ELSEVIER

ScienceDirect

Contents lists available at **sciencedirect.com**
Journal homepage: **www.elsevier.com/locate/jval**

Preference-Based Assessments

Parallel Valuation of the EQ-5D-3L and EQ-5D-5L by Time Trade-Off in Hungary

Fanni Rencz, PhD,* Valentin Brodszky, PhD, László Gulácsi, DSc, Dominik Golicki, PhD, Gábor Ruzsa, MSc, A. Simon Pickard, PhD, Ernest H. Law, PharmD, PhD, Márta Péntek, PhD

ABSTRACT

Objectives: The wording of the Hungarian EQ-5D-3L and EQ-5D-5L descriptive systems differ a great deal. This study aimed to (1) develop EQ-5D-3L and EQ-5D-5L value sets for Hungary from a common sample, and (2) compare how level wording affected valuations.

Methods: In 2018 to 2019, 1000 respondents, representative of the Hungarian general population, completed composite time trade-off tasks. Pooled heteroscedastic Tobit models were used to estimate value sets. Value set characteristics, single-level transition utilities from adjacent corner health states, and mean transition utilities for all possible health states were compared between the EQ-5D-3L and EQ-5D-5L.

Results: Health utilities ranged from -0.865 to 1 for the EQ-5D-3L and -0.848 to 1 for the EQ-5D-5L. The relative importance of the 5 EQ-5D-5L dimensions was as follows: mobility, pain/discomfort, self-care, anxiety/depression, and usual activities. A similar preference ranking was observed for the EQ-5D-3L with self-care being more important than pain/discomfort. The EQ-5D-5L demonstrated lower ceiling effects (range of utilities for the mildest states: 0.900-0.958 [3L] vs 0.955-0.965 [5L]) and better consistency of mean transition utilities across the range of scale. Changing “confined to bed” (3L) to “unable to walk” (5L) had a large positive impact on utilities. Smaller changes with more negative wording in the other dimensions (eg, “very much anxious/feeling down a lot” [3L] vs “extremely anxious/depressed” [5L]) had a modest negative impact on utilities.

Conclusion: This study developed value sets of the EQ-5D-3L and EQ-5D-5L for Hungary. Our findings contribute to the understanding of how the wording of descriptive systems affects the estimates of utilities.

Keywords: EQ-5D, value set, composite time trade-off, QALY, Europe.

VALUE HEALTH. 2020; 23(9):1235–1245

Introduction

Health technology assessment (HTA) is increasingly used to inform resource allocation decisions and set priorities in healthcare in Hungary.[1–4] National bodies within the Ministry of Human Capacities and the Division for Health Technology Assessment at the National Institute for Pharmacy and Nutrition publish guidelines and recommendations on conducting economic evaluations of health interventions.[5,6] In economic evaluations, health benefits of an intervention are commonly expressed in quality-adjusted life years (QALYs). The QALY is a widely used metric that captures both quantity (ie, survival) and quality (ie, utility) of life into a single outcome. In Hungary, as in many other European countries,[7] the EQ-5D descriptive system is on the list of preferred measures to generate QALYs.[8] Yet the absence of country-specific value sets creates a barrier to its widespread use. In the past 2 decades, over 30 countries adopted the EQ-5D and developed their own national value sets, enabling health policy decisions to be based on the preferences of the population they are serving.[9,10]

The EQ-5D consists of a 5-item descriptive system and a self-rating of overall health status on a 0-100 visual analog scale (EQ VAS).[11,12] The descriptive system has 2 versions suitable for adults, the EQ-5D-3L and EQ-5D-5L (hereafter 3L and 5L) that both measure health status on 5 dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD). In the 3L, each dimension has 3 levels of severity: no problems, some/moderate problems, and confined to bed/unable to/extreme problems. For the 5L, the levels of severity are expanded from 3 to 5: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems.[13]

In most language versions, 2 important changes in wording of the labels were introduced in the 5L version, which included using

* Address correspondence to: Fanni Rencz, MD, MSc, PhD, Department of Health Economics, Corvinus University of Budapest, 8 Fővám tér, H-1093, Budapest, Hungary. Email: fanni.rencz@uni-corvinus.hu

"unable to walk" (5L) instead of "confined to bed" (3L) in the descriptor of the most severe level of MO and standardizing the middle levels to consistently use moderate (5L) in all dimensions.[13] In addition to these changes, there are a number of other differences between the Hungarian 3L and 5L versions that affect both modifiers (eg, "very strong" [3L] vs "extreme" [5L]) and descriptors (eg, "anxiety/feeling down" [3L] vs "anxiety/depression" [5L]) (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019). Of the 15 matched labels, the 5L uses words with more negative meaning in 8 cases, whereas in 1 case a more severe problem appears in the 3L descriptive system (ie, confined to bed).

Changes in wording of the EQ-5D may affect self-reporting of health as well as health state valuations. Few parallel 3L and 5L valuations have been carried out to date, and very limited evidence is available on how changes in wording are reflected by health state valuations.[14–17] Therefore, the primary objective of this study was to develop country-specific 3L and 5L value sets for Hungary in a parallel valuation study. Secondarily, we aimed to add to the literature in comparing the 3L and 5L value set characteristics and analyzing the impact on utilities of wording differences in the descriptive systems.

Methods

Study Design

The study followed the criteria on the Checklist for Reporting Valuation Studies of the EQ-5D.[18] Data were collected via computer-assisted personal interviews between May 2018 and March 2019. The latest available version of EuroQol Valuation Technique (EQ-VT) was used for this study (version 2.1).[19] As a methodological add-on to this protocol, a 3L valuation was embedded in the design. In 2017, exactly the same valuation framework was used in the United States.[15,20,21] The study received approval from the Scientific and Ethical Committee of the Medical Research Council (reference no. 12006-2/2018/EKU) prior to data collection. The target sample size was 1000 respondents complying with the EuroQol Group's valuation protocol.[22]

A non-probability quota sampling was used, and quotas were set for age and sex according to the latest data reported by the Hungarian Central Statistical Office.[23] Inclusion criteria to the study were (1) aged ≥18 years, (2) cognitive ability to read and interpret questions, and (3) signed an informed consent form. Participation in the study was voluntary and no remuneration was provided. The interviewer team comprised 12 university students studying economics or medicine and 1 of the principal investigators (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019). Over the entire data collection period, interviewer performance was monitored as a part of the quality-control procedure developed by the EuroQol Group.[24] Details of the quality-control process are available in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019.

Health State Selection

A detailed description of 3L and 5L health state selections is reported elsewhere[15,25]; however, it is briefly summarized here. Two preference elicitation techniques, the composite time trade-off (cTTO) and discrete choice experiment (DCE), were used. The study design included a set of 30 (3L) health states divided into 10 cTTO blocks, 86 (5L) states divided into 10 cTTO blocks, and 196 pairs of 5L health states divided into 28 DCE blocks of 7 pairs. Blocks as well as the order of health states within the blocks were presented in a random order both for the cTTO and DCE. Each 3L block contained 3 health states, and the pits state (33333) appeared only in 1 of the 10 3L blocks. Each 5L block contained 10 health states including the pits state (55555) and 1 of the mildest states (21111, 12111, 11211, 11121, or 11112). The DCE data collected are not used in the present study. The interview tasks are presented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019.

