement. The first command (`mrs2eq`) uses results of a response mapping model to transform data from the stroke-specific modified Rankin scale (mRS) into EQ-5D index values and predicted probabilities of being at a particular level on each domain. The second command (`oks2eq`) uses a response mapping model to estimate index values and predicted probabilities on the EQ-5D instrument based on patients' responses to the Oxford Knee Score (OKS).

1. A new EQ-5D instrument with 5 levels (known as EQ-5D-5L) is now also available. However, at the time of the writing of this article, no country-specific value set to estimate utility values was available.

2 mrs2eq: A command to estimate EQ-5D responses and utilities based on mRS data

2.1 Description

`mrs2eq` uses a response mapping approach to transform data from the stroke-specific mRS into the EQ-5D-3L version. `mrs2eq` predicts EQ-5D index values from 13 country-specific value sets and reports average predicted probabilities of being in a particular level for each EQ-5D domain (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Details of the algorithm development, prediction accuracy, and external validation can be found in Rivero-Arias et al. (2010).

The mRS is a disease-specific instrument that measures dependency and has been widely used in stroke patients for more than two decades (van Swieten et al. 1988). The scale spans seven grades from 0 to 6, with 0 representing no symptoms at all and 5 representing severe disability. Grade 6 is used for death.

2.2 Syntax

`mrs2eq` *varname1* [*if*] [*in*] [, `calculate(ev|mc)` `mc(#)` `probability` `country(CA|DE|DK|ES|FR|GB|IT|JP|KR|NL|TH|US|ZW)` `saving(`*newvar*`)` `level(#)` `seed(#)`]

The mRS variable (*varname1*) needs to be coded as follows:

- `0` for "No symptoms at all"
- `1` for "No significant disability despite symptoms; able to carry out all usual duties and activities"
- `2` for "Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance"
- `3` for "Moderate disability; requiring some help, but able to walk without assistance"
- `4` for "Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance"
- `5` for "Severe disability; bedridden, incontinent, and requiring constant nursing care and attention"

Sometimes, the mRS is coded `6` to indicate "death", and in this case, the index value is forced to `0` (which indicates "death" in the EQ-5D value set). If the mRS has values outside the 0–6 range, an error is issued to warn the user that the mRS variable is coded incorrectly. When the mRS variable has missing values for a particular individual, the index value calculation for that individual will also be missing.

2.3 Options

`calculate(ev|mc)` identifies the calculation method to estimate index values. Two methods are available: an expected value (`ev`) and a Monte Carlo (`mc`) approach to estimate EQ-5D responses. The default is `calculate(ev)`.

`mc(#)` sets the number of simulations to run if the Monte Carlo method is selected to calculate index values. # refers to the number of simulations. The default is `mc(10000)`. A large number of Monte Carlo simulations (> 10,000) is needed to match the results of the expected value method to three or four decimal places unless the sample size is very large.

`probability` reports the predicted average probability of being in a particular level for each EQ-5D domain.

`country(CA|DE|DK|ES|FR|GB|IT|JP|KR|NL|TH|US|ZW)` specifies the country-specific value set to use in the estimation of the EQ-5D index values. The country code should to be specified in capital letters as follows: Canada (`CA`), Germany (`DE`), Denmark (`DK`), Spain (`ES`), France (`FR`), United Kingdom (`GB`), Italy (`IT`), Japan (`JP`), South Korea (`KR`), Netherlands (`NL`), Thailand (`TH`), United States (`US`), and Zimbabwe (`ZW`). The default is `country(GB)`.

`saving(`*newvar*`)` specifies the name of the new variable under which the EQ-5D index value will be stored.

`level(#)` specifies the confidence level, as a percentage, for confidence intervals. The default is `level(95)`.

`seed(#)` sets the random-number seed to # for the Monte Carlo simulations. To reproduce the same results, one should use the same random-number seed. The default is `seed(0)`, which means a random seed is set by the program.

