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Comparing the UK EQ-5D-3L and English EQ-5D-5L value sets

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Authors:

Brendan Mulhern[1], Yan Feng[2], Koonal Shah[2], Ben van Hout[3], Bas Janssen[4], Michael Herdman[2], and Nancy Devlin[2]

[1] Centre for Health Economics Research and Evaluation, University of Technology Sydney, Australia
[2] Office of Health Economics, London, UK
[3] School of Health and Related Research, University of Sheffield, UK
[4] Department of Medical Psychology and Psychotherapy, Erasmus University, Amsterdam, The Netherlands

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Contact details:

Brendan Mulhern
Centre for Health Economics Research and Evaluation (CHERE)
University of Technology Sydney
1-59 Quay St, Haymarket
NSW 2000

Tel: + 61 2 9514 4725
Fax: + 61 2 9514 4730
Email: brendan.mulhern@chere.uts.edu.au

Disclaimers:

The EQ-5D-5L value set for England reported by Devlin et al. (2016) and analysed in this paper remains provisional at the time of writing. It should be considered as having interim status as the peer review process may necessitate changes to the analyses and results.

Keywords: health state valuation, quality adjusted life years, EQ-5D-3L, EQ-5D-5L, value set

Table of Contents

Abstract **6**

1 Introduction **7**

2 Methods **9**

2.1 The value sets 9

2.2 Analysis 11

2.3 Comparison of predicted values 11

2.4 Analysis on patient data 12

3 Results **13**

3.1 Comparison of models 13

3.2 Comparison of value sets overall 14

3.3 Comparison of predicted values for matched states 14

3.4 Comparing difference in adjacent states 15

3.5 Comparisons using patient data 15

4 Discussion **17**

References **21**

Tables and Figures **23**

Abstract

Background: Three EQ-5D value sets (the EQ-5D-3L, crosswalk and EQ-5D-5L) are now available for cost utility analysis in the UK and/or England. The value sets' characteristics differ, and it is important to systematically assess the implications of these differences for the value generated. The aim of this paper is to compare the characteristics of three value sets

Methods: We carried out analysis comparing the predicted values from each of the three value sets, and also using EQ-5D-3L and EQ-5D-5L data from patients who completed both measures. We assessed descriptive statistics and distributions for all theoretical values and comparable states across the EQ-5D-3L and EQ-5D-5L. We assessed values for individual health states and at the overall level, to highlight where the largest differences occur across the predictions. We also investigated how differences in health on the descriptive system is reflected in the utility score by assessing the value of adjacent states. Agreement was assessed using Bland Altman plots.

Results: There are systematic differences in the distribution of the EQ-5D-3L and EQ-5D-5L value sets. The EQ-5D-5L values are higher than the EQ-5D-3L values for matched states, and the overall range, and therefore differences between adjacent states is smaller than for the EQ-5D-3L. There are similar differences between the EQ-5D-5L and crosswalk value sets. Regarding the patient data, the EQ-5D-5L value set produces higher values across all of the conditions included, and the differences are generally significant. There is some evidence that the value sets rank different health conditions in a similar order of severity, particularly for the most and least severe conditions.

Discussion: Although there are important differences between the value sets, the impact on quality-adjusted life years (QALYs) gained is unclear as they will apply to both control and intervention groups, and will depend on whether the gain is in quality of life, survival, or a mix of both. The increased sensitivity of the EQ-5D-5L may also favour QALY gains even if the changes in utility are smaller. Further work should assess the impact of the EQ-5D-5L value set on cost effectiveness by repeating the analysis on clinical trial data.

1 Introduction

In the economic evaluation of health interventions, the quality adjusted life year (QALY) is a commonly used metric that combines length and quality of life into a single figure. The quality, or utility, weight used in the estimation of QALYs is anchored on a full health (1) to dead (0) scale, with negative values assigned to health states considered worse than dead. Utility values for health states associated with a particular condition or disease can be derived in several ways, one of which is via the use of preference based measures (PBM) of health. Of currently available PBMs, the EQ-5D (Brooks, 1996; Devlin & Brooks, 2016) is the most widely used.

EQ-5D classifies health on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The original version of the EQ-5D (described as EQ-5D-3L) included three severity levels (none, some, extreme/unable), thereby describing (35 =) 243 health states. In the UK, utility values for EQ-5D-3L health states were derived using the Time Trade Off (TTO) preference elicitation technique (Dolan, 1997). The resulting 'value set' has been widely influential, and is preferred by the National Institute for Health and Care Excellence (NICE) for use in the cost utility analysis of health interventions (NICE, 2013). A summary of the source of utility values in NICE submissions found that the majority used values sourced directly from the EQ-5D, or used mapped values (Tosh et al, 2011). EQ-5D-3L values are also accepted by reimbursement agencies worldwide including the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia (PBAC, 2008) and the Canadian Agency for Drugs and Technology in Health (CADTH, 2006) in Canada. The instrument itself is also used in a wide range of settings including population health surveys and routine clinical practice (Appleby, Devlin & Parkin, 2015).

Notwithstanding their widespread use, research has suggested that both the descriptive system and the utility scale of the EQ-5D-3L have a number of limitations. Regarding the descriptive system, it has been shown that the EQ-5D-3L is not sensitive to the health-related quality of life impacts of all conditions (Longworth et al, 2014; Brazier et al, 2014). It may also not be sensitive to smaller changes in health as it only has three response levels in each dimension and, in general public samples and some patient populations, a substantial proportion of respondents report themselves as being in the best health state, i.e. no problems

on any dimension (11111). This is known as a ceiling effect (Brazier et al, 2004). Regarding the value set, the procedure and modelling used to elicit values for worse than dead health states has been criticised (Lamers et al 2007).

In an effort to improve the instrument's sensitivity and reduce the ceiling effect, a five-level descriptive system, the EQ-5D-5L (Herdman et al, 2011) was developed which included five response levels (none, slight, moderate, severe, extreme/unable to) and standardised the wording across dimensions. The major change in wording was in the mobility dimension where 'confined to bed' was replaced with 'unable to walk about' as the most severe level. The EQ-5D-5L increases the number of states described to (55=) 3,125. Research has shown increased sensitivity for the EQ-5D-5L compared to the EQ-5D-3L across a number of patient samples (Janssen et al, 2012).

One consequence of this initiative was the need to develop value sets for the new descriptive system, and this resulted in two separate developments. Firstly, an interim 'crosswalk' value set was developed by van Hout et al (2012), whereby EQ-5D-3L values were used to predict EQ-5D-5L values. Secondly, in order to elicit values for health states generated by the EQ-5D-5L descriptive system, the EuroQol Research Foundation developed a new valuation protocol which combined TTO and Discrete Choice Experiment (DCE) methods (Oppe et al, 2014). This protocol used a 'composite' TTO approach combining standard and 'lead time' TTO (Janssen et al 2013). In England, health states generated by the EQ-5D-5L were valued using this protocol and subsequently modelled using newly developed techniques which combined TTO and DCE data in a hybrid model to produce an EQ-5D-5L value set (Devlin et al, 2016; Feng et al, 2016).

