******WORK IN PROGRESS NOT FOR QUOTATION******

THE IMPACT OF USING DIFFERENT TARIFFS TO VALUE EQ-5D: A COMPARISON OF EQ-5D SCORES OBTAINED USING THE EUROPEAN HARMONISED VALUE SET WITH EQ-5D SCORES OBTAINED USING COUNTRY SPECIFIC VALUE SETS AND UK VALUE SET IN PATIENTS WITH LOWER RESPIRATORY INFECTIONS

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ABSTRACT

Aims: There is no consensus over whether and/or when the European value (EVS) set should be used in place of country specific value sets (CVS) when assessing quality of life using the EQ-5D in European cross-national studies. This study compares EQ-5D scores obtained using the EVS with those obtained using Country specific value sets and the UK value set (UKVS) with the aim of determining what effect the different tariffs have on valuation of EQ-5D health states for patients with cough and lower respiratory tract infections.

Methods: Data on health outcomes were collected in 7 European countries. EQ-5D index scores were generated for each country using the CVS, EVS and UKVS. The correlation coefficient and Bland-Altman plots were used to test the agreement between the index scores generated from the three value sets in each country. Regression analysis was used to test the relationship between severity scores and the EQ-5D index scores generated from the different value sets in each country. The construct validity of EQ-5D with each tariff was also assessed in patients with lower respiratory tract infections.

Results: EQ-5D scores obtained using the EVS showed a similar trend to values obtained using the individual country tariffs in all countries. However, there was a significant difference

scores obtained with different value sets. EQ-5D scores obtained with the EVS were higher than those obtained using the CVS in Wales, England, Finland and Belgium whilst in the Netherlands and Germany; country specific tariffs generated higher index scores than the EVS. There was considerable agreement between the three set of scores for each country. All value sets were able to discriminate between factors that were related to dimensions in the EQ-5D.

Discussion: We would welcome discussion on the following issues: Should all countries use similar methods? Should all countries use a single value set? What value set should be used in multi-country studies? Comments on the methods used in this study

BACKGROUND

Under an extra-welfarist perspective, the economic evaluation of interventions is particularly aided by the use of a generic preference based measure that can provide a single index for overall health. The EuroQol's EQ-5D measure provides such an index (The EuroQol group, 1990; Sullivan and Ghushchyan, 2006). This measure comprises a visual analogue scale (the thermometer) with which individuals can rate their own health state and a descriptive system with five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which is sub-divided into 3 levels:. The levels for each dimension are, effectively, no problems, some problems and severe problems, resulting in the definition of 243 separate states (Drummond et al., 2005). States are defined by a number representing the level on each of the five dimensions. For example state 21223 would be a state with some problems in terms of mobility, no problems in terms of self-care, some problems in terms of usual activities, some pain and severe anxiety/depression. State 11111 is equivalent to full health and dead is given a value of 0.

Individual's self-rated assessment of their health state on this measure can then be used to generate a single health related quality of life value (Kind, 2003). To generate this single index for all 243 states, value sets for individual countries have been developed. Currently, there are value sets for 12 different countries (Luo et al., 2007). The UK value set (UKVS) is the most common and frequently used value set (Huang et al., 2007; Sakthong et al., 2009). The UKVS has also been used in cases where there is no country specific value set (Huang et al., 2007; Sakthong et al., 2009).

For the UK valuation study, data were collected from non-institutionalised adults in England, Scotland and Wales between August and December 1993. Respondents were drawn from the

national postcode address file. In a face-to-face time trade-off exercise, each respondent valued 2 very mild states, 3 mild states, 3 moderate states, and 3 severe states drawn from a subset of 41 health states. All respondents also valued full health (11111), the most severe state (33333), as well as unconscious and dead (Dolan, 1997; MVH Group, 1995). After applying exclusion criteria (respondents without complete valuation data were excluded), a total of 2997 patients were included in the analysis. A generalised least square technique was used to develop an algorithm. Dummy variables allowed for interactions between dimensions and a dummy N3 which indicated if any variable was at level 3. The model used to produce the value set is commonly known as the N3 model.