Composite Time Trade-Off

The cTTO approach combines conventional 10-year TTO for health states considered better than dead (BTD) and lead-time TTO (ie, 10 years in full heath followed by 10 years in a less than healthy EQ-5D state) for health states considered worse than dead (WTD).[26] The cTTO utilities in this study ranged between -1 and 1 and were calculated according to the following formulas:

BTD responses: $U = t/10$

WTD responses: $U = (t - 10) / 10$

where U is the utility and t is the number of years required in full health.

Data Analysis

Descriptive statistics of the sample characteristics and cTTO utilities were computed. No exclusions were made on the basis of data quality, inconsistent responses (ie, a higher utility is attached to a health state that is unambiguously more severe than another), or non-trading (ie, assigning a utility of 1 to all health states). In line with former valuation studies,[27–29] 5L cTTO responses flagged by respondents in the feedback module were excluded. The effect of the re-inclusion of these responses was assessed through a sensitivity analysis. Data management and statistical analyses were performed using STATA 13.0 (StataCorp LP, College Station, TX) and R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a P value $<.05$ was taken as statistically significant.

Modeling

The cTTO utilities for health states described by the 3L and 5L were modeled separately. The dependent variable consisted of the cTTO utility elicited. Main effects models including 10 and 20 dummy-coded parameters were applied both for the 3L and 5L, respectively. A dummy was created for each level of health in respect of each dimension, whereby level 1 was considered the reference category. Both for 3L and 5L, we estimated 4 regression model versions: a pooled homoscedastic linear model (model 1); a pooled heteroscedastic linear model (model 2); a pooled homoscedastic Tobit model, left-censored at -1 (model 3); and a pooled heteroscedastic Tobit model, left-censored at -1 (model 4). All models were estimated by maximum likelihood using the R package crch.[30] To account for the non-zero covariances between error terms clustered within individuals (resulting from the repeated measure design), we calculated robust standard errors using the clustered covariance estimator incorporated to the R package sandwich.[31]

We considered multiple criteria for model selection, including theoretical considerations (eg, the censored nature of cTTO utilities and heteroscedasticity), the number of illogical and insignificant parameters, and prediction accuracy (eg, Pearson's and Spearman's correlations between predicted and observed utilities, mean absolute error between predicted and observed utilities, and proportion of health states with absolute prediction errors greater

Table 1. Characteristics of the sample.

Variables	n	%	General population (%)[24,51]	Proportional difference (%)
Sex				
Female	533	53.3	53.1	0.2
Male	467	46.7	46.9	-0.2
Age (years)				
18-24	100	10.0	10.0	0
25-34	152	15.2	15.2	0
35-44	194	19.4	19.5	-0.1
45-54	164	16.4	16.0	0.4
55-64	164	16.4	16.8	-0.4
65-74	130	13.0	13.0	0
75+	96	9.6	9.5	0.1
Highest level of education				
Primary school or less	157	15.7	23.8	-8.1
Secondary school*	502	50.2	55.0	-4.8
College/ university degree	341	34.1	21.2	12.9
Place of residence				
Capital	348	34.8	17.9	16.9
Other town	454	45.4	52.6	-7.2
Village	198	19.8	29.5	-9.7
Geographical region†				
Central Hungary	533	53.3	30.4	22.9
Transdanubia	177	17.7	30.2	-12.5
Great Plain and North	290	29.0	39.5	-10.5
Employment status‡				
Employed	620	62.0	53.1	8.9
Unemployed	10	1.0	3.1	-2.1
Retired	250	25.0	26.1	-1.1
Disability pensioner	26	2.6	3.1	-0.5
Student	75	7.5	4.7	2.8
Homemaker/ housewife	19	1.9	1.0	0.9
Marital status				
Single	239	23.9	18.5	5.4
Married	419	41.9	45.6	-3.7
Domestic partnership	137	13.7	13.4	0.3
Divorced	83	8.3	11.1	-2.8
Widowed	122	12.2	11.4	-0.8
3L EQ VAS (mean, SD)§	82.5	13.2	71.6	10.9
5L EQ VAS (mean, SD)	81.6	13.8	N/A	-
Self-perceived health status				
Excellent	135	13.5	N/A	-
Very good	322	32.2	N/A	-
Good	374	37.4	N/A	-
Fair	154	15.4	N/A	-
Poor	15	1.5	N/A	-

Continued in the next column

Table 1. Continued

Variables	n	%	General population (%)[24,51]	Proportional difference (%)
History of chronic illness				
Yes	559	55.9	45.0	10.9
No	426	42.6	55.0	-12.4
Refused to answer	15	1.5	N/A	-

N/A indicates data not available; VAS, visual analog scale.
*With completed final exam or professional certificate.
†For the general population, figures represent the population aged 15 or over.
‡The sum of the general population is <100% owing to an other category accounting for 8.9%.
§Year of data collection was 2000.[52]

than 0.05 and 0.1.) The preferred model was selected in favor of accounting for the censored nature of cTTO utilities (ie, preferences of certain respondents may be even lower than -1),[32] accommodating heteroscedasticity stemming from the variation of cTTO utilities between the mild and severe health states,[33] and reducing the number of illogical and insignificant parameters. The intercept was interpreted as the utility decrement associated with any deviation from full health. For the final value sets, it was decided to constrain the intercept to be equal to 1 (full health) if it was insignificant.

Comparing the Characteristics of the 3L and 5L Value Sets

Building on the methodology described by previous studies,[14,34] the 2 final value sets (model 4 [3L] and model 5 [5L]) were compared across a number of characteristics. For the analyses, levels 3 and 5 on the 5L were considered as matched levels for levels 2 and 3 on the 3L.[14] For example, 12111 (3L) and 13111 (5L) are matched health states.

Ceiling effects in the context of health state valuations were examined by directly comparing the mildest 3L and 5L health states.[14] For the mildest and most severe health states, differences in changes in single-level transition utilities between adjacent 3L, 5L, and matched 5L states were compared (ie, decrease in utility from 11111 or increase from the pits state).[34] Single-level transition utilities between adjacent 3L and adjacent 5L corner health states (ie, health states described by an unhealthy level in 1 dimension, and no problems in all others) were computed. Then, differences were calculated in single-level transition utilities between 3L and matched 5L health states.[14,34]

A Kernel density plot was created to visualize the modality of the distributions of utilities for 3L (n = 243), 5L (n = 3125) and matched 5L health states (n = 243). The 2 models were further compared with respect to parameter estimates, order of dimension importance, range of utilities, and proportion of health states valued as WTD. The agreement between matched utilities of the 2 models was examined using a Bland-Altman plot.[35]

Overall, mean transition utilities were computed for the 3L and 5L by averaging all single-level mean transition utilities of the 243 (3L) and 3125 (5L) health states.[36,37] To estimate single-level mean transition utilities for a health state (referred to here as the baseline health state), all possible single-level movements to adjacent from that given state were estimated. For example, all possible single-level transitions from the baseline state of 44444 included 5 possible transitions to a better state (34444, 43444, 44344, 44434, and 44443) and 5 transitions to a worse state

Table 2. Parameter estimates of the Hungarian EQ-5D-3L value set.