Three EQ-5D value sets are therefore now available for use in cost utility analysis in the UK and/or England, those being the EQ-5D-3L value set, the crosswalk value set mapping the EQ-5D-5L descriptive system onto the EQ-5D-3L value set, and the new EQ-5D-5L value set developed using the new EuroQol valuation protocol. The first two of these were developed based on valuations from respondents in the UK while the latter was based on valuations from respondents in England only. However, this is only one way in which they differ. As noted, they are also based on different descriptive systems, valuation protocols, and modelling methods. Given widespread and increasing use of the EQ-5D-5L, it is important to

systematically assess the differences between the value sets, and the implications of the new values. Therefore, the aim of this paper is to compare the UK EQ-5D-3L and English EQ-5D-5L value sets, and the EQ-5D-5L and crosswalk value sets.[1]

2 Methods

2.1 The value sets

In the sections below, EQ-5D health states are described using five numbers corresponding to each dimension and each level. The dimensions are listed in the order presented on the questionnaire (Mobility-Self Care-Usual Activities-Pain/discomfort-Anxiety/depression). For the EQ-5D-3L, 1 represents no problems, 2 some problems, and 3 extreme problems/confined to bed. Therefore state 22222 has some problems on each of the five dimensions. For the EQ-5D-5L, 1 represents no problems, 2 slight problems, 3 moderate problems, 4 severe problems, and 5 extreme problems/unable to. Therefore, in this case state 22222 has slight problems on each dimension.

2.1.1 EQ-5D-3L

The UK EQ-5D-3L value set (Dolan, 1997) was developed using data collected from 2,997 general population respondents who were sampled from the postcode address file. Each respondent completed a face-to-face interview and valued 13 states (12 EQ-5D-3L profiles plus 'unconscious') using TTO which included one procedure for states valued better than dead, and a different process for states valued worse than dead (for more information see Dolan, 1997). In total, 42 of the 243 EQ-5D-3L states were valued. The data were modelled using additive generalised least squares (GLS) regression to produce a value set ranging from 1 (for the best state, 11111) to -0.594 (for the worst state, 33333), with 34% of states given a negative value (i.e. valued as worse than dead). The model includes a constant subtracted for any move away from full health, a further decrement for each move away from 'no problems' for each dimension, and an additional term that is subtracted if any dimension is at the worst

[1] The EQ-5D-5L value set for England reported by Devlin et al. (2016) and analysed in this paper remains provisional at the time of writing. It should be considered as having interim status as the peer review process may necessitate changes to the analyses and results.

level (known as the N3 term). Another feature of the EQ-5D-3L value set is the large change in utility between 11111 and the next best state (11211) which is scored at 0.883.

2.1.2 Crosswalk

The interim crosswalk value sets were developed by van Hout et al (2012) from a multi-country study of respondents who completed both the EQ-5D-3L and EQ-5D-5L. The crosswalk used a non-parametric response mapping method to predict values that are anchored onto the EQ-5D-3L value set The decrements for the equivalent levels of the two descriptive systems are the same. This means that the decrements for level 3 of the EQ-5D-5L (moderate problems) are the same as level 2 of the EQ-5D-3L (some problems), and those for level 5 of the EQ-5D-5L are the same as level 3 of the EQ-5D-3L. This means that the range of values is the same (55555 on the EQ-5D-5L has the same value as 33333 on the EQ-5D-3L, and, taking an example intermediate state, 35353 on the EQ-5D-5L has the same value as 23232 on the EQ-5D-3L). The crosswalk can link EQ-5D-5L data to a range of existing international EQ-5D-3L value sets. For the purposes of this paper, we focus on the crosswalk to the UK value set developed by Dolan (1997).

2.1.3 EQ-5D-5L

The English EQ-5D-5L value set (Devlin et al 2016) was developed from 996 members of the general population who were purposively sampled from the Postcode Address File. Preferences were elicited using computer-assisted face-to-face valuation interviews. Respondents valued 10 EQ-5D-5L states using composite TTO (Janssen et al 2013), and completed seven DCE paired comparison tasks. In total 86 states were valued in the TTO exercise and 196 pairs in the DCE tasks. The data was modelled using heterogeneous hybrid approaches combining the TTO and DCE data (Feng et al, 2016). The resulting tariff ranges from 1 to -0.281, with 4.9% of the states valued as worse than dead. The model includes a decrement for each dimension for each move away from full health, and an extra ‘scalar’ coefficient. The range of values is therefore smaller than for the EQ-5D-3L, despite the considerable increase in the number of possible health states. The value of the mildest health states (21111 and 11211) is 0.951.

2.2 Analysis

We carried out analysis comparing the predicted values from each of the three value sets, and also using patient reported EQ-5D-3L and EQ-5D-5L data. The patient data used was taken from the crosswalk development study dataset where all respondents self-reported their health using both the EQ-5D-3L and EQ-5D-5L descriptive systems thereby enabling direct comparisons between the measures. The key comparisons carried out were between the EQ-5D-3L and EQ-5D-5L value sets, and the EQ-5D-5L value set and the crosswalk tariff.

2.3 Comparison of predicted values

2.3.1 Comparing value set models

Firstly, we compared the coefficient models used to calculate the values. This was done to assess the overall magnitude of the coefficients for each dimension, and the impact of the various interaction coefficients included in each model on the values produced. We also compared the process for calculating values using each method using an example health state.

2.3.2 Comparing value set characteristics

We assessed a range of descriptive statistics for all of the possible theoretical values (i.e. 243 for the EQ-5D-3L and 3,125 for the EQ-5D-5L), including the value set range, number of states valued as worse than dead, and the state with the smallest utility decrement from 11111. We looked at the modality of the overall distributions using kernel density histograms, and also compared the values of selected states to demonstrate differences between the value sets. This was done for the three value sets compared in this study

2.3.3 Comparing value set characteristics for matched states

We carried out a comparative analysis on the states that are comparable across the EQ-5D-3L and EQ-5D-5L (i.e. the matched 243 states). The crosswalk value set is not relevant here as for these states the values are the same as the EQ-5D-3L tariff due to the response mapping procedure used. We considered comparable states to be those from the intermediate levels of the EQ-5D-5L descriptive system (none, moderate and extreme/unable to) which, to a certain extent, 'match' the three-level states (as an example the EQ-5D-3L state 12321 is defined as

comparable to 13531 on the EQ-5D-5L). We assessed similarities and differences, both for individual states and overall, to highlight where the largest differences occur across the value sets.