2.4 Example

To illustrate how `mrs2eq` works, we have simulated a hypothetical dataset of 30 individuals with mRS data, age, and sex. The data have been stored in `mrs_data.dta`.

```
. use mrs_data

. describe

Contains data from mrs_data.dta
  obs:            30
 vars:             4                            13 Mar 2012 16:58
 size:           330
-------------------------------------------------------------------------------
              storage  display    value
variable name   type   format     label      variable label
-------------------------------------------------------------------------------
id              int    %8.0g                 Identifier
mrs             byte   %8.0g                 mRS values
age             float  %9.0g                 Age
sex             float  %9.0g      Sex        Gender
-------------------------------------------------------------------------------
Sorted by:  id
```

```
. list, nolabel

     ┌──────────────────────────┐
     │ id   mrs       age   sex │
     ├──────────────────────────┤
  1. │  1     1  63.14795     1 │
  2. │  2     2  60.41644     1 │
  3. │  3     1  60.80274     1 │
  4. │  4     3  88.03835     0 │
  5. │  5     1  66.20822     0 │
     ├──────────────────────────┤
  6. │  6     1  92.12329     1 │
  7. │  7     2  69.86028     0 │
  8. │  8     2  83.18904     1 │
  9. │  9     1  78.87671     0 │
 10. │ 10     2  72.50685     0 │
     ├──────────────────────────┤
 11. │ 11     0  53.33699     1 │
 12. │ 12     3  45.46027     1 │
 13. │ 13     3  67.69315     0 │
 14. │ 14     0  44.48767     0 │
 15. │ 15     2  74.16164     0 │
     ├──────────────────────────┤
 16. │ 16     2  83.41096     1 │
 17. │ 17     3  65.98082     1 │
 18. │ 18     2  63.06849     1 │
 19. │ 19     3  92.03561     0 │
 20. │ 20     4  75.82466     1 │
     ├──────────────────────────┤
 21. │ 21     1  60.66849     0 │
 22. │ 22     3  78.11781     1 │
 23. │ 23     3  69.19178     0 │
 24. │ 24     1   85.8548     0 │
 25. │ 25     1  63.78082     0 │
     ├──────────────────────────┤
 26. │ 26     1  73.01644     1 │
 27. │ 27     2  85.30959     1 │
 28. │ 28     0  81.27123     1 │
 29. │ 29     2  53.15617     1 │
 30. │ 30     3  68.34795     1 │
     └──────────────────────────┘
```

The sample comprises 15 males and 15 females with an average age of 71 years. The mRS values indicate that most subjects have some level of disability.

```
. tabulate mrs

 mRS values │      Freq.     Percent        Cum.
────────────┼───────────────────────────────────
          0 │          3       10.00       10.00
          1 │          9       30.00       40.00
          2 │          9       30.00       70.00
          3 │          8       26.67       96.67
          4 │          1        3.33      100.00
────────────┼───────────────────────────────────
      Total │         30      100.00
```

The EQ-5D index value for the whole group, using the United Kingdom value set with the expected value method, is calculated and reported as follows:

```
. mrs2eq mrs, calculate(ev) country(GB) level(95)
Calculation Method: Expected Value
Country value set: GB
obs: 30
obs included: 30
obs valid: 30
```

Variable	Mean	Std. Dev.	Min	Max	[95% Conf.	Interval]
EQ-5D Index	.68721776	.1561129	.2360689	.9289616	.6289243	.7455113

`mrs2eq` generates a variable called `_est_index` with the predicted EQ-5D health state preference value that can be used in any subsequent calculations by the user. Variables with predicted probabilities of reporting each level on each EQ-5D domain are also generated. If the option `saving(`*newvar*`)` is selected, `_est_index` is renamed *newvar*.

`mrs2eq` reports the options chosen (in this case, the expected value method for calculation and the `GB` value set). The number of observations is reported as follows: `obs` indicates the total number of observations in the dataset; `obs included` indicates the total number of observations meeting the specified `if`/`in` criteria; and `obs valid` indicates the number of observations for which EQ-5D utilities are calculated (that is, the number that meet the `if`/`in` criteria and have no missing data). By default, `mrs2eq` presents the summary statistics for the EQ-5D utility (`_est_index`) across the entire sample, or for those observations captured by the `if` and `in` qualifiers. The confidence interval presented represents the sampling uncertainty around the population means for the sample selected, assuming that the coefficients of the mapping algorithm are fixed; the confidence level for this interval can be set using the `level(`#`)` option.