	Model 1 Pooled linear model, homoscedastic			Model 2 Pooled linear model, heteroscedastic			Model 3 Pooled Tobit model, homoscedastic			Model 4 Pooled Tobit model, heteroscedastic (value set)‡		
	β	SE	*P* value*	β	SE	*P* value*	β	SE	*P* value*	β	SE	*P* value*
Intercept†	0.961	0.015	.012	0.979	0.008	.009	0.965	0.016	.028	0.980	0.008	.013
MO2	-0.026	0.014	.061	-0.022	0.008	.008	-0.025	0.014	.080	-0.022	0.008	.006
MO3	-0.596	0.026	<.001	-0.619	0.028	<.001	-0.611	0.027	<.001	-0.648	0.031	<.001
SC2	-0.064	0.017	<.001	-0.051	0.009	<.001	-0.064	0.017	<.001	-0.051	0.009	<.001
SC3	-0.318	0.020	<.001	-0.347	0.020	<.001	-0.328	0.021	<.001	-0.355	0.022	<.001
UA2	0.003	0.016	.852	-0.024	0.008	.004	0.003	0.016	.853	-0.025	0.008	.003
UA3	-0.229	0.019	<.001	-0.243	0.019	<.001	-0.234	0.019	<.001	-0.246	0.021	<.001
PD2	-0.093	0.014	<.001	-0.081	0.010	<.001	-0.093	0.015	<.001	-0.080	0.010	<.001
PD3	-0.322	0.019	<.001	-0.334	0.018	<.001	-0.328	0.020	<.001	-0.338	0.019	<.001
AD2	-0.069	0.018	<.001	-0.077	0.011	<.001	-0.070	0.018	<.001	-0.078	0.011	<.001
AD3	-0.249	0.019	<.001	-0.257	0.019	<.001	-0.253	0.020	<.001	-0.258	0.020	<.001
Illogical parameters	1			0			1			0		
Insignificant parameters ($P \geq .05$)	2			0			2			0		
MAE (predicted vs observed)	0.034			0.033			0.035			0.036		
Health states >|0.05|, n (%)	7 of 30 (23.3)			4 of 30 (13.3)			4 of 30 (13.3)			5 of 30 (16.7)		
Health states >|0.10|, n (%)	1 of 30 (3.3)			2 of 30 (6.7)			2 of 30 (6.7)			2 of 30 (6.7)		
Pearson's correlation (predicted vs observed)	0.995			0.994			0.995			0.994		
Spearman's correlation (predicted vs observed)	0.990			0.993			0.991			0.992		
Dimension importance	MO > PD > SC > AD > UA			MO > SC > PD > AD > UA			MO > PD > SC > AD > UA			MO > SC > PD > AD > UA		
No. (%) of health states WTD	53 (21.8)			58 (23.9)			54 (22.2)			63 (25.9)		
U (11111)	0.961			0.979			0.965			0.980		
U (22222)	0.712			0.724			0.716			0.724		
U (33333)	-0.753			-0.821			-0.789			-0.865		
Mean utilities (SD)	0.307 (0.368)			0.294 (0.387)			0.297 (0.378)			0.280 (0.400)		
Median utilities (IQR)	0.326 (0.547)			0.325 (0.578)			0.320 (0.565)			0.311 (0.601)		

AD indicates anxiety/depression; IQR, interquartile range; MAE, mean absolute error; MO, mobility; SC, self-care; PD, pain/discomfort; SE, standard error; UA, usual activities; WTD, worse than dead.
**P* values indicate the incremental disutility from the preceding level.
†*P* values for the intercept refer to the difference between the intercept and 1.
‡Example for using the Hungarian EQ-5D-3L value set: the predicted utility value for state 12321 is 0.980-0-0.051-0.246-0.080-0 = 0.603.

(54444, 45444, 44544, 44454, and 44445). The absolute differences in utilities between each single-level transition utility and their baseline health state were calculated and averaged to obtain a single mean transition utility for every baseline health state. In total there were 1 620 (3L) and 25 000 (5L) single-level transitions, respectively. Four separate analyses were carried out: (1) single-level transitions for all 3L states, (2) single-level transitions for all 5L states, (3) single-level transitions for all matched 5L states, and (4) 2-level transitions for 5L states.[14]

The relationship between mean transition and baseline utilities was estimated by using ordinary least squares regression with standard errors adjusted for heteroscedasticity. All transition utilities were plotted against baseline 3L or 5L utilities to illustrate the consistency of transition utilities by misery scores (ie, the sum of the levels across dimensions ranging from 5 to 15 [3L] or 25 [5L]). Within the context of the QALY model, utilities are measured on an interval scale, where the same change in health status is expected to represent the same, irrespective of the part of the scale being considered.[38] Thus, in general, the more consistent the mean transition utilities on the entire scale, the better the instrument is.

Results

Respondent Characteristics

A total of 1000 respondents, representative of the Hungarian general population for age and sex, were successfully interviewed.

In total, 1177 potential respondents were approached (response rate 85%). Reasons for interview failure are provided in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019.

The characteristics of the sample are summarized in Table 1. The distribution of the sample in marital status, employment status, and area of residence reasonably approximated that of the general population. Higher-educated respondents and inhabitants of Central Hungary were slightly overrepresented.

Data Characteristics

There were no missing responses for any valuation task resulting in a total of 3000 (3L) and 10 000 (5L) cTTO responses from 1000 respondents. A flowchart presenting an overview of the results of the 5L quality-control process is provided in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019. Before the feedback module, a total of 196 (19.6%) respondents had at least 1 inconsistent 5L response. In the feedback module, 634 cTTO responses were removed by 481 (48.1%) respondents. The proportion of respondents with logical inconsistencies was reduced to 70 (7.0%) after the feedback module. Thus, data analysis included 9366 (5L) cTTO observations from 1000 respondents.

For the 3L, logical inconsistencies occurred in 13 (1.3%) of the respondents. No feedback module was built into the EQ-VT for reconsideration of 3L responses, thus we included all the 3000 (3L) responses in the data analysis. Distribution and summary statistics of the observed cTTO utilities for the 3L and 5L are presented in Appendices 5, 6, and 7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019.

EQ-5D-3L Value Set

The 3L model results are presented in Table 2. In model 1 (3L) and model 3 (3L), the estimates for UA2 were both insignificant and illogically ordered from UA1, and in addition the difference between MO1 and MO2 was insignificant. In model 2 (3L) and model 4 (3L), all coefficients were consistent with the monotonic nature of the descriptive system and statistically significant from the preceding level. In these 2 models, only 2 (6.7%) of the predicted 30 health state utilities differed from observed utilities by more than 0.10. Model 4 (3L) was selected as the final value set on the basis of considerations outlined in the Methods section, such as handling left-censored data, accounting for heteroscedasticity and logical ordering, and statistical significance of parameters.