2.3.4 Comparing differences in utility between adjacent states

Analysis was also carried out to understand how changes in health that could be reported by patients on the descriptive system are reflected by changes in utility within the value sets. This was done by assessing the values of adjacent states within the descriptive system, and comparing the differences across the three value sets. An adjacent state pair was defined as having one (and only one) dimension with a one-level change (for example calculating the change in value between 21111 and 11111). This was done for states where only one dimension changed at a time, so we focused on the change in utility between level 3/5 and level 1 on one dimension, with the other four dimensions held at the same level. For example, for mobility we compared the changes between 51111-41111-31111-21111 and 11111, and we repeated this for each of the five dimensions. The size of the descriptive system means that many comparisons are possible. However, we decided to focus on a small number of adjacent states so that an overall view of the change could be interpreted. The magnitude of the change between all level changes, and the matched states, was assessed. This analysis reflects the coefficient decrements in a different way and provides an insight about how change in self-reported health would lead to change in utility in the absence of longitudinal data.

2.4 Analysis on patient data

2.4.1 Data used:

The data used to develop the crosswalk value sets were used for the analysis. The data were collected online across a range of patient groups with different health conditions who completed both the EQ-5D-3L and EQ-5D-5L descriptive systems. Respondents from seven countries took part, but given the value sets that we are comparing, the analysis reported here only used the English and Scottish data. The characteristics of the 1,501 respondents from England and Scotland are reported in Table 1.

2.4.2 Comparing the descriptive system and value sets

Firstly, we compared the number of respondents reporting each level of the three-level and five-level descriptive system. This was done to understand how the addition of the extra levels changes response patterns. We compared the values reported using density plots, and also by assessing the scores overall and across patient groups (with the exception of those with a sample size of less than 50) using one way ANOVA. The mean difference statistics were also assessed. We also compared the agreement between the value sets using Bland Altman plots (Bland and Altman, 1986). These present the mean of two scores on the x axis and the difference on the y axis, with lines indicating the upper and lower limits of agreement (calculated as mean +/- 1.96 x standard deviation) added. Agreement across the full severity range can then be assessed, with points outside the limits defined as outliers.

3 Results

3.1 Comparison of models

The models used to derive EQ-5D-3L and EQ-5D-5L values are displayed in Table 2. In each case, the coefficient decrements are larger for the more severe levels of each dimension and are therefore ordered as expected. Both models include a constant term, and in the EQ-5D-3L this involves a decrement of 0.081 for the move away from the best health state (11111). The EQ-5D-5L constant is 1, but the model includes a set of scalar coefficients (which relate to the probability of belonging to one of the three latent classes in the model, and the slope of each group). The scalar coefficient has the overall impact of increasing the value of each state, and therefore reducing the overall utility range. The magnitude of the dimension level coefficients between the EQ-5D-3L and EQ-5D-5L varies (for example, pain/discomfort has a larger overall decrement on the EQ-5D-3L and anxiety/depression has a larger decrement on the EQ-5D-5L), and the extra interactions and scalars included in the models have a large impact. The EQ-5D-3L N3 term is an extra decrement when at least one of the levels is at the most severe (i.e. level 3), and therefore this reduces the value of the more severe states. As an example, table 2 also displays how to calculate a value for a state. The calculation of the value for EQ-5D-5L state 21223 and the corresponding EQ-5D-5L state 31335, and shows that the EQ-5D-3L coefficients produce a substantially lower value (0.186 vs. 0.510).

3.2 Comparison of value sets overall

Table 3 compares the descriptive characteristics of the three value sets. The EQ-5D-5L value set has a higher value for the worst possible health state and substantially fewer worse than dead values. Also, the decrement from the best (11111) to next best health state (11211) is smaller for the EQ-5D-5L value set, as expected given differences in the number of levels and labelling between the instruments (e.g. 11211 describes 'slight' problems performing usual activities in the five-level instrument and 'some' problems in the three-level version). In all three value sets, pain/discomfort has the largest overall decrement (but not at the less severe levels), while self-care and usual activities have the smallest.

Figure 1 compares all unique theoretical values for the EQ-5D-5L and EQ-5D-3L value sets, and the EQ-5D-5L and crosswalk. The results demonstrate that the range for the EQ-5D-3L (and therefore the crosswalk) is quite different from that for the EQ-5D-5L. Comparing panel 1, the large coefficients for level 3 on the EQ-5D-3L (and the impact of the N3 term) means that there is a higher density of lower values. The EQ-5D-5L is unimodal with moderate negative skew, whereas the EQ-5D-3L is more bimodal as has previously been observed (Parkin et al 2016).

3.3 Comparison of predicted values for matched states

Figure 2 displays the values of the comparable states from the EQ-5D-3L and the EQ-5D-5L value sets ordered by the EQ-5D-5L value (in descending order). The EQ-5D-3L health state values are consistently lower across the full severity range. Figure 3 shows a histogram of the differences for each comparable state across the value sets, and a box plot of the mean difference by utility score category as a proxy for severity (1 to 0.500; 0.499 to 0.200; 0.199 to 0; <0). The mean difference is large overall at 0.313 (sd 0.102; range 0.023 to 0.484). The mean difference increases as severity increases, and the difference is significant ($F_{2,238} = 184.3$, $p < 0.001$). The majority of the differences are between 0.3 and 0.4. Only 16 (6.6%) of 243 states have a mean difference smaller than 0.1, and 40 (16.4%) states have a difference of at least 0.4. The state with the largest difference is 32131 (0.484) and the state with the smallest difference is 11212 (0.023).

3.4 Comparing difference in adjacent states

Table 4 displays the change in utility between adjacent and matched states. Comparisons of the matched states between the EQ-5D-3L and EQ-5D-5L demonstrate that the change in adjacent states is substantially larger for the three-level tariff across all five dimensions, which again would suggest that the use of the EQ-5D-3L value set would result in larger QALY gains. Regarding the EQ-5D-5L value set, the largest change in value occurs in the moves from severe (level 4) to moderate (level 3) reported health problems. This is followed by the move from slight (2) to no problems (1). In contrast, the largest change in the crosswalk value set is between extreme/unable (5) to and severe (4) (linked to the N3 term in the EQ-5D-3L model) which is comparatively small in the EQ-5D-5L value set. The change in the crosswalk values from slight (2) to no problems (1) is larger than in the EQ-5D-5L value set. This means that interventions resulting in an improvement in both mild and more severe health may result in larger QALY gains if the crosswalk values were used.