Similar results are obtained if 10,000 Monte Carlo simulations are used to calculate the index:

```
. mrs2eq mrs, calculate(mc) mc(10000) country(GB) level(95)
  (output omitted)
Calculation Method: Monte Carlo
Country value set: GB
Numer of MC simulations: 10000
obs: 30
obs included: 30
obs valid: 30
```

Variable	Mean	Std. Dev.	Min	Max	[95% Conf.	Interval]
EQ-5D Index	.68707451	.1560345	.2368911	.9308678	.6288103	.7453388

mrs2eq displays the predicted probability for each level of the EQ-5D domains when the probability option is used.

```
. mrs2eq mrs, calculate(ev) country(GB) level(95) pr
Calculation Method: Expected Value
Country value set: GB
obs: 30
obs included: 30
obs valid: 30
_________________________

    Variable |      Mean  Std. Dev.         Min        Max    [95% Conf. Interval]
-------------+---------------------------------------------------------------------
 EQ-5D Index | .68721776   .1561129   .2360689   .9289616       .6289243   .7455113

 Probability |      Mob.     S. Care      U. Act.       Pain        Anx/Depr
-------------+-------------------------------------------------------------
           1 |    42.84%      71.27%      47.03%      55.66%      66.96%
           2 |    55.41%      26.97%      43.76%      39.22%      30.28%
           3 |    1.748%      1.766%      9.202%      5.125%      2.767%
```

mrs2eq also displays summary statistics for a specific group of observations determined by conditions if and in. For example, for a group of patients within a particular age interval, we could explore the summary statistics for the EQ-5D index values as follows:

```
. mrs2eq mrs if age>32 & age<70, calculate(ev) country(GB)
Calculation Method: Expected Value
Country value set: GB
obs: 30
obs included: 16
obs valid: 16
_________________________

    Variable |      Mean  Std. Dev.         Min        Max   [95% Conf.  Interval]
-------------+---------------------------------------------------------------------
 EQ-5D Index | .70315348   .1434246   .5302404   .9289616       .6267279   .779579
```

3 oks2eq: A command to estimate EQ-5D responses and utilities based on OKS data

3.1 Description

oks2eq uses a response mapping model to estimate index values and predicted probabilities for the EQ-5D-3L version, based on patients' responses to the disease-specific OKS. oks2eq calculates EQ-5D index values using 13 different country-specific value sets and reports the mean predicted probabilities of a respondent being at each level on each EQ-5D domain.

OKS is a disease-specific instrument assessing functional impairment and HRQoL due to knee problems; it is validated and widely used to assess outcomes of knee replacement (Dawson et al. 1998). OKS includes 12 questions on different aspects of knee symptoms and function, each with five levels. Scores on each question range from 4 (no problems) to 0 (severe problems) and are summed without weighting to produce total scores ranging from 0 to 48 (Murray et al. 2007). `oks2eq` is based on a response mapping algorithm developed by Dakin, Gray, and Murray (2013) that predicts patients' responses to each of the five EQ-5D domains based on their responses to OKS. The mapping algorithm has been validated using external registry data and has good prediction accuracy (Dakin, Gray, and Murray 2013).

3.2 Syntax

`oks2eq` *varlist* [*if*] [*in*] [`, calculate(ev|mc) mc(#) probability country(CA|DE|DK|ES|FR|GB|IT|JP|KR|NL|TH|US|ZW) saving(`*newvar*`) level(#) seed(#)`]

The *varlist* entered in the command must comprise exactly 12 numeric variables representing a patient's level on each of the 12 OKS questions. The variables must be entered in the following order:

1. Pain: How would you describe the pain you usually have from your knee?
2. Wash/dry: Have you had any trouble with washing and drying yourself (all over) because of your knee?
3. Transport: Have you had any trouble getting in and out of a car or using public transport because of your knee?
4. Walking: For how long have you been able to walk before the pain from your knee becomes severe?
5. Chair: After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?
6. Limping: Have you been limping when walking, because of your knee?
7. Kneeling: Could you kneel down and get up again afterwards?
8. NightPain: Have you been troubled by pain from your knee in bed at night?
9. Work: How much has pain from your knee interfered with your usual work (including housework)?
10. Giveway: Have you felt that your knee might suddenly "give way" or let you down?
11. Shopping: Could you do the household shopping on your own?
12. Stairs: Could you walk down a flight of stairs?

Each question must be coded using the new OKS scoring system as integers between 0 and 4, where 4 represents no problems on that item (for example, "no pain", "no trouble at all", or "yes, easily") and 0 represents the most severe problems on that item (for example, "severe" pain or "impossible") (Murray et al. 2007). Some studies use an older scoring system where questions are scored from 1 to 5, where 1 represents no problems and 5 represents the most severe problems (Murray et al. 2007). If data are in the 1–5 format, scores must be transformed into the new scoring system by subtracting each question score from 5 before using the `oks2eq` algorithm.