EQ-5D-5L Value Set

The parameter estimates and prediction accuracy of the 5L models are shown in Table 3. For all models, every coefficient was consistent; however, UA5 and PD3 in model 1 (5L), UA5 in model 2 (5L), and PD3 in models 3 (5L) and 4 (5L) were insignificant. Model 4 (5L) produced a slight improvement in prediction accuracy. In this model, utilities for 2 (2.3%) of 86 heath states differed by more than 0.10 from their observed utilities. The parameter of the intercept did not differ significantly from 1. A constrained version of model 4 (5L) was selected as the final value set (model 5 [5L]). Sensitivity analysis indicated no significant impact of exclusions on parameter estimates.

Comparison of 3L and 5L Value Sets

A comparison of the matched regression parameters of the 2 value sets (model 4 [3L] vs model 5 [5L]) is presented in Appendix 8 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019. The 3L parameter estimates were higher (less negative) for all matched levels, with the exception of the most severe level of MO and the middle level of PD. A good concordance was observed in the preference ranking of the 5 dimensions; MO was consistently placed the most, while UA the least important (Tables 2 and 3). The proportion of health states valued as WTD was higher for the 3L (25.9% [3L] vs 21.7% [5L]). The 3L value set demonstrated lower minimum utility compared with 5L (-0.865 [3L] vs -0.848 [5L]). The 5L demonstrated lower ceiling effects (range of utilities for the mildest states: 0.900-0.958 [3L] vs 0.955-0.965 [5L]) (Table 4).

Figure 1 depicts the Kernel density estimates of all attainable 3L, 5L, and matched 5L utilities. Distribution of the 5L was unimodal, whereas the 3L had few clusters. A higher density of the 3L compared with 5L was demonstrated on both ends of the utility scale. Of the 243 matched health states, 160 (65.8%) showed a higher utility for the 3L, while 83 (34.2%) for the 5L. The Bland-Altman plot (Fig. 2) indicated a good level of agreement between 3L and matched 5L utilities. Of the 81 matched pairs in which the most severe level of MO was affected, 77 (95.1%) indicated a lower utility for the 3L. Conversely, a higher 3L utility was predicted in 156 (96.3%) of the other 162 health states.

Comparison of Transitions From 11111 and the Pits State

For the mildest health states, differences in single-level transition utilities from 11111 between 3L and unmatched 5L ranged from 0.035 to 0.045 (see Appendix 9 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019). The largest difference between the 3L and matched 5L states was found for MO: 0.022 (3L) versus 0.089 (5L). Unmatched differences in single-level transition utilities from the pits state were considerably larger for the 3L (range: -0.626 to -0.180) compared with 5L (-0.192 to -0.059). Matched differences in single-level transition utilities from pits between 3L and 5L health states were of similar size for all dimensions with the exception of MO (“confined to bed” [3L]: -0.626 vs “unable to walk” [5L]: -0.366).

Comparison of Transitions for Adjacent Corner States

Single-level transitions between adjacent corner states for the 2 value sets are compared in Table 4. In all dimensions, the largest differences in utilities occurred between levels 2 and 3 for the 3L and between levels 3 and 4 for the 5L with the exception of MO (5L). The transition utilities well reflected the divergence of wording between the 2 descriptive systems. The largest difference was found for the most severe level of MO (“confined to bed” [3L] vs “unable to walk” [5L]: 0.260). In all but 1 matched middle or extreme level categories where the 5L uses a more negative word (middle levels of MO, SC, UA, and AD, and the extreme levels of PD and AD), differences between levels were larger for the 5L. Changing the descriptor “feeling down” (3L) to “depressed” (5L) parallel to changing the adjectives “a little” (3L) and “a lot” (3L) to “moderately” (5L) and “extremely” (5L), respectively, had a small negative impact on single-level transition utilities (matched middle level -0.015 and extreme level -0.067).

Comparison of Mean Transition Utilities

Appendix 10 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.019 displays the mean single-level 3L, 5L, matched 5L and 2-level transition utilities as a function of their respective baseline utilities. Mean $\pm$ SD single-level transition utility of all possible health states was substantially higher for the 3L (0.185 $\pm$ 0.049) compared with the 5L (0.092 $\pm$ 0.021). Mean single-level transition utilities were larger by, on average, 0.097 (3L) and 0.043 (5L) for every 1-point decrease in utilities (P<.0001). Likewise, a significant negative relationship was found

Table 3. Parameter estimates of the Hungarian EQ-5D-5L value set.

	Model 1 Pooled linear model, homoscedastic			Model 2 Pooled linear model, heteroscedastic		
	β	SE	*P* value*	β	SE	*P* value*
Intercept[†]	1.002	0.014	.912	1.009	0.007	.229
MO2	-0.051	0.013	<.001	-0.047	0.008	<.001
MO3	-0.113	0.014	<.001	-0.117	0.014	<.001
MO4	-0.289	0.014	<.001	-0.282	0.014	<.001
MO5	-0.434	0.014	<.001	-0.427	0.014	<.001
SC2	-0.041	0.012	<.001	-0.053	0.007	<.001
SC3	-0.079	0.014	.013	-0.089	0.010	.001
SC4	-0.252	0.018	<.001	-0.243	0.016	<.001
SC5	-0.313	0.012	<.001	-0.326	0.014	<.001
UA2	-0.037	0.013	.004	-0.043	0.007	<.001
UA3	-0.081	0.017	.005	-0.087	0.013	.001
UA4	-0.209	0.013	<.001	-0.222	0.012	<.001
UA5	-0.228	0.012	.212	-0.240	0.013	.315
PD2	-0.057	0.011	<.001	-0.051	0.007	<.001
PD3	-0.084	0.014	.117	-0.085	0.014	.028
PD4	-0.281	0.015	<.001	-0.284	0.014	<.001
PD5	-0.377	0.014	<.001	-0.398	0.017	<.001
AD2	-0.043	0.014	.002	-0.045	0.006	<.001
AD3	-0.122	0.018	<.001	-0.112	0.014	<.001
AD4	-0.282	0.014	<.001	-0.268	0.013	<.001
AD5	-0.316	0.013	.028	-0.315	0.012	<.001
Illogical parameters	0			0		
Insignificant parameters (*P* ≥ .05)	2			1		
MAE (predicted vs observed)	0.033			0.032		
Health states >|0.05|, n (%)	20 of 86 (23.3)			18 of 86 (20.9)		
Health states >|0.10|, n (%)	4 of 86 (4.7)			3 of 86 (3.5)		
Pearson's correlation (predicted vs observed)	0.994			0.994		
Spearman's correlation (predicted vs observed)	0.990			0.991		
Dimension importance	MO > PD > AD > SC > UA			MO > PD > SC > AD > UA		
No. (%) of health states WTD	592 (18.9)			606 (19.4)		
U (11111)	1.002			1.009		
U (33333)	0.523			0.519		
U (55555)	-0.666			-0.697		
Mean utilities (SD)	0.264 (0.294)			0.262 (0.296)		
Median utilities (IQR)	0.275 (0.415)			0.275 (0.420)		

AD indicates anxiety/depression; IQR, interquartile range; MAE, mean absolute error; MO, mobility; PD, pain/discomfort; SC, self-care; SE, standard error; UA, usual activities; WTD, worse than dead.
*P values indicate the incremental disutility from the preceding level.
†P values for the intercept represent the difference between the intercept and 1.
‡Example for using the Hungarian EQ-5D-5L value set: the predicted utility value for state 12345 is 1-0-0.045-0.085-0.288-0.340 = 0.242.