3.5 Comparisons using patient data

3.5.1 Descriptive system comparisons

Table 5 displays the dimension level responses to the EQ-5D-3L and EQ-5D-5L and shows that the largest impact of the addition of the two intermediate levels (slight and severe) is to spread the 'some' responses on the EQ-5D-3L between levels 2 to 4 on the EQ-5D-5L. The introduction of 'slight' modestly reduces the ceiling effect as respondents move away from reporting no problems given the increased sensitivity for measuring less severe health problems. There is clear dispersion of scores from 'some' on the EQ-5D-3L across 'slight', 'moderate' and 'severe' on the EQ-5D-5L.

3.5.2 Value set comparisons

Figure 4 compares the EQ-5D-3L and EQ-5D-5L values, and EQ-5D-5L and crosswalk values. It can be seen that for the EQ-5D-3L there is not only a large decrease in the very mild area (due to the upper gap reflected by the large constant), but also in the moderate area around the values 0.25 to 0.45. In contrast the EQ-5D-5L has a smoother distribution. This reflects the added benefit of EQ-5D-5L: the increased sensitivity results in a much smoother

transition between adjacent values that are closer together than on the EQ-5D-3L. Comparing the EQ-5D-5L and crosswalk value sets, it can be seen that the crosswalk data is smoother, whereby the lack of EQ-5D-3L values in the range between 0.25 and 0.45 is not apparent.

Figure 5 compares the EQ-5D-3L and crosswalk values with the EQ-5D-5L and shows that there are differences in values across the entire severity scale, but greater variation for more severe health states (where the mean utility value is lower). Figure 6 displays Bland Altman plots comparing EQ-5D-3L and EQ-5D-5L, and EQ-5D-5L and crosswalk scores. There is evidence of disagreement between values across the severity scale, where the difference in utility values is outside the +/- 2 SD range. Disagreement means more diverse utility scores for states of a similar severity.

The mean difference between the EQ-5D-3L and EQ-5D-5L values as reported by the patient sample is 0.086 (range 0.952 to -0.897). Some respondents are inconsistent and this results in the wide range overall. For example, the difference of 0.952 results from a patient reporting 11112 on EQ-5D-3L and 44444 on EQ-5D-5L. Comparing the EQ-5D-5L and crosswalk value sets, the mean difference is 0.091 with a range from 0.001 for the smallest non zero difference (states 43544 and 41221) to 0.45 (for state 44444).

Table 6 compares the value set scores overall and across the different health conditions reported in the patient data with significance statistics reported for the conditions including more than 50 patients. As would be expected, the EQ-5D-5L value set scores are higher for all conditions than the EQ-5D-3L and crosswalk, and the difference is significant for all conditions except for rheumatoid arthritis and ADHD. The percentage of states worse than dead overall and also across each condition is lower for the EQ-5D-5L. Table 6 also displays the rank order of the severity of the conditions according to the mean utility values generated for each value set. There is evidence of consistency for seven of the 12 conditions, including the most (Parkinson's disease) and third most (back pain) severe conditions, and the five least severe (ADHD, breathing problems, arthritis, depression and diabetes) as scored by the value sets. The most variable condition is multiple sclerosis, which is second most severe for the EQ-5D-3L, but fifth and seventh overall for the crosswalk and EQ-5D-5L value sets respectively.

4 Discussion

We have compared three EQ-5D value sets for use in HTA in the UK. The comparison firstly investigated differences in the 'theoretical' values possible from the value sets for health states matched across the EQ-5D-3L and EQ-5D-5L descriptive systems and secondly compared values observed in patient data.

Regarding the theoretical values, the results demonstrate that there are differences between the EQ-5D-3L and EQ-5D-5L value sets, where the EQ-5D-5L values for matched states are higher, and the overall range and therefore change between adjacent states is smaller than for the EQ-5D-3L. The distribution of values also differs. There are also similar differences between the EQ-5D-5L value set and the crosswalk tariff given that the latter is linked to the EQ-5D-3L value set. However, it is also worth noting that some underlying features of the preferences, and therefore utility scales, are similar. For example, the overall importance of each dimension is similar, with only one difference (where the rank order of the dimensions is the same, apart from two dimensions, mobility and anxiety/depression, changing position in the ordering), and the relative distance between the levels for different dimensions is similar.

Regarding the observed values from the patient data, the EQ-5D-5L value set produces higher values overall and across all of the conditions included, and the differences are generally significant. This is expected given the overall increase in the values of matched states and reduction in the overall utility scale. There is some evidence that the value sets rank different health conditions in a similar order, particularly the most and least severe conditions as measured by the descriptive system. However, this requires further exploration across a larger range of conditions.

There are a number of possible reasons why the EQ-5D-3L and EQ-5D-5L value sets differ. These include differences in the samples used in terms of demographics and country. The project team has since collected EQ-5D-5L valuation data for the other countries in the UK so will be able to compare using a more representative sample (albeit one that is smaller than that used for the EQ-5D-3L). Assessing the impact of other demographic differences is

difficult, as is assessing potential changes in population preferences over time, which is another possible reason why the value sets demonstrate differences. One indication of this might be the increased magnitude of the anxiety/depression dimension given increased focus on the detrimental aspects of mental health conditions in policy (Layard, 2015), and reduction in stigma surrounding conditions such as depression (Rusch et al, 2005). Overall the dimension preference structure between the EQ-5D-3L and EQ-5D-5L is similar, with only one inversion (anxiety/depression and mobility) which is encouraging given the differences between the studies. This may demonstrate that preferences for the dimensions are generally consistent over time and changes in population preferences for the dimensions are not a major factor in the differences seen.

Other reasons why the value sets may differ relate to the descriptive system and the valuation method used. Firstly, regarding the descriptive system, the EQ-5D-5L uses more consistent wording, particularly for the more severe levels, and it is possible that the change in labelling of the mobility dimension (from 'confined to bed' to 'unable to walk about') has impacted on the values, where mobility has a smaller weighting in the EQ-5D-5L than in the EQ-5D-3L. The increase in levels and associated sensitivity also may impact the magnitude of the difference and transition between the intermediate levels and therefore the overall value set.

Secondly, the valuation method differs, particularly regarding the process used to value states worse than dead which was problematic for the EQ-5D-3L (Lamers et al 2007). The methodological change to a new approach to eliciting values < 0, the lead time TTO meant that the lowest possible value for an EQ-5D-5L health state in the protocol used was -1 (Devlin et al 2010; Janssen et al 2013), in contrast to -39 in the Dolan (1997) study, which was rescaled to -1, and this therefore led to a reduction in the overall scale. The inclusion of DCE tasks, which provides a different type of valuation data focusing on the choices between states rather than measuring direct values for states as is the case with TTO, and the development of innovative modelling methods combining TTO and DCE data in one model (see e.g. Rowen et al 2014; Ramos-Goni et al 2015) is another reason for differences in the value sets. The modelling process for the EQ-5D-5L data also developed heterogeneous models for the TTO data only (Feng et al 2016), and further work is underway to model the EQ-5D-3L valuation data applying the methods developed for the 5L.