Predicted utilities will not be calculated for any observations that have missing values or values other than integers between 0 and 4 on any of the 12 variables; an error message will appear if any of the 12 variables in *varlist* include any other value for any observation.

3.3 Options

The options for `oks2eq` are identical to those for `mrs2eq` (section 2.3).

3.4 Example

To illustrate how `oks2eq` works, we have simulated a hypothetical dataset of OKS responses for 11 individuals before and after knee replacement. This dataset is stored in `oks_data.dta`. Of the 22 observations, one has missing data and another has values that are not integers between 0 and 4.

```
. use oks_data

. describe

Contains data from oks_data.dta
  obs:            22
 vars:            14                          27 Apr 2012 11:52
 size:           308
-------------------------------------------------------------------------------
              storage  display    value
variable name   type   format     label      variable label
-------------------------------------------------------------------------------
patientid       byte   %8.0g                 Patient identifier
timepoint       byte   %8.0g                 Time: 0=pre-op; 1=post-op
oxpain          byte   %8.0g                 Q1 pain severity
washdry         byte   %8.0g                 Q2 washing and drying
trans           byte   %8.0g                 Q3 transport
walk            byte   %8.0g                 Q4 walking
meal            byte   %8.0g                 Q5 standing from sitting at meal
limp            byte   %8.0g                 Q6 limping
kneel           byte   %8.0g                 Q7 kneeling
night           byte   %8.0g                 Q8 pain at night
work            byte   %8.0g                 Q9 problems working
giveway         byte   %8.0g                 Q10 worried knee will give way
shopping        byte   %8.0g                 Q11 problems shopping
stairs          byte   %8.0g                 Q12 problems climbing stairs
-------------------------------------------------------------------------------
Sorted by:  timepoint  patientid
```

The sample data have been sorted by `timepoint` and then `patientid`, where a `timepoint` of 0 indicates scores before knee replacement and 1 indicates scores after knee replacement. However, `oks_data.dta` includes one observation (patient 11, timepoint 0) that is coded as integers between 1 and 5 (not between 0 and 4). Running `oks2eq` on the whole dataset therefore generates an error for the first variable coded incorrectly.

```
. oks2eq oxpain-stairs
The trans variable is not coded properly. All variables need to be coded
using integers from 0 to 4 indicating decreasing levels of severity.
Please tabulate your data and check how variables are coded.
If you have used the old OKS scoring (1 to 5 indicating increasing severity)
all variables need to be recoded before using oks2eq by subtracting them from 5.
r(410);
```

This error message indicates that at least one observation must either be corrected or be omitted from the analysis. In this case, we find that the baseline data for patient 11 is coded using the old 1–5 coding, which can be easily corrected by subtracting each response level from 5 (for example, `replace oxpain = 5-oxpain if patientid==11 & timepoint==0`), enabling `oks2eq` to run. `oks2eq` ignores the postoperative data for patient 11 and excludes them from the count of valid observations because of missing data.

```
. oks2eq oxpain washdry trans walk meal limp kneel night work giveway shopping
> stairs
Calculation Method: Expected Value
Country value set: GB
obs: 22
obs included: 22
obs valid: 21
___________________________

    Variable |      Mean  Std. Dev.         Min        Max    [95% Conf. Interval]
-------------+--------------------------------------------------------------------
 EQ-5D Index | .46008126   .3557272  -.2767188   .9152518       .2981562   .6220064
```

oks2eq's reporting of the index and predicted probabilities is identical to mrs2eq. oks2eq also generates similar temporary variables as mrs2eq and renames _est_index as *newvar* if the option saving(*newvar*) is selected.

```
. oks2eq oxpain washdry trans walk meal limp kneel night work giveway shopping
> stairs, calculate(mc) mc(1000) probability country(JP)
Calculation Method: Expected Value
Country value set: JP
obs: 22
obs included: 22
obs valid: 21
```

Variable	Mean	Std. Dev.	Min	Max	[95% Conf.	Interval]
EQ-5D Index	.59720877	.1877083	.160788	.8915899	.511765	.6826526

Probability	Mob.	S. Care	U. Act.	Pain	Anx/Depr
1	33.17%	54.3%	29.57%	26.23%	66.14%
2	62.82%	34.83%	47.46%	45.35%	26.01%
3	4.01%	10.87%	22.97%	28.42%	7.849%

4 Calling the eq5d command

Note that mrs2eq and oks2eq use the user-written package eq5d to calculate index values from country-specific value sets when the option calculate(mc) is used. eq5d needs to be installed for mrs2eq and oks2eq to work properly. Details on the eq5d package can be found at http://www.stata-journal.com/article.html?article=st0220 (Ramos-Goñi and Rivero-Arias 2011).