Table 3. Continued

Model 3 Pooled Tobit model, homoscedastic			Model 4 Pooled Tobit model, heteroscedastic			Model 5 Pooled Tobit model, heteroscedastic, constrained (value set)‡		
β	SE	*P* value*	β	SE	*P* value*	β	SE	*P* value*
1.003	0.014	.827	1.005	0.007	.498	1.000	-	-
-0.045	0.013	<.001	-0.038	0.008	<.001	-0.035	0.006	<.001
-0.100	0.014	<.001	-0.090	0.014	<.001	-0.089	0.013	<.001
-0.278	0.014	<.001	-0.264	0.014	<.001	-0.263	0.014	<.001
-0.445	0.014	<.001	-0.455	0.015	<.001	-0.455	0.015	<.001
-0.040	0.012	.001	-0.048	0.007	<.001	-0.045	0.005	<.001
-0.078	0.015	.016	-0.088	0.010	<.001	-0.089	0.010	<.001
-0.251	0.018	<.001	-0.242	0.016	<.001	-0.241	0.016	<.001
-0.337	0.013	<.001	-0.366	0.016	<.001	-0.366	0.016	<.001
-0.034	0.013	.007	-0.038	0.007	<.001	-0.035	0.004	<.001
-0.081	0.017	.004	-0.086	0.013	<.001	-0.085	0.013	<.001
-0.208	0.013	<.001	-0.219	0.012	<.001	-0.217	0.012	<.001
-0.250	0.012	.008	-0.277	0.014	.002	-0.276	0.014	.001
-0.053	0.011	<.001	-0.046	0.006	<.001	-0.043	0.005	<.001
-0.082	0.014	.099	-0.073	0.014	.084	-0.073	0.014	.038
-0.286	0.015	<.001	-0.287	0.014	<.001	-0.288	0.014	<.001
-0.391	0.015	<.001	-0.413	0.018	<.001	-0.411	0.018	<.001
-0.042	0.014	.003	-0.042	0.006	<.001	-0.040	0.005	<.001
-0.115	0.019	<.001	-0.095	0.014	<.001	-0.093	0.014	<.001
-0.281	0.014	<.001	-0.262	0.013	<.001	-0.261	0.013	<.001
-0.329	0.013	.003	-0.341	0.013	<.001	-0.340	0.013	<.001
0			0			0		
1			1			0		
0.032			0.032			0.032		
16 of 86 (18.6)			17 of 86 (19.8)			17 of 86 (19.8)		
3 of 86 (3.5)			2 of 86 (2.3)			2 of 86 (2.3)		
0.994			0.993			0.993		
0.991			0.993			0.993		
MO > PD > SC > AD > UA			MO > PD > SC > AD > UA			MO > PD > SC > AD > UA		
623 (19.9)			676 (21.6)			677 (21.7)		
1.003			1.005			1.000		
0.513			0.573			0.571		
-0.703			-0.847			-0.848		
0.256 (0.296)			0.251 (0.317)			0.251 (0.318)		
0.269 (0.420)			0.266 (0.448)			0.265 (0.449)		

Table 4. Comparison of adjacent corner health states for changes.

	Exact wording in Hungarian translated to English	3L state	3L utility	Diff. [A]	Exact wording in Hungarian translated to English	5L state	5L utility	Diff. [B]	Diff. [C]	More negative word	Diff. [A]-[C]*
MO	No problems in walking about	11111	1.000		No problems in walking about	11111	1.000			Id.	
					Slight problems in walking about	21111	0.965	0.035			
	Some problems in walking about	21111	0.958	0.022	**Moderate** problems in walking about	31111	0.911	0.054	0.089	5L	-0.067
					Severe problems in walking about	41111	0.737	0.174			
	<u>Confined to bed</u>	31111	0.332	0.626	**<u>Unable to walk about</u>**	51111	0.545	0.192	0.366	3L	0.260
SC	No problems with **<u>self-care</u>**	11111	1.000		No problems **<u>washing or dressing</u>**	11111	1.000			Id.[†]	
					Slight problems washing or dressing	12111	0.955	0.045			
	Some problems with washing or dressing	12111	0.929	0.051	**Moderate** problems washing or dressing	13111	0.911	0.044	0.089	5L	-0.038
					Severe problems washing or dressing	14111	0.759	0.152			
	Unable to wash or dress	13111	0.625	0.304	Unable to wash or dress	15111	0.634	0.125	0.277	Id.	0.027
UA	No problems performing usual activities	11111	1.000		No problems doing usual activities	11111	1.000			Id.	
					Slight problems doing usual activities	11211	0.965	0.035			
	Some problems with performing usual activities	11211	0.922	0.058	**Moderate** problems doing usual activities	11311	0.915	0.050	0.085	5L	-0.027
					Severe problems doing usual activities	11411	0.783	0.132			
	Unable to perform usual activities	11311	0.734	0.188	Unable to do usual activities	11511	0.724	0.059	0.191	Id.	-0.003
PD	No pain or discomfort	11111	1.000		No pain or discomfort	11111	1.000			Id.	
					Slight pain or discomfort	11121	0.957	0.043			
	Moderate pain or **a little** discomfort	11121	0.900	0.080	Moderate pain or **moderate** discomfort	11131	0.927	0.030	0.073	5L	0.007
					Severe pain or discomfort	11141	0.712	0.215			
	Very strong pain or **very large** discomfort	11131	0.642	0.258	**Extreme** pain or **extreme** discomfort	11151	0.589	0.123	0.338	5L	-0.080
AD	Not anxious or not **<u>feeling down</u>**	11111	1.000		Not anxious or **<u>depressed</u>**	11111	1.000			5L	
					Slightly anxious or depressed	11112	0.960	0.040			
	Moderately anxious or **<u>feeling down</u> a little**	11112	0.902	0.078	Moderately anxious or **moderately <u>depressed</u>**	11113	0.907	0.053	0.093	5L	-0.015
					Severely anxious or depressed	11114	0.739	0.168			

continued on next page

Table 4. Continued

Exact wording in Hungarian translated to English	3L state	3L utility	Diff. [A]	Exact wording in Hungarian translated to English	5L state	5L utility	Diff. [B]	Diff. [C]	More negative word	Diff. [A]-[C]*
Very much anxious or **feeling down a lot**	11113	0.722	0.180	**Extremely** anxious or **extremely depressed**	11115	0.660	0.079	0.247	5L	-0.067