There are also large differences in the proportion of states valued as worse than dead (i.e. with a negative value) and the associated values assigned to these states which has resulted in a smaller range. The impact of this is unclear, as it is not well established how often states that are actually worse than dead appear in cost effectiveness models, and there are not many in the crosswalk data we use in this study. As the overall scale of the EQ-5D-5L is smaller, the change in QALYs (for estimates generated from quality of life changes) will be reduced across the whole scale for states both better and worse than dead.

It is unclear how the differences between the value sets indicated in both analysis of the estimates and patient data will impact the HTA process. This is because the utility values will be applied to both treatments and their comparators, and therefore to some extent the differences may be even, and the estimates of improvements in quality of life between arms of a clinical trial will be similar using the EQ-5D-3L or EQ-5D-5L value sets. The increased sensitivity of the EQ-5D-5L may also favour QALY gains even if the changes in utility are smaller, and an added complexity is whether the gain is linked to quality of life or survival. This requires further investigation on clinical trial data, which is the next proposed step of this programme of research, and is being investigated by other researchers (Hernandez et al 2016).

There are also implications for the NICE reference case. The improvement in the methods used to both collect and model the valuation data, and the increased use of the improved descriptive system, make a strong case for the use of the new EQ-5D-5L value set. The EQ-5D-3L value set has benefits if the instrument is still being used in trials and other settings, but is based on societal preferences from decades ago. The crosswalk draws on the EQ-5D-3L values so is prone to the same issues as that value set. There is also the potential for 'gaming' where the crosswalk may be used instead of the EQ-5D-5L value set to inflate QALY gains (as the utility range, and therefore change between states, is larger). One important point is how to compare results of cost utility analyses using the EQ-5D-5L against those using the EQ-5D-3L and establishing the cost per QALY thresholds that should be used. Further work is required to explore this.

The main limitation of this study is that we have not tested the impact of the value sets on any clinical trial data which would have enabled us to directly compare QALY estimations. This would allow us to test some of the issues raised in data previously used for cost utility

analysis, and is the next planned stage of this programme of research. It will also be important to compare the psychometric performance, and impact on cost utility analysis, of the EQ-5D-5L descriptive system and value set with those of other widely used generic measures. In particular, comparisons with version two of the SF-6D (SF-6Dv2; Mulhern & Brazier, 2014) which has been valued using DCE with duration methods would be interesting.

In conclusion, we have demonstrated key differences in the theoretical and observed values from a number of EQ-5D value sets that can be used in HTA. The value sets will lead to differences, and the use of the EQ-5D-5L value set will have implications for the decision-making process carried out by NICE and may require revision to the guidelines used.

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Tables and Figures

Table 1: Demographic characteristics of the crosswalk data used for the comparative analysis

Demographic	N(%)
N	1,501
Country	
Scotland	500
England	1,001
Age	
Mean (sd)	57 (16)
Range	19 - 94
Gender male	734 (49)
Education	
1	485 (32)
2	339 (23)
3	353 (24)
4	290 (19)
5	34 (2)
Condition	
COPD	320 (21)
Heart problems	251 (17)
Arthritis	250 (17)
Depression	250 (17)
Rheumatoid arthritis	87 (6)
Stroke	85 (6)
Back pain	70 (5)
ADHD	69 (5)
Diabetes	45 (3)
Parkinson's	37 (3)
Breathing problems	22 (2)
Multiple sclerosis	15 (1)

Taken from van Hout et al (2012)

Table 2: Comparing the EQ-5D-3L and EQ-5D-5L models

Parameters	EQ-5D-3L	EQ-5D-5L	Value calculation (21223/31335)	
			EQ-5D-3L	EQ-5D-5L
Constant	0.081			
EQ-5D dimensions				
Mobility	0	0		
None				
Slight		0.051		
Some/Moderate	0.069	0.063	0.069	0.063
Severe		0.212		
CTB*/Unable to	0.314	0.275		
Self-care	0	0	0	0
None				
Slight		0.057		
Some/Moderate	0.104	0.076		
Severe		0.181		
Unable to	0.214	0.217		
Usual Activities	0	0		
None				
Slight		0.051		
Some/Moderate	0.036	0.067	0.036	0.067
Severe		0.174		
Unable to	0.094	0.190		
Pain/discomfort	0	0		
None				
Slight		0.060		
Some/Moderate	0.123	0.075	0.123	0.075
Severe		0.276		
Extreme	0.386	0.341		
Anxiety/depression	0	0		
None				
Slight		0.079		
Some/Moderate	0.071	0.104		
Severe		0.296		
Extreme	0.236	0.301	0.236	0.301
Interactions				
EQ-5D-3L N3 term	0.269		0.269	
EQ-5D-5L scalars				0.397x0.427+0.270x 0.939+0.333x1.635=0.9675
Prob. (group 1)		0.397		
Prob. (group 2)		0.270		
Prob. (group 3)		0.333		
Slope (group 1)		0.427		
Slope (group 2)		0.939		
Slope (group 3)		1.635		
Value of state			1-0.081-0.069-0-0.036-0.123-0.236-0.269=0.186	1-0.9675x(0.063+0+0.067+0.075+0.301) = 0.510

*CTB: Confined to bed

Table 3: Overall descriptive characteristics of the three value sets (modelled values)

	EQ-5D-3L value set	EQ-5D-5L crosswalk	EQ-5D-5L value set
Range	1 to -0.594	1 to -0.594	1 to -0.281
% health states worse than dead	34.6% (84 out of 243)	26.7% (833 out of 3,125)	4.93% (154 out of 3,125)
Dimension importance order §	Pain/Discomfort Mobility Anxiety/depression Self-care Usual Activities	Pain/Discomfort Mobility Anxiety/Depression Self-care Usual Activities	Pain/Discomfort Anxiety/depression Mobility Self-care Usual Activities
Health state values			
'Mildest' state (11211)*	0.883	0.906	0.951 (11211/21111)
'Moderate' state (22222 (3L) or 33333 (5L))	0.516	0.516	0.628
'Worst' state (33333 (3L) or 55555 (5L))	-0.594	-0.594	-0.281

§Importance is judged by the size of the coefficient for level 5 in each dimension.

*Note that for each of the asterisked health states, the level of problems indicated on the five-level and three-level versions of EQ-5D differ: for example, on the EQ-5D-5L, 11112 means no problems on any dimension except *slight* problems with anxiety/depression, whereas on the EQ-5D, 11112 means no problems on any dimensions except *some* problems with anxiety/depression. A priori, we would expect the values for these health states to be higher in the EQ-5D-5L value set than the EQ-5D value set, which is what we observe.