Most other countries that have developed country specific value sets have followed the general form of the UK protocol (Greiner et al., 2005; Lamers et al., 2006; Ohinmaa et al., 1996 Ohinmaa et al., 1999; Badia et al., 1997), including all those European countries whose tariff has then been used in the development of a combined value set. These European countries comprise Finland, Germany, Netherlands, Spain as well as the UK. None of the studies were as large as that conducted in the UK, with numbers included in the development of value sets ranging from 294 in Spain to 1634 in Finland. Other differences from the UK study include the total number of scenarios valued (ranging from 11 to 43), the means of data collection which in some cases was by postal survey rather than face-to-face interview (Dolan, 1997), the use of different 'props' to aid the collection of time trade-off data (Lamers et al., 2006), and the application of different exclusion criteria in the analysis of data (Greiner et al., 2005).

From the European studies that have been conducted, a further combined value set has been generated to aid the comparison of health state values in multinational studies. This is known as the European value set (EVS) and, in generating this tariff, data were included from 11 studies across the six European countries for which individual country tariffs are available. In some countries, (for example, Germany) more than one study was used (Wolfgang et al., 2003). After applying the exclusion criteria, (respondents with incomplete data and respondents with inconsistent responses) the number of patients that were included in the analysis was 6870. To generate the EVS, a multi-level random effects model with evaluations of health states (level 1) nested within respondents (level 2) and respondents nested within studies (level 3) was used. This model included dummies to account for differences in study designs (Wolfgang et al., 2003).

This EVS contains data from both Northern and Southern European countries (although not from Eastern European states) and thus provides, potentially, a particularly useful means of applying values to EQ-5D outcomes in large cross-European economic evaluations. Potential advantages of using the EVS are that it can be applied in European countries for which there is no country specific value set available, and that it provides consistency in the values applied to those countries for which there is a country specific value set. With respect to this latter potential advantage, however, there is little discussion, and no consensus, on when it is appropriate to use the EVS in place of a country's own value set (Huang et al., 2007). Only one recent study has looked at the alternative value sets in Europe (Bernert et al., 2009) which produces valuable findings but is not related to a patient population and is unable to look at change following interventions. Given that some European studies have chosen to use the UKVS rather than the EVS, it is also worth asking whether the UKVS can be generalised to other settings.

This study aims to compare the EQ-5D scores obtained with the EVS with scores obtained from the country specific value sets (CVS) and the UKVS. The UKVS is chosen as a separate comparator because of its use in other non-UK studies. The comparison is undertaken in the context of lower respiratory tract infections (LRTI) for which EQ-5D has been used in the past (Allin et al., 2001). Although the EQ-5D has been validated in related areas such as COPD and asthma (Pickard et al., 2008; McTaggart Cowan et al., 2008) it has not been formally validated in the context of LRTI for any of the value sets potentially available for use in a European context. As a secondary objective, therefore, the paper also considers the validity of the EQ-5D with its various tariff options in relation to LRTI.

METHODS

Study Population

This study used data collected alongside the *Genomics to combat Resistance against Antibiotics in Community- acquired LRTI in Europe* (GRACE) observational study of the management of patients with cough and LRTI in primary care (Butler et al., 2009). Data were collected from adult patients over the age of 18 reporting to their primary care clinician with cough and LRTI in 13 European countries. The countries included in the GRACE study were UK (Wales and England), Netherlands, Spain, Germany, Hungary, Belgium, Poland, Italy, Sweden, Norway, Finland and Slovakia. However, for the purpose of this study, data from just the seven countries

for which CVSs were available were included. These countries were Belgium, England, Finland, Germany, Netherlands, Spain and Wales.

Data collection

Two main sources of data were used for the study, a patient completed diary and a case report form (CRF).

Patient diary

The patient diary was provided to patients at their entry to the study and asked for both baseline data and date over the subsequent four weeks. Data collected included EQ-5D, symptom scores and socio-demographic data.

EQ-5D

Patients were asked to complete the EQ-5D questionnaire at baseline and then weekly for four weeks or until he/she felt well. Value sets for the various countries and the EU harmonised value set were obtained from the EuroQol group and were applied to data from the seven countries that were included in the study to generate EQ-5D index scores.

Symptoms Diary

Patients filled in a symptoms diary on a daily basis for 28 days or until they got well. Patients were asked to score the severity of symptoms associated with LRTI (cough, phlegm, shortness of breath, wheezing, blocked nose, chest pain, fever, muscle ache, headache, disturbed sleep, feeling unwell, interference with normal activities, and interference with social activities) using a validated measure (Watson et al., 2001). The scores on this instrument range from 0 to 6 for each item. Higher scores indicate worse symptoms. To develop a severity score from the patient diary, the 13 symptoms were summed and then the resultant score was scaled to range between 0 and 100 (Butler et al., 2009).