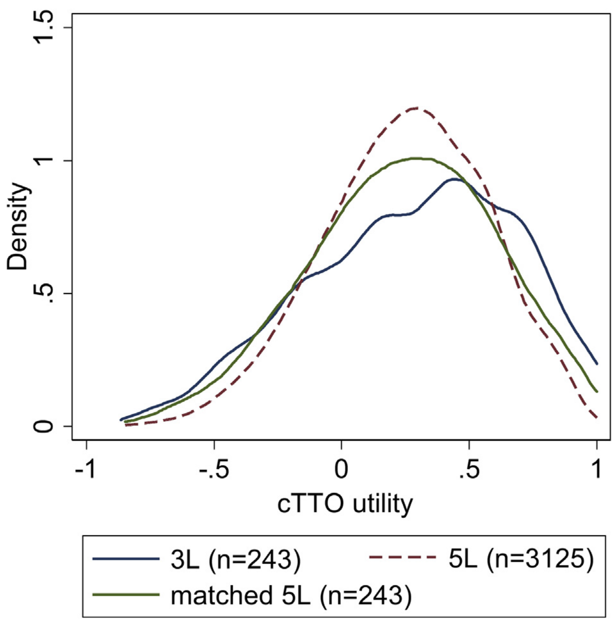
Note. [A] difference from less severe adjacent 3L state; [B] difference from less severe adjacent 5L state; [C] difference between 3L and matched 5L states. Bold words indicate a change in the strength of adjective. Bold and underlined words indicate a change of a descriptor (ie, noun/verb) that determines the label/dimension. AD indicates anxiety/depression; 5L, 5-level; MO, mobility; PD, pain/discomfort; SC, self-care; 3L, 3-level; UA, usual activities.
*Negative numbers indicate that differences between levels are larger for the 5L.
†Can be considered identical.

between baseline 5L utilities and single-level transitions computed for matched 5L health states and for 2-level mean transition utilities.

Discussion

In this study, we determined the utilities of the 2 adult versions of the EQ-5D health status questionnaire (3L and 5L) from the perspective of the general population in Hungary. In accordance with national HTA recommendations,[6] our sample was representative of the Hungarian general population for age and sex. Up to now, only Poland (3L and 5L) and Slovenia (3L) in the Central and Eastern European region have developed TTO-based value sets.[39–42] The present study overall marks a considerable achievement in taking HTA to the next level in Hungary. Furthermore, the study created a unique opportunity to compare the characteristics of the 2 value sets derived from a common sample and to analyze the impact of differences in wording of the descriptive systems on changes in utilities.

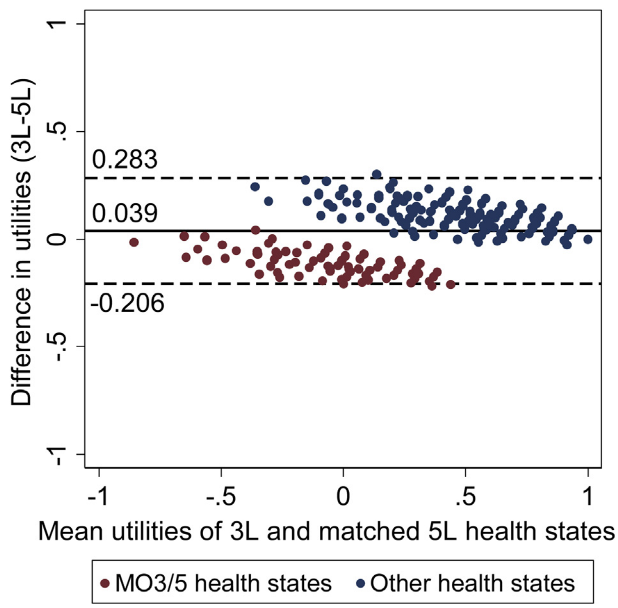
Figure 1. Kernel density plot of 3L, 5L, and matched 5L utilities.



3L indicates 3-level; 5L, 5-level.

Both for the 3L and 5L, the Hungarian value sets are based on a main effects model, because the EQ-VT design is optimized for such models.[25] For the 3L, model 1 (3L) and model 3 (3L) produced inconsistent estimates for UA2 owing to heteroscedasticity being present in data. Very likely the different study design of the 3L valuation exercise, in particular, the smaller proportion of mild states among the 30 (3L) states valued, resulted in a stronger heteroscedasticity for the 3L. The 5L value set outperformed the 3L in many ways, such as ceiling effects and the consistency of mean transitions across the range of baseline utilities. Acknowledging the limitations of the 3L descriptive system[43–46] and the Hungary-specific differences in wording, in future studies both in and outside HTA, generally the 5L descriptive system and value set are recommended to be used in Hungary. Nevertheless, the Hungarian 3L value set will be useful in many cases including clinical trials administering the 3L, studies aiming to reanalyze previously collected local 3L data, and conditions where the 3L is a more

Figure 2. Bland-Altman plot of 3L and matched 5L utilities (n = 243). The horizontal line represents the mean of the differences (d) between 3L and 5L utilities, while the 95% limits of agreement, obtained as d ± 1.96 * SD of d, are indicated by dashed lines.



MO3/5 indicates most severe level of mobility; 3L, 3-level; 5L, 5-level.

suitable instrument to assess quality of life (eg, where the response level “confined to bed” (3L) is actually relevant for the patient population).

This is the first study in Europe to derive cTTO-based value sets of the 3L and 5L from a common sample. The 3L and 5L value sets for Hungary are rather close to each other in many aspects including the range of utilities and rank ordering of the 5 dimensions. Consistently with previous studies,[14,25,34] changing the wording of the most severe level of mobility was responsible for the major differences seen between the 3L and 5L value sets. For most 3L and matched 5L health state pairs in which the most severe level of mobility was affected, a lower utility was demonstrated for the 3L. Thus, the large positive impact of changing “confined to bed” (3L) to “unable to walk” (5L) exceeded the overall impact of smaller changes with more negative wording in the other 4 dimensions. It appears that the overall impact of “confined to bed” (3L) and whether it is attenuated by other dimensions will depend on the disease studied.

Differences in wording of the anxiety/depression dimension slightly affected the utilities (“feeling down” [3L] vs “depressed” [5L]). There seem to be 2 major reasons underlying this observation. First, only a part of a composite dimension is involved by this wording change. Prior findings suggest that in valuation the composite dimension of anxiety/depression is interpreted to mean an average of anxiety and depression, but weighted more toward anxiety.[47] Secondly, anxiety/depression had a lower relative importance in the ranking of dimensions in Hungary, thus its impact on utilities was modest. It is plausible that in a country where anxiety/depression is among the most important dimensions, the impact of such a change in wording would be reflected more markedly. Further research is warranted to investigate how the differences in wording alter people’s ratings on their own health.