5 Stored results

mrs2eq and oks2eq store the following in e():

Scalars

e(Ntotal)	number of total observations on the data file
e(Nincluded)	number of included observations on if/in restrictions
e(Nvalid)	number of valid observations on if/in restrictions without missing values
e(mean)	mean
e(lb)	lower confidence interval
e(ub)	upper confidence interval
e(sd)	standard deviation
e(min)	minimum
e(max)	maximum

Matrices

e(frequencies)	predicted frequencies for each level and EQ-5D dimension

6 Methods and formulas

The relationship between the disease-specific data and the EQ-5D responses was originally estimated using multinomial logit models predicting the probability of being at a particular EQ-5D level on each of the EQ-5D domains conditional on responses to mRS (Rivero-Arias et al. 2010) or OKS (Dakin, Gray, and Murray 2013). `mrs2eq` and `oks2eq` replicate these predictions on a user-defined sample by using the original coefficients from these models, which are programmed as part of this command.

The probability that a particular EQ-5D domain y_i has a response at level m, given a set of mRS or OKS responses x, can be written as[2]

$$\Pr(y_i = m|x) = \frac{\exp(x\beta_{im})}{\sum_{j=1}^{J} \exp(x\beta_{ij})} \tag{1}$$

where $i = 1, 2, \ldots, 5$ indicates each EQ-5D domain, $m = 1, 2, 3$ indicates EQ-5D response levels, and $j = 1, 2, \ldots, J$ represents the number of equations j from the multinomial logit i. In the specific mapping exercise from mRS to EQ-5D and OKS to EQ-5D, $J = 3$. For `mrs2eq`, β_{ij} is a vector of six coefficients for the jth equation for the response level j on each domain i. For `oks2eq`, β_{ij} comprises a vector of 49 coefficients for each response level j on each domain i.

Once the probabilities of being in a given level for a particular dimension are predicted, there are at least two methods that can be used to select the response level for each EQ-5D domain. In the expected value approach (Le and Doctor 2011), the predicted probabilities of being in a particular EQ-5D level and domain are multiplied by the decrement that corresponds to that level and domain in the selected EQ-5D value set. They are then summed, allowing for the interaction terms specific to the selected value set.

In the Monte Carlo method (Rivero-Arias et al. 2010), individuals are assigned to one of the three levels on each EQ-5D domain by comparing the predicted probabilities with a random number from a uniform distribution. An estimated EQ-5D index is obtained for each subject in the dataset for each Monte Carlo simulation. The final EQ-5D index is the average for each subject across the number of simulations. The default number of Monte Carlo simulations is 10,000; we recommend that large numbers of simulations be used when conducting and reporting results from these analyses.

The expected value and the Monte Carlo methods provide virtually the same results when the simulations in the Monte Carlo approach are repeated a large number of times. We demonstrate in section 6.3 that both approaches produce the same results when the number of simulations approaches infinity. The default calculation method in `mrs2eq` and `oks2eq` is the expected value approach because it is less computationally intensive and, hence, faster.

2. To simplify the exposition, we have omitted the subscript that indicates the observation on the data.

6.1 Monte Carlo method

In the Monte Carlo approach, individuals are assigned to one of the three levels by using a Monte Carlo simulation approach where the predicted probabilities are compared with a random number from a uniform distribution. Formally, for each domain, three estimated probabilities are obtained from the estimation model that can be expressed as $\Pr(\widehat{y}_i = 1)$, $\Pr(\widehat{y}_i = 2)$, and $\Pr(\widehat{y}_i = 3)$, where $\widehat{y}_i$ indicates the predicted response level for EQ-5D domain i. Random numbers from a uniform distribution [$u_k \sim \text{uniform}(0,1)$] are compared with these probabilities to predict the response in each EQ-5D dimension for each individual as follows:

$$\widehat{y}_i = \begin{cases} 1 & \text{if} \quad u_k \leq \Pr(\widehat{y}_i = 1) \\ 2 & \text{if} \quad u_k > \Pr(\widehat{y}_i = 1) \quad \text{and} \quad u_k \leq \Pr(\widehat{y}_i = 1) + \Pr(\widehat{y}_i = 2) \\ 3 & \text{if} \quad u_k > 1 - \Pr(\widehat{y}_i = 3) \end{cases} \tag{2}$$