Socio-demographic data

The patient diary included information on the age, gender, employment status as well as years spent in education.

Case Report Form

Primary care physicians collected a variety of data at baseline using the CRF. These data included the clinician's view of the symptoms with which the patient was presenting including cough, phlegm, shortness of breadth, wheeze, coryza (blocked/runny nose), fever, chest pains, muscle aching, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation, and diarrhoea. The clinician rated each symptom using a score of 0 to 4. The same method was used to generate clinician severity scores as was used to generate patient severity scores from the symptoms. It should be noted, however, that these scores are not directly comparable because of the different perspectives, the different initial scoring systems and the different symptoms included. Clinicians also indicated whether a patient had co morbidities in the CRF and recorded the use of medical investigations and the choice about whether to prescribe antibiotics.

Data Analysis

Descriptive summary statistics were generated for all the main variables. Plots of the mean EQ-5D scores as measured by the different value sets were constructed to examine trends from baseline to week four. As a result of the non-normality of the EQ-5D scores, the Kruskal-Wallis test (Ott, 1993) was applied to measure the mean difference in the EQ-5D scores across the seven countries. The Wilcoxon signed rank sum test, spearman correlation coefficients and Bland-Altman plots were used to determine whether there was agreement between the EQ-5D scores obtained from the CVS, EVS and the UKVS at baseline, weeks one, two, three and four. In addition, the ability of the scores obtained from the CVS, EVS and UKVS to discriminate between patients with particular characteristics was tested. The characteristics tested were three specific symptoms (headache, interference with normal activities and disturbed sleep) and three co-morbidities (diabetic, heart and respiratory). The particular symptoms were chosen from those available within the symptom diary as being particularly likely to be related to particular dimensions of the EQ-5D (headache to pain; interference with normal activities to usual activities; and disturbed sleep to anxiety/depression). In considering the ability of the different tariffs to discriminate, it is helpful to choose those symptoms that are most likely to be related to EQ-5D scores. Differences in the EQ-5D score (with each value set) between the groups with and without the symptom or co-morbidity were tested using the Mann-Whitney test and the relative precision was calculated using the ratio of the Z-statistics (Sakthong et al., 2009; Huang

et.,al 2007; McHorney et al., 1992) to determine which value set discriminated between the known groups more efficiently.

In order to ascertain the construct validity of EQ-5D in patients with LRTI, a number of *a priori* hypotheses were developed and tested. In all cases, the relationships were tested with all the value sets. The following hypotheses were tested:

EQ-5D scores should increase if symptom scores decrease

It was expected that there would be an inverse relationship between severity scores and EQ-5D. Controlling for co morbidities at baseline, regression analysis was used to explore the relationship between severity scores and EQ-5D. The same process was used to establish whether there was a negative relationship between severity scores and EQ-5D at week one to week four.

Antibiotics are prescribed to patients with a lower EQ-5D score

It was anticipated, based on current literature, that clinicians would be more likely to prescribe antibiotics to patients with lower EQ-5D scores. Due to diagnostic uncertainties, clinicians normally rely on medical history and physical examination (Metlay et al., 1997). Evidence also shows that antibiotics are given to patients presenting with headache, breathing, thoracic pain abnormalities and auscultation abnormalities (Coenen et al., 2006).

Medical investigations are given to patients with lower EQ-5D scores

It was also expected that medical investigations such as chest x-rays are performed on patients with lower EQ-5D scores. When patients present with clinical symptoms such as shortness of breadth, auscultation abnormalities and fever, medical investigations such as chest x-rays are used to determine and confirm the presence of the disease (Hoare and Lim, 2006) and also to determine the type of treatment that is suitable for a patient.

EQ-5D scores increase over time

It was anticipated that EQ-5D scores would increase over time in patients presenting with LRTI. This is for two main reasons. Firstly, most LRTIs are self limiting (Wise et al., 1998; Van Duijn et al., 2005), and secondly, for those patients prescribed some sort of treatment, this would be anticipated to improve their symptom score although recent results suggest that there is only a very small difference in recovery between patients who receive treatment and those who do not receive any treatment (Butler et al., 2009). The Wilcoxon sign rank test was used to test the

difference between EQ-5D scores at baseline and week four with all value sets. In addition, the test was also used to test whether the difference obtained from all value sets was statistically significant.