Table 4: Comparing the change in utility between adjacent health states

	EQ-5D-5L value set			Crosswalk value set			EQ-5D-3L value set		
EQ-5D-5L state	Value	Difference	Difference matched	Value	Difference	Difference matched	EQ-5D-3L state	Value	Difference
11111	1.000			1.000			**11111**	1.000	
21111	0.951	0.049		0.877	0.123				
31111	0.939	0.012	0.061	0.850	0.027	0.150	**21111**	0.850	0.150
41111	0.795	0.144		0.813	0.037				
51111	0.734	0.061	0.205	0.336	0.477	0.514	**31111**	0.336	0.514
11111	1.000			1.000			**11111**	1.000	
12111	0.945	0.055		0.846	0.154				
13111	0.926	0.019	0.074	0.815	0.031	0.185	**12111**	0.815	0.185
14111	0.825	0.101		0.723	0.092				
15111	0.790	0.035	0.136	0.436	0.287	0.379	**13111**	0.436	0.379
11111	1.000			1.000			**11111**	1.000	
11211	0.951	0.049		0.906	0.094				
11311	0.935	0.016	0.065	0.883	0.023	0.117	**11211**	0.883	0.117
11411	0.832	0.103		0.776	0.107				
11511	0.816	0.016	0.119	0.556	0.220	0.327	**11311**	0.556	0.327
11111	1.000			1.000			**11111**	1.000	
11121	0.942	0.058		0.837	0.163				
11131	0.927	0.015	0.073	0.796	0.041	0.204	**11121**	0.796	0.204
11141	0.733	0.194		0.584	0.212				
11151	0.670	0.063	0.257	0.264	0.320	0.532	**11131**	0.264	0.532
11111	1.000			1.000			**11111**	1.000	
11112	0.924	0.076		0.879	0.121				
11113	0.899	0.025	0.101	0.848	0.031	0.152	**11112**	0.848	0.152
11114	0.714	0.185		0.635	0.213				
11115	0.709	0.005	0.190	0.414	0.221	0.434	**11113**	0.414	0.434

Table 5: Dimension level responses across the EQ-5D-3L/EQ-5D-5L (English and Scottish data)

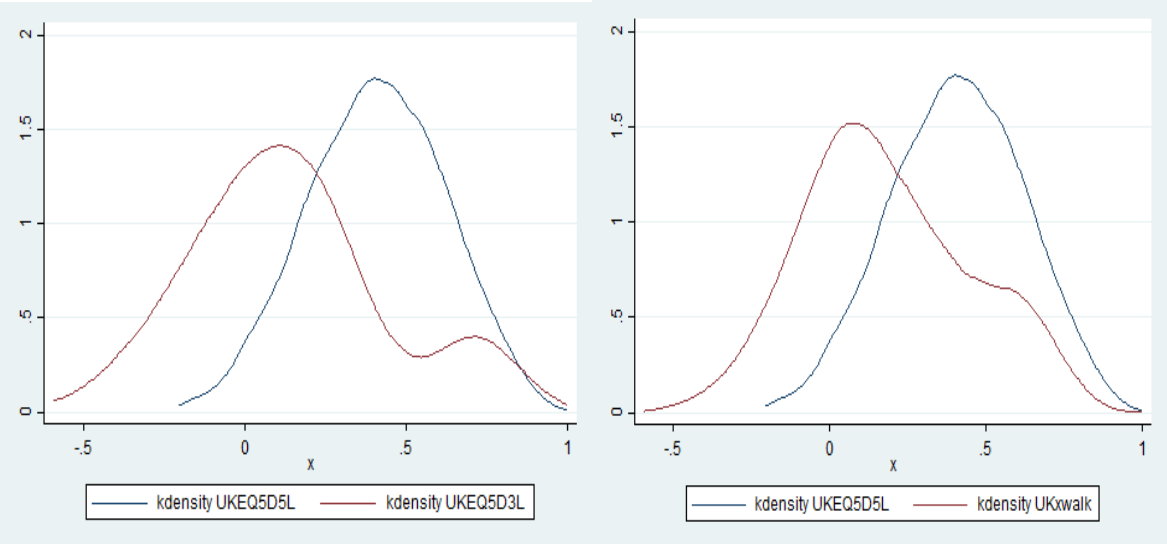
Dimension responses	EQ-5D-3L (n,%)	EQ-5D-5L (n,%)
Mobility		
None	506 (33.7)	435 (29.0)
Slight		392 (26.1)
Some/Moderate	983 (65.5)	377 (25.1)
Severe		277 (18.5)
CTB*/Unable to	12 (0.8)	20 (1.3)
Self-care		
None	951 (63.4)	907 (60.4)
Slight		301 (20.1)
Some/Moderate	517 (34.4)	201 (13.4)
Severe		74 (4.9)
Unable to	33 (2.2)	18 (1.2)
Usual Activities		
None	464 (30.9)	390 (26.0)
Slight		447 (29.8)
Some/Moderate	881 (58.7)	358 (23.9)
Severe		228 (15.2)
Unable to	156 (10.4)	78 (5.2)
Pain/discomfort		
None	380 (25.3)	303 (20.2)
Slight		447 (29.8)
Some/Moderate	947 (63.1)	449 (29.9)
Severe		243 (16.2)
Extreme	174 (11.6)	59 (3.9)
Anxiety/depression		
None	672 (44.8)	571 (38.0)
Slight		444 (29.6)
Some/Moderate	721 (48.0)	324 (21.6)
Severe		111 (7.4)
Extreme	108 (7.2)	51 (3.4)