The main limitations of our study are related to the valuation of 3L health states. First, each respondent valued only 3 3L health states after the 5L, and not all respondents valued the pits state or any mild state. Secondly, respondents were not informed that the last 3 health states refer to a different descriptive system. The way the respondents interpreted the 3L states may not have been how they would have interpreted them if they had not seen 5L states beforehand. Future studies may be conducted using different study designs (eg, between-sample design or dropping levels 2 and 4 of the 5L) to further explore the differences between the 3L and 5L in the context of valuation. Thirdly, DCE data were not used in developing the 5L value set, since the cTTO data alone resulted in a fully consistent 5L model. Our choice was mainly motivated by avoiding unnecessary conceptual and statistical assumptions. Moreover, using an identical preference elicitation method to develop 3L and 5L value sets is expected to ensure consistency across HTA reports. Finally, we acknowledge that wording changes in the 3L compared to other language versions detract from the aim of methodological standardization of the EQ-5D at a supranational level. In the past 2 decades, the 3L has been administered to over 25 000 people in nearly 50 clinical and population studies in Hungary.[8,48–50] Being aware of the substantial collection of Hungarian studies, we believe that a revision of the translation before this valuation study would have caused more harm than good.

Conclusion

This study developed Hungarian value sets of the EQ-5D 3L and 5L questionnaires based on cTTO valuations from the general population in Hungary. More similarities were noted between the 2 value sets than in any previous study. Consistent with a similar study in the United States, the most severe level of mobility appeared to be responsible for the major differences seen between the 3L and 5L value sets. It is hoped that the value sets will facilitate the uptake in the use of EQ-5D in economic evaluations and the advancement of HTA in Hungary. These findings contribute to the understanding of how the wording of descriptive systems affects the estimates of utilities.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.03.019.

Article and Author Information

Accepted for Publication: March 25, 2020

Published Online: August 6, 2020

doi: https://doi.org/10.1016/j.jval.2020.03.019

Author Affiliations: Department of Health Economics, Corvinus University of Budapest, Budapest, Hungary (Rencz, Brodsky, Péntek); Hungarian Academy of Sciences, Premium Postdoctoral Research Programme, Budapest, Hungary (Rencz); Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland (Golicki); Institute of Psychology, Doctoral School of Psychology, Eötvös Loránd University of Sciences, Budapest, Hungary (Ruzsa); Department of Statistics, Corvinus University of Budapest, Budapest, Hungary (Ruzsa); Department of Pharmacy Systems, Outcomes and Policy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA (Pickard); Patient & Health Impact, Pfizer Inc, New York, NY, USA (Law)

Author Contributions: *Concept and design:* Rencz, Brodszky, Gulácsi, Golicki, Pickard, Péntek
Acquisition of data: Rencz, Gulácsi, Péntek
Analysis and interpretation of data: Rencz, Brodszky, Golicki, Ruzsa, Law, Péntek
Drafting of the manuscript: Rencz, Pickard, Law, Péntek
Critical revision of the paper for important intellectual content: Rencz, Brodszky, Gulácsi, Golicki, Ruzsa, Pickard, Law
Statistical analysis: Rencz, Ruzsa, Law
Provision of study materials or patients: Rencz
Obtaining funding: Rencz, Péntek
Administrative, technical, or logistic support: Rencz, Gulácsi
Supervision: Rencz, Péntek

Conflict of Interest Disclosures: Drs Golicki, Pickard and Law are members of the EuroQol Group, a not-for-profit organization that develops and distributes instruments that assess and value health. Dr Law is an employee and a minor shareholder of Pfizer. No other disclosures were reported.
The views expressed in the paper are the authors’ and do not necessarily represent those of the EuroQol Research Foundation.

Funding/Support: Dr Rencz’s work was supported by the Premium Postdoctoral Research Programme of the Hungarian Academy of Sciences (MTA-BCE PPD 462025). This study received a grant from the EuroQol Research Foundation (EQ Project 20170500).

Role of the Funder/Sponsor: The funding agreement ensured the authors’ independence in designing the study, interpreting the data, and preparing and publishing the manuscript.

Acknowledgment: The authors thank the EuroQol support team for the help provided throughout the project: Elly Stolk, Kristina Ludwig, Mark Oppe, Bram Roudijk, Juan M. Ramos-Goñi, Arnd J. Prause and Gerben Bakker. We thank Aki Tsuchiya (University of Sheffield) for her useful comments on an earlier draft of this manuscript. The authors are grateful for the excellent work of the interviewer team: Zita Bagdi, Péter Balázs, Alex Bató, Andrij Donilas, Szimonetta Dropsa, Dávid Fehér, Bence Horák, Balázs Jenei, Péter M. Juhász, Anna Nikl, Laura Rádi and Viktória Vig. Finally, we thank the study respondents for making this possible.