RESULTS

Patient Characteristics

This study included a total of 1327 Patients who complete both the CRF forms and the patient diary from the GRACE study and were based in one of the 7 countries with its own CVS. From the study population, 61.42% were female and 38.58% were male. The number of patients in each country ranged from 90 in Finland to 348 in Spain. Table 1 includes information about both the number of patients in each country and other relevant patient characteristics.

Mean EQ-5D Scores

All mean EQ-5D scores are shown in table 2. Mean EQ-5D scores obtained using the EVS showed a similar trend to mean scores obtained using the CVS and UKVS in all countries, with the mean EQ-5D scores increasing over the four week period. On average, values obtained using the EVS were higher than those obtained using the CVS for all countries except the Netherlands and Germany. With the exception of Spain, where the difference was not significant at baseline, week 3 or week 4, the mean EQ-5D scores obtained from the CVS and EVS were significantly different in all other countries over the four week period.

At baseline, the differences between the EQ-5D scores obtained from the UKVS and EVS were statistically significant for all countries except for Finland. Using both value sets, England had the highest scores whilst Finland had the lowest scores (Table 2). For weeks one to four, the differences between the mean EQ-5D scores obtained from each of the two value sets were in all cases statistically significant. However, the direction of the differences were not the same in all cases, with the mean EVS scores being higher than UKVS in Netherlands and Germany at week one and the mean EVS score being lower than the UKVS for Finland, Belgium and Spain at weeks one to four. On average, the highest scores (for both value sets) were recorded in Spain (weeks one to three) and Finland (for week four). The lowest scores were recorded in Wales over the four weeks. There were also statistically significant differences between the mean scores obtained from the UKVS and CVS in Netherlands, Spain, Germany, Belgium and Finland at baseline and weeks one to four.

Agreement between value sets

The correlation coefficients between the EQ-5D scores obtained from the CVS, EVS and the UKVS were very high in all countries (table 3). Between the EVS and CVS, the highest correlation was in Belgium at week 4 whilst the lowest correlation was in Germany at week 4. Between the UKVS and EVS, the highest correlation was in Germany and Finland whilst the lowest was in Netherlands. Between the UKVS and CVS, the highest correlation was in Belgium at week 4 whilst the lowest was in Germany at baseline. The results from the Bland-Altman plots also showed that there was agreement between the two value sets in each country. Most points fell within the limits of agreement in all countries and with all value sets.

Antibiotic Prescribing

As shown in table 4, there was only one country for which a significant difference was found in the EQ-5D score relative to the prescription or not of antibiotics (Netherlands for EVS and UKVS). However, the direction of difference was as anticipated in the majority of cases, with patients who received antibiotics recording lower mean EQ-5D scores for all three value sets in Wales, England, Netherlands, Belgium and Finland. The exceptions were in Germany where the scores in the antibiotic group were as anticipated with the CVS, but not with the EVS and UKVS, where scores for those receiving antibiotics were generally higher (i.e. the patient had a higher health status), and in Spain where the counter-intuitive result was obtained with all datasets.

Medical Investigations

The results for medical investigations were not as anticipated. For the EVS, patients who had medical investigations performed had higher EQ-5D scores in Wales, Netherlands, Germany and Belgium. For the CVS and UKVS, the results were the same as the EVS. The only different result was recorded in Belgium with the UKVS. The only significant results were recorded in Netherlands and Finland with all value sets. Table 4 gives a breakdown of the results. The small number of investigations carried out in most countries could possibly explain this result.

EQ-5D scores and Severity scores

As expected, there was a negative statistically significant relationship between severity scores (from both patients and clinicians) and EQ-5D scores with all value sets and in all countries at baseline. These results are presented in table 5. At weeks one to four, there was also a negative

relationship between EQ-5D and severity scores with the EVS, UKVS and CVS in all countries. It is important to note here that a higher severity score indicates worse symptoms and vice versa.