Table 6: Comparing value set scores overall and across different conditions

Demographic	N	EQ-5D-3L				Crosswalk				EQ-5D-5L				Significance	
		Mean (sd)	Range	% SWD	Sev order	Mean (sd)	Range	% SWD	Sev order	Mean (sd)	Range	% SWD	Sev order	3L - 5L	5L - Xwalk
Overall	1,501	0.577 (0.31)	1 to -0.594	8.6		0.571 (0.28)	1 to -0.594	4.5		0.662 (0.27)	1 to -0.281	2.2		<0.001	<0.001
Condition															
COPD	320	0.546 (0.32)	1 to -0.349	11.3	6	0.558 (0.29)	1 to -0.292	1.9	6	0.641 (0.28)	1 to -0.185	5.0	5	<0.001	<0.001
Heart problems	251	0.567 (0.32)	1 to -0.429	6.8	7	0.559 (0.29)	1 to -0.594	4.8	7	0.649 (0.27)	1 to -0.281	1.2	6	0.002	<0.001
Arthritis	250	0.636 (0.23)	1 to -0.181	5.6	10	0.618 (0.21)	1 to -0.134	0.8	10	0.718 (0.21)	1 to -0.063	0.4	10	<0.001	<0.001
Depression	250	0.643 (0.30)	1 to -0.349	6.8	11	0.640 (0.27)	1 to -0.160	3.6	11	0.727 (0.24)	1 to -0.165	2.0	11	0.001	<0.001
Rheumatoid arthritis	87	0.480 (0.34)	1 to -0.239	14.9	4	0.455 (0.31)	1 to -0.353	8.0	2	0.544 (0.32)	1 to -0.185	8.0	2	0.200	0.062
Stroke	85	0.521 (0.32)	1 to -0.074	9.4	5	0.523 (0.29)	1 to -0.122	9.4	4	0.620 (0.27)	1 to -0.021	1.2	4	0.022	0.024
Back pain	70	0.475 (0.28)	1 to -0.319	10.0	3	0.466 (0.28)	1 to -0.472	8.6	3	0.579 (0.26)	1 to -0.231	4.3	3	0.025	0.015
ADHD	69	0.587 (0.33)	1 to -0.349	8.7	8	0.571 (0.28)	1 to -0.116	2.9	8	0.661 (0.27)	1 to -0.117	2.9	8	0.150	0.056
Diabetes	45	0.723 (0.25)	1 to -0.016	2.2	12	0.707 (0.24)	1 to 0.093	0	12	0.783 (0.22)	1 to 0.018	0	12	NR	NR
Parkinson's	37	0.431 (0.43)	1 to -0.594	18.9	1	0.410 (0.36)	1 to -0.594	13.5	1	0.497 (0.36)	1 to -0.281	16.2	1	NR	NR
Breathing problems	22	0.616 (0.26)	1 to -0.181	4.5	9	0.616 (0.22)	1 to 0.206	0	9	0.703 (0.22)	1 to 0.185	0	9	NR	NR
Multiple sclerosis	15	0.474 (0.37)	1 to -0.074	20.0	2	0.533 (0.31)	1 to -0.104	6.7	5	0.653 (0.26)	1 to 0.030	0	7	NR	NR

Sev order: Most severe mean value for each condition (where 1 is the most severe)

Figure 1: All unique theoretical values



Panel 1: All unique "theoretical" EQ-5D-3L and EQ-5D-5L values
Panel 2: All unique "theoretical" Crosswalk and EQ-5D-5L values

Figure 2: Values of comparable states ordered by EQ-5D-5L value

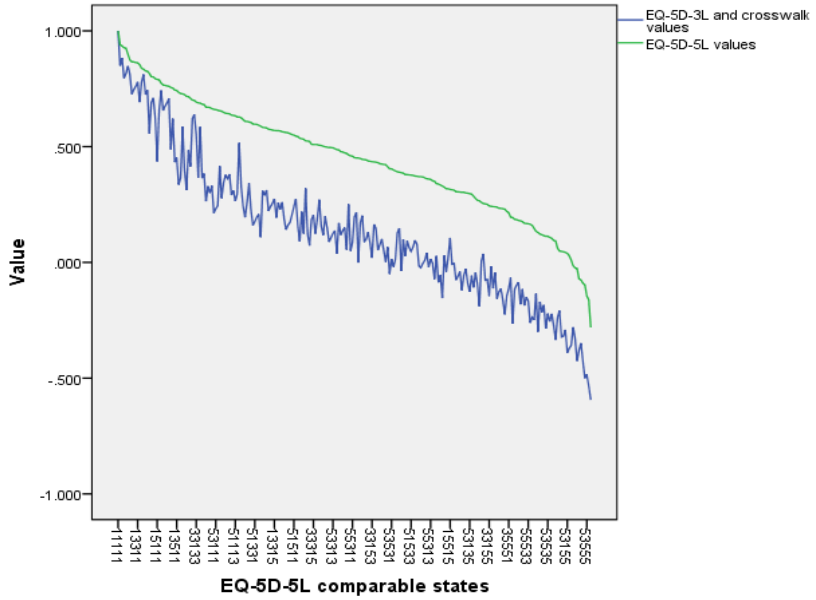


Figure 3: Histogram and boxplot of differences between the EQ-5D-3L and EQ-5D-5L value sets

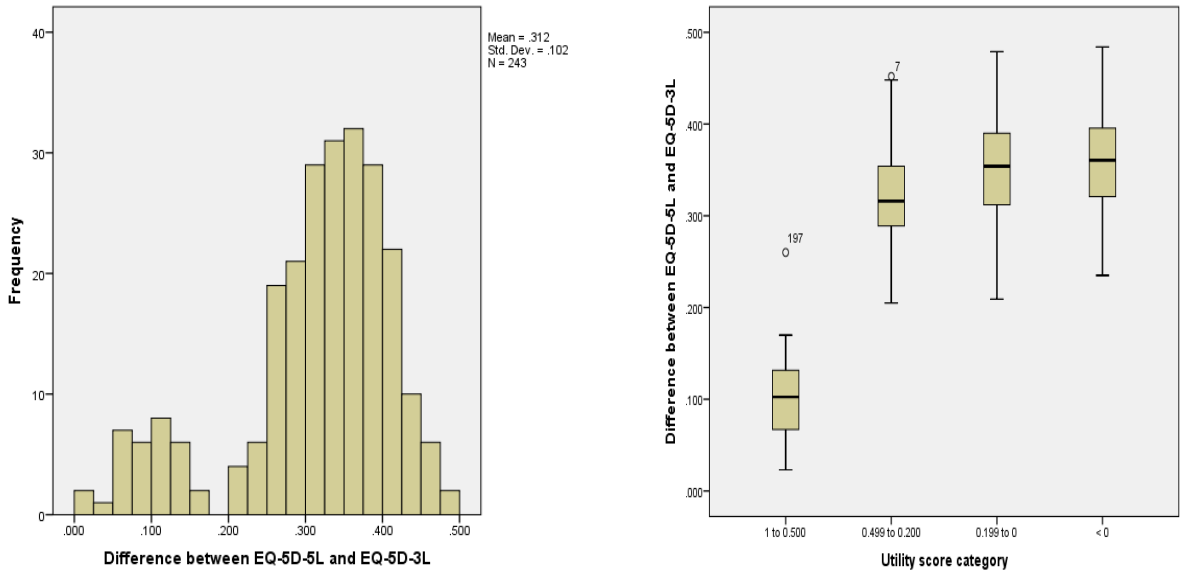
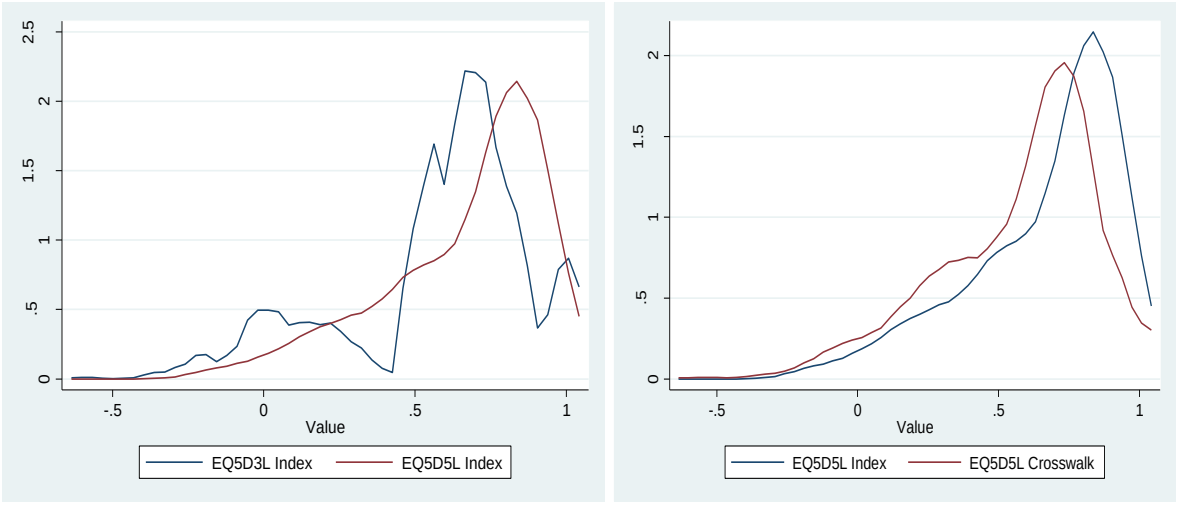