For each response level and each of the EQ-5D dimensions, a random number u_k is generated and compared with predicted probabilities to randomly assign a specific response level using (2). An EQ-5D index is obtained based on $\widehat{y}_i$ using a country-specific value set. This process is repeated for each of the Monte Carlo iterations. The default number of Monte Carlo simulations in `mrs2eq` and `oks2eq` is 10,000. The average of the EQ-5D index for each individual patient is then calculated by the formula

$$\overline{Y} = \sum\nolimits_{h=1}^{H} Y_h / H \tag{3}$$

where Y_h is the EQ-5D index value for the hth simulation and $\overline{Y}$ represents the average across H Monte Carlo simulations (which `mrs2eq` and `oks2eq` report as *newvar* or `_est_index` when the `calculate(mc)` option is selected).

6.2 The expected value method

The probability that a particular EQ-5D domain y_i has a response at level $\Pr(y_i = m)$ is given by the multinomial model in (1). The expected value method multiplies these predicted probabilities by EQ-5D value set decrements from a particular country-specific value set, assuming independence among $\Pr(y_i = m)$. Most country-specific value sets available (`CA`|`DE`|`DK`|`ES`|`FR`|`GB`|`IT`|`JP`|`KR`|`NL`|`TH`|`US`|`ZW`) estimate utilities with an $N3$ model similar to the original exercise conducted in the UK (Szende, Oppe, and Devlin 2007; Bansback et al. 2012; Chevalier and de Pouvourville 2013; Lee et al. 2009; Tongsiri and Cairns 2011).[3] However, the modeling exercise conducted in the United States (Szende, Oppe, and Devlin 2007) and in Italy (Scalone et al. 2013) followed different strategies. Therefore, the expected value method implemented in `mrs2eq` and `oks2eq` within the value sets from the United States and Italy differs from that in the other national tariffs.

3. For a full explanation on the modeling approach used in the estimation of the different country-specific value sets, see Szende, Oppe, and Devlin (2007).

If value sets from `CA | DE | DK | ES | FR | GB | JP | KR | NL | TH | ZW` are called, the EQ-5D index using the expected value method is calculated as

$$\begin{aligned}\text{Index}_{\text{EV}} = 1 &- \sum_{i=1}^{5}\{P(y_i=2)\times TTO_{y_i=2} + P(y_i=3)\times TTO_{y_i=3}\}\\ &- \left[\left\{1-\sum_{i=1}^{5}P(y_i=1)\right\}\times TTO_{\text{constant}}\right]\\ &- \left(\left[1-\sum_{i=1}^{5}\{1-P(y_i=3)\}\right]\times TTO_{N3}\right)\end{aligned}$$

where $TTO_{y_i=m}$ is the EQ-5D decrement from the country-specific value set for the domain y_i and level m, TTO_{constant} is the EQ-5D decrement corresponding to the constant on the country-specific value set, and TTO_{N3} is the EQ-5D value corresponding to the $N3$ decrement term on the country-specific value set, used when any of the domains are at level 3.

If the value set from the United States is called, the computational process is more complex, and the EQ-5D index using the expected value method is calculated as

$$\begin{aligned}\text{Index}_{\text{EV}} = 1 &- \sum_{i=1}^{5}\{P(y_i=2)\times TTO_{y_i=2} + P(y_i=3)\times TTO_{y_i=3}\}\\ &- E(D1)\times TTO_{D1} + E(I2^2)\times TTO_{I2^2} + E(I3)\times TTO_{I3}\\ &+ E(I3^2)\times TTO_{I3^2} \end{aligned} \tag{4}$$

where $D1$ is an ordinal variable that represents the number of deviations from full health beyond the first movement, $I2$ is an ordinal variable that represents the number of domains with "some problems" beyond the first movement, and $I3$ is an ordinal variable that represents the number of domains with "extreme problems" beyond the first movement and its square. Therefore, $D1$, $I2$, and $I3$ are calculated as

$$D1 = \begin{cases} 4 - I_1 & \text{if} \quad I_1 > 4 \\ 0 \quad \text{if} \quad I_1 \leq 4 \end{cases}$$