Discriminating between known groups

When the factors headache, interference with normal activities and disturbed sleep were considered, as expected, all tariffs resulted in higher scores for the groups without the condition. The resulting differences were statistically significant in most cases (table 6). On average, the UK tariff was able to discriminate for headache, interference with normal activities and disturbed sleep. For headache, with the exception of the CVS in Germany, the UKVS was able to discriminate more efficiently. With disturbed sleep, the UKVS also performed better in four countries (England, Wales, Netherlands and Spain). The CVS for Finland and Spain performed better for interference with normal activities. EVS discriminated better in Wales and Germany and the UKVS discriminated better in England, Belgium and Netherlands.

For patients with co morbidities, the results were not as expected. In many instances, patients with co-morbidities had higher EQ-5D scores (table 7). It should be noted here that in most cases, the difference was not significant and the number of patients with co morbidities were very small in some countries.

EQ-5D scores over time

As expected, there was an improvement in the health of patients over the four week period in all countries and with all value sets (CVS, EVS and UKVS). This can be seen in table 2 where there was a rise in EQ-5D scores in all countries. This result was in line with the a priori expectation. Finland recorded the largest difference with the UKVS whilst the smallest difference was recorded in Germany with the CVS. The difference was significant in all countries and with all value sets. When the difference between EQ-5D scores at baseline and week four was tested, the values obtained with the EVS and UKVS were significantly different in Netherlands, Spain and Germany but not in Belgium and Finland results are presented in Table 8. Between the EVS and CVS, there was a significant difference in Netherlands, Germany and Belgium but not in Finland and Spain. With the exception of Belgium and Finland, there was a significant difference between the UKVS and CVS in all other countries. The size of the difference could have important implications for cost utility analysis (CUA). For example, the largest difference was seen in Germany which suggests that using different value sets may result in different QALY estimates in Germany.

DISCUSSION

The study has successfully explored the different value sets available for the EQ-5D for seven European countries in the context of LRTI. There was considerable agreement between all value sets although some differences were noted and are explored below. The study has also demonstrated the validity of the EQ-5D with all European value sets for use in patients with LRTI.

Before exploring the findings in more detail it is worth noting a number of limitations with the research. First, some of the analyses that might have been helpful were limited by the small numbers of patients with co-morbidities or undergoing medical investigations. Second, to date, all analyses have been conducted excluding missing data. Further analysis will be conducted at a later date to compare the results if data are imputed with those obtained with non-imputed data to establish whether missing data introduced bias. Finally, the study was limited to patients with LRTI, and so it may not be possible to extrapolate findings about the relative value of the different tariffs to patients with other conditions.

The results of this study indicate that there were significant differences between the EQ-5D scores obtained from the CVS, EVS and UKVS in all countries. The only exceptions were between the EVS and CVS in Spain at baseline and weeks three and four, and between the UKVS and CVS at baseline in Finland. In addition, the EVS yielded higher EQ-5D scores than the CVS in some countries (e.g. Wales, England) and lower scores than the CVS in other countries (e.g. Netherlands, Germany). The high EQ-5D scores that were obtained in Germany could have been as a result of the exclusion of the non-significant factors in the model that was used in the development of Germany's CVS.

There was considerable agreement between all value sets as shown by the correlation coefficient and the Bland-Altman plots. However, there was more agreement between the EVS and UKVS in all countries. This is not surprising, as the EVS includes a much higher number of respondents (approximately 47%) and valuations from the UK than from any other country in the EVS valuation study.

Regardless of the tariff used, there was an improvement in the health of patients in all countries and there was a statistically significant relationship between the EQ-5D and severity scores (for both patients and clinicians) in all countries suggesting that the measure is valid for use in patients with LRTI.

Results from the study indicate that the EVS did not perform better than the UKVS. Thus, for multinational studies and international comparisons either the UKVS or the EVS is currently an appropriate option. Bernert et al's (2009) cross-sectional study of the general population also produced a similar conclusion. Considering the fact that the EVS was developed from studies from different countries, it would seem as if it would be appropriate to use the EVS for multinational studies in Europe. However, other researchers (Wolfgang, 2003 and Greiner 2003) have observed that some of the studies that were used in the development of the EVS were not representative of the individual countries and also the countries that were selected only represent a small portion of Europe (Western and Northern Europe). None of these studies inform the question of what value set is most appropriate for Eastern and Southern European countries.

Studies have previously concluded that cultural and other factors affect valuation of health states (Guillemin et al., (1993), and Badia et al., (2001). For studies in individual countries, therefore, it is clearly preferable that country specific tariffs should be used. However, Bernert et al's, (2009) point, that there is a need for much larger studies which are more representative of the individual country to be used in the development of CVSs, is important.