Figure 4: Density plot of all observed values from the English/Scottish crosswalk dataset



Panel 1: All observed EQ-5D-3L and EQ-5D-5L values
Panel 2: All observed crosswalk and EQ-5D-5L values

Figure 5: EQ-5D-3L and crosswalk patient values ordered by EQ-5D-5L

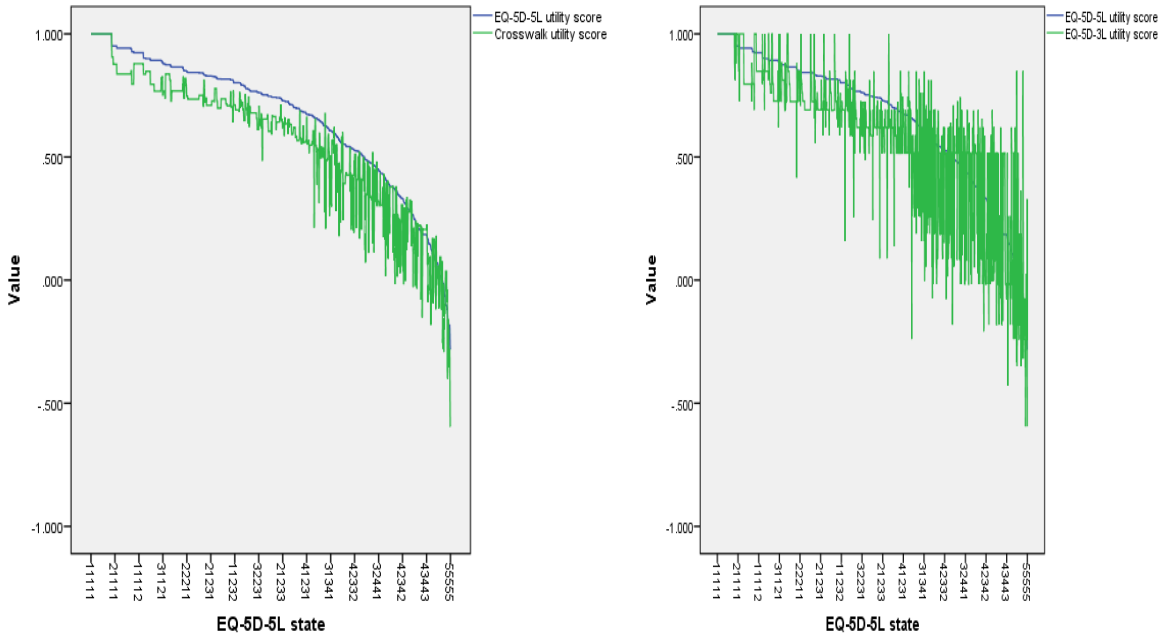
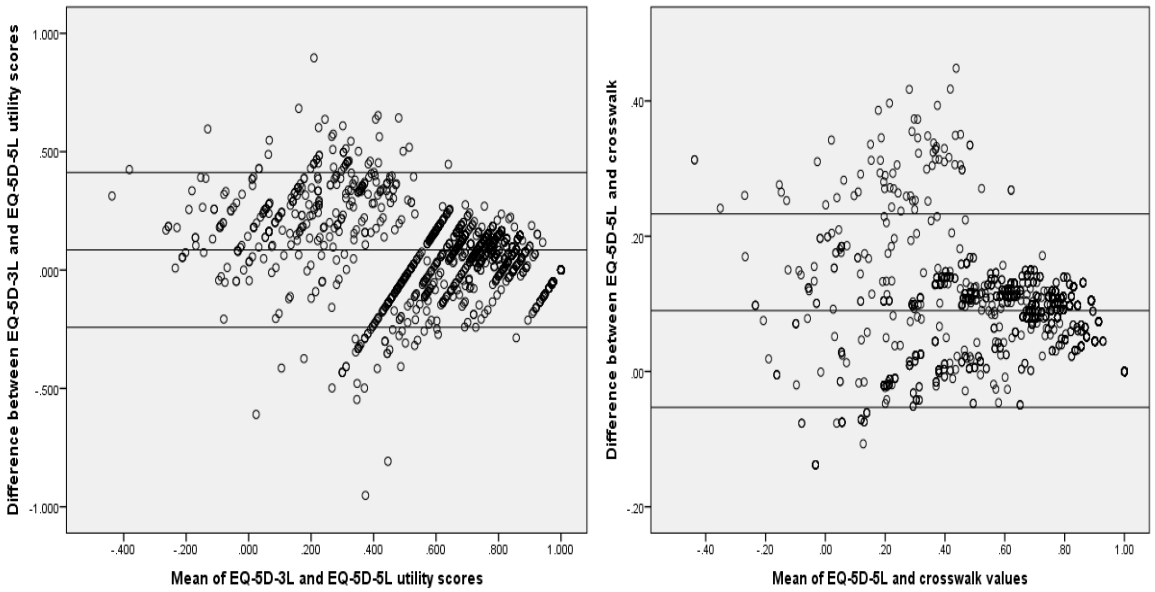



Figure 6: Bland Altman plots comparing EQ-5D-3L and EQ-5D-5L, and EQ-5D-5L and crosswalk scores