$$I2 = \begin{cases} I_2 - 1 & \text{if} \quad I_2 > 0 \\ 0 \quad \text{if} \quad I_2 \leq 0 \end{cases}$$

$$I3 = \begin{cases} I_3 - 1 & \text{if} \quad I_3 > 0 \\ 0 \quad \text{if} \quad I_3 \leq 0 \end{cases}$$

where I_m is defined as the number of EQ-5D domain responses at level m with $m = 1, 2, 3$. The expected values of $D1$, $I2^2$, $I3$, and $I3^2$ in (4) are calculated as follows:

$$E(D_1) = \sum_{i=1}^{4} i \times P(I_1 = 4 - i) \tag{5}$$

$$E(I2^2) = \sum_{i=1}^{4} i^2 \times P(I_2 = 1 + i)$$

$$E(I3) = \sum_{i=1}^{4} i \times P(I_3 = 1 + i)$$

$$E(I3^2) = \sum_{i=1}^{4} i^2 \times P(I_3 = 1 + i)$$

Finally, the probabilities of I_m in (5) are calculated using the following formulas with a, b, c, d indicating the indices for each of the EQ-5D domains:

$$P(I_m = 0) = \sum_{a=1}^{5} P(y_a \neq m) = \sum_{a=1}^{5} \{1 - P(y_a = m)\}$$

$$P(I_m = 1) = \sum_{b=1}^{5} \left[P(y_b = m) \times \sum_{\substack{a=1 \\ a \neq b}}^{5} \{1 - P(y_a = m)\} \right]$$

$$P(I_m = 2) = \sum_{\substack{b,a=1 \\ b<a}}^{5} \left[P(y_b = m) \times P(y_a = m) \sum_{\substack{c=1 \\ c \neq b \\ c \neq a}}^{5} \{1 - P(y_c = m)\} \right]$$

$$P(I_m = 3) = \sum_{\substack{c,b,a=1 \\ c<b<a}}^{5} \left[P(y_c = m) \times P(y_b = m) \times P(y_a = m) \sum_{\substack{d=1 \\ d \neq c \\ d \neq b \\ d \neq a}}^{5} \{1 - P(y_l = m)\} \right]$$

$$= 1 - \sum_{\substack{f=1 \\ f \neq 3}}^{5} P(I_m = f)$$

$$P(I_m = 4) = \sum_{b=1}^{5} \left[\{1 - P(y_b = m)\} \times \sum_{\substack{a=1 \\ a \neq b}}^{5} \{1 - P(y_a = m)\} \right]$$

$$P(I_m = 5) = \sum_{a=1}^{5} P(y_a = m)$$

The country-specific value set for Italy omits the I_2 and I_3 terms; thus (4) is simplified to

$$\text{Index}_{\text{EV}} = 1 - \sum_{i=1}^{5} \{P(y_i = 2) \times TTO_{y_i=2} + P(y_i = 3) \times TTO_{y_i=3}\} - E(D1) \times TTO_{\text{D1}}$$

6.3 Equivalence between Monte Carlo and expected value

EQ-5D valuation modeling exercises have the following general functional form:

$$Y = 1 - \sum_{l=1}^{L} \varphi_l \times \omega_l \tag{6}$$

Y indicates the EQ-5D index value, φ_l indicates the estimated value set coefficient of variable ω_l, and l indicates the number of dummies included in the model (which depends on the country-specific modeling strategy implemented). The average of the EQ-5D index in the Monte Carlo method is given by (3). Substituting (6) in (3) and applying limits when h tend to infinity gives

$$\begin{aligned} E\left(\overline{Y}\right) &= \lim_{H\to\infty} \sum\nolimits_{h=1}^{H} Y_h/H = \lim_{H\to\infty} \left(1 - \sum\nolimits_{l=1}^{L} \varphi_l \times \frac{\sum_{h=1}^{H} \omega_{lh}}{H}\right) \\ &= 1 - \sum\nolimits_{l=1}^{L} \varphi_l \times \lim_{H\to\infty} \frac{\sum_{h=1}^{H} \omega_{lh}}{H} = 1 - \sum\nolimits_{l=1}^{L} \varphi_l \times E(\omega_l) \end{aligned}$$

which is the expected value method. Because the covariates included in the original valuation modeling exercises are dummies, $E[\omega_l]$ indicates the probability of being in a particular EQ-5D domain and level.

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