REFERENCES

1. Gulacsi L, Brodszky V, Pentek M, et al. History of health technology assessment in Hungary. *Int J Technol Assess Health Care*. 2009;25(suppl 1):120–126.
2. Gulacsi L, Rotar AM, Niewada M, et al. Health technology assessment in Poland, the Czech Republic, Hungary, Romania and Bulgaria. *Eur J Health Econ*. 2014;15(suppl 1):S13–S25.
3. Gulacsi L. The time for cost-effectiveness in the new European Union member states: the development and role of health economics and technology assessment in the mirror of the Hungarian experience. *Eur J Health Econ*. 2007;8:83–88.
4. Boncz I, Sebestyen A. Financial deficits in the health services of the UK and Hungary. *Lancet*. 2006;368:917–918.
5. National Institute of Pharmacy and Nutrition (OGYÉI). https://www.ogyei.gov.hu/ajanlasok. Accessed April 28, 2019.
6. Az Emberi Erőforrások Minisztériuma szakmai irányelve az egészségügyi technológia értékelés módszertanáról és ennek keretében költséghatékonysági elemzések készítéséről. *Egészségügyi Közlöny*. 2017;3(10):821–842.
7. Rowen D, Azzabi Zouraq I, Chevrou-Severac H, van Hout B. International regulations and recommendations for utility data for health technology assessment. *Pharmacoeconomics*. 2017;35:11–19.
8. Rencz F, Gulacsi L, Drummond M, et al. EQ-5D in Central and Eastern Europe: 2000-2015. *Qual Life Res*. 2016;25:2693–2710.
9. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health Econ Health Policy*. 2017;15:127–137.
10. Roudijk B, Donders ART, Stalmeier PFM. Cultural values: can they explain differences in health utilities between countries? *Med Decis Making*. 2019;39(5):605–616.
11. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16:199–208.
12. Brooks R. EuroQol: the current state of play. *Health Policy*. 1996;37:53–72.
13. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–1736.
14. Mulhern B, Feng Y, Shah K, et al. Comparing the UK EQ-5D-3L and English EQ-5D-5L value sets. *Pharmacoeconomics*. 2018;36:699–713.
15. Law EH, Pickard AS, Xie F, et al. Parallel valuation: a direct comparison of EQ-5D-3L and EQ-5D-5L societal value sets. *Med Decis Making*. 2018;38:968–982.
16. Selivanova A, Buskens E, Krabbe PFM. Head-to-head comparison of EQ-5D-3L and EQ-5D-5L health values. *Pharmacoeconomics*. 2018;36:715–725.
17. Craig BM, Pickard AS, Rand-Hendriksen K. Do health preferences contradict ordering of EQ-5D labels? *Qual Life Res*. 2015;24:1759–1765.
18. Kreimeier S, Oppe M, Ramos-Goni JM, et al. Valuation of EuroQol Five-Dimensional Questionnaire, Youth Version (EQ-5D-Y) and EuroQol Five-Dimensional Questionnaire, Three-Level Version (EQ-5D-3L) health states: the impact of wording and perspective. *Value Health*. 2018;21:1291–1298.
19. Xie F, Gaebel K, Perampaladas K, Doble B, Pullenayegum E. Comparing EQ-5D valuation studies: a systematic review and methodological reporting checklist. *Med Decis Making*. 2014;34:8–20.
20. Stolk E, Ludwig K, Rand K, van Hout B, Ramos-Goni JM. Overview, update, and lessons learned from the international EQ-5D-5L Valuation Work: version 2 of the EQ-5D-5L Valuation Protocol. *Value Health*. 2019;22:23–30.
21. Pickard AS, Law EH, Jiang R, et al. United States valuation of EQ-5D-5L Health States using an international protocol. *Value Health*. 2019;22:931–941.
22. Cha AS, Law EH, Shaw JW, Pickard AS. A comparison of self-rated health using EQ-5D VAS in the United States in 2002 and 2017. *Qual Life Res*. 2019;28:3065–3069.
23. Oppe M, Devlin NJ, van Hout B, Krabbe PF, de Charro F. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. *Value Health*. 2014;17:445–453.
24. Hungarian Central Statistical Office. Microcensus 2016. http://www.ksh.hu/docs/eng/xftp/idoszaki/microcensus2016/microcensus_2016_3.pdf. Accessed February 24, 2019.
25. Ramos-Goni JM, Oppe M, Slaap B, Busschbach JJ, Stolk E. Quality control process for EQ-5D-5L valuation studies. *Value Health*. 2017;20:466–473.
26. Oppe M, van Hout B. The “power” of eliciting EQ-5D-5L values: the experimental design of the EQ-VT. EuroQol Group. http://euroqol.org/wp-content/uploads/2016/10/EuroQol-Working-Paper-Series-Manuscript-17003-Mark-Oppe.pdf. Accessed August 19, 2019.
27. Janssen BM, Oppe M, Versteegh MM, Stolk EA. Introducing the composite time trade-off: a test of feasibility and face validity. *Eur J Health Econ*. 2013;14(suppl 1):S5–S13.
28. Ludwig K, Graf von der Schulenburg JM, Greiner W. German value set for the EQ-5D-5L. *Pharmacoeconomics*. 2018;36:663–674.
29. Hobbins A, Barry L, Kelleher D, et al. Utility values for health states in Ireland: a value set for the EQ-5D-5L. *Pharmacoeconomics*. 2018;36:1345–1353.
30. Purba FD, Hunfeld JAM, Iskandarsyah A, et al. The Indonesian EQ-5D-5L value set. *Pharmacoeconomics*. 2017;35:1153–1165.
31. Messner JW, Mayr GJ, Zeileis A. Heteroscedastic censored and truncated regression with crch. *R J*. 2016;8:173–181.
32. Berger S, Graham N, Zeileis A. Various versatile variances: an object-oriented implementation of clustered covariances in R. http://EconPapers.RePEc.org/RePEc:inn:wpaper:2017-12. Accessed January 6, 2020.
33. Versteegh MM, Vermeulen KM, Evers SMAA, et al. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19:343–352.
34. Feng Y, Devlin NJ, Shah KK, Mulhern B, van Hout B. New methods for modelling EQ-5D-5L value sets: an application to English data. *Health Econ*. 2018;27:23–38.
35. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1:307–310.
36. Luo N, Johnson J, Coons SJ. Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments. *Med Care*. 2010;48:365–371.
37. McClure NS, Sayah FA, Xie F, Luo N, Johnson JA. Instrument-defined estimates of the minimally important difference for EQ-5D-5L Index scores. *Value Health*. 2017;20:644–650.
38. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull*. 2010;96:5–21.
39. Golicki D, Jakubczyk M, Niewada M, Wrona W, Busschbach JJ. Valuation of EQ-5D health states in Poland: first TTO-based social value set in Central and Eastern Europe. *Value Health*. 2010;13:289–297.
40. Golicki D, Niewada M, Hout BV, Janssen MF, Pickard AS. Interim EQ-5D-5L value set for Poland: first crosswalk value set in Central and Eastern Europe. *Value Health Reg Issues*. 2014;4:19–23.
41. Golicki D, Jakubczyk M, Graczyk K, Niewada M. Valuation of EQ-5D-5L health states in Poland: the first EQ-VT-based study in Central and Eastern Europe. *Pharmacoeconomics*. 2019;37:1165–1176.
42. Prevolnik Rupel V, Srakar A, Rand K. Valuation of EQ-5D-3L health states in Slovenia: VAS based and TTO based value sets. *Slovenian J Public Health*. 2019;59:8–17.
43. Buchholz I, Janssen MF, Kohlmann T, Feng YS. A systematic review of studies comparing the measurement properties of the three-level and five-level versions of the EQ-5D. *Pharmacoeconomics*. 2018;36:645–661.
44. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22:1717–1727.
45. Janssen MF, Bonsel GJ, Luo N. Is EQ-5D-5L better than EQ-5D-3L? A head-to-head comparison of descriptive systems and value sets from seven countries. *Pharmacoeconomics*. 2018;36:675–697.
46. Devlin N, Brazier J, Pickard AS, Stolk E3L. 5L, what the L? A NICE conundrum. *Pharmacoeconomics*. 2018;36:637–640.
47. Mullett TL, McDonald R, Tsuchiya A. Understanding the composite dimensions of the EQ-5D: an experimental approach. Presented at: EuroQol 35th Plenary Meeting; September 19-21, 2018; Lisbon, Portugal.
48. Zrubka Z, Rencz F, Zavada J, et al. EQ-5D studies in musculoskeletal and connective tissue diseases in eight Central and Eastern European countries: a systematic literature review and meta-analysis. *Rheumatol Int*. 2017;37:1957–1977.
49. Zrubka Z, Beretzky Z, Hermann Z, et al. A comparison of European, Polish, Slovenian and British EQ-5D-3L value sets using a Hungarian sample of 18 chronic diseases. *Eur J Health Econ*. 2019;20:119–132.
50. Batog P, Rencz F, Pentek M, et al. EQ-5D studies in cardiovascular diseases in eight Central and Eastern European countries: a systematic review of the literature. *Kardiol Pol*. 2018;76:860–870.
51. KSH A. *2014-ben végrehajtott Európai lakossági egészségfelmérés (ELEF) eredményei*; 2018.
52. Szende A, Nemeth R. Health-related quality of life of the Hungarian population. *Orv Hetil*. 2003;144:1667–1674.