It is also worth considering the implication of using different value sets for CUA. Some studies have concluded that the choice of value set for CUA does not matter (Sakthong et al., 2009). Others have suggested that the use of different value sets matters and have suggested that different weights may result in differences in QALYs which would yield different cost-effectiveness estimates (Huang et al., 2007; Johnson et al., 2005). In this study, it was established that the difference in the EQ-5D scores for the different value sets between baseline and week four were statistically significant in most case. This implies that using different value sets may result in difference in cost-effectiveness results. However, it is recommended that future studies should explore the implications of using different tariffs in CUA.

We would welcome discussion on the following issues:

- Should we look at the validity of EVS across all countries in the GRACE study, even those whose value sets did not contribute to the EVS?
- Should all countries use similar methods?
- Should all countries use a single value set?
- What value set should be used in multi-country studies?

- Comments on the methods used in this study.

Table 1: Study population characteristics

	Wales	England	Netherlands	Spain	Germany	Belgium	Finland
Total no of patients	181	168	195	348	181	164	90
Age mean (SD)	52.85 (16.31)	49.87 (16.49)	52.26 (16.18)	49.28 (16.49)	45.07 (15.92)	51.56 (15.44)	46.73 (14.14)
Female (%)	55.25	60.12	55.90	63.79	69.61	52.44	78.89
Male (%)	44.75	39.88	44.10	36.21	30.39	47.56	21.11
Employed (%)	90.06	88.10	84.62	95.40	93.90	90.24	95.56
Years in Education mean (SD)	9.40 (3.02)	9.66 (4.17)	9.50 (5.50)	10.28 (4.85)	9.40 (3.38)	11.30 (5.05)	12.78 (3.84)

Table 2: Mean EQ-5D Scores (Standard Deviation)

Country		Baseline	Week 1	Week 2	Week 3	Week 4	Difference Week 4-Baseline
WALES	**EVS**	0.697 (0.235)	0.719 (0.233)	0.777 (0.241)	0.809 (0.238)	0.827 (0.234)	0.130**
	CVS	0.675 (0.296)	0.711 (0.279)	0.770 (0.284)	0.803 (0.282)	0.821 (0.282)	0.146**
	EVS- CVS	0.022**	0.008**	0.007**	0.006**	0.006**	
ENGLAND	**EVS**	0.739 (0.188)	0.794 (0.206)	0.866 (0.184)	0.876 (0.194)	0.896 (0.185)	0.157**
	CVS	0.737 (0.221)	0.792 (0.239)	0.864 (0.215)	0.873 (0.229)	0.893 (0.216)	0.156**
	EVS- CVS	0.002 **	0.002**	0.002**	0.003**	0.003**	
NETHERLANDS	**EVS**	0.725 (0.210)	0.765 (0.200)	0.854 (0.163)	0.892 (0.157)	0.902 (0.154)	0.177**
	CVS	0.768 (0.209)	0.807 (0.193)	0.883 (0.154)	0.915 (0.140)	0.922 (0.139)	0.154**
	UKVS	0.719 (0.257)	0.764 (0.237)	0.856 (0.184)	0.897 (0.167)	0.905 (0.166)	0.186**
	EVS- CVS	-0.043**	-0.042**	-0.038**	-0.023**	-0.020**	
	EVS-UKVS	0.006**	0.001**	-0.002**	-0.005**	-0.003**	
	UKVS- CVS	-0.049**	-0.043**	-0.027**	-0.018**	-0.017**	
SPAIN	**EVS**	0.730	0.812	0.905	0.930	0.932	0.202**

	CVS	0.730 (0.179)	0.799 (0.145)	0.901 (0.138)	0.927 (0.128)	0.930 (0.128)	0.200**
	UKVS	0.721 (0.236)	0.823 (0.163)	0.912 (0.140)	0.935 (0.133)	0.938 (0.132)	0.217**
	EVS- CVS	0.000	0.013**	0.004*	0.003	0.002	
	EVS-UKVS	0.009**	-0.011**	-0.007**	-0.005**	-0.006**	
	UKVS- CVS	-0.009**	0.024**	0.011**	0.008**	0.008**	
GERMANY	**EVS**	0.717 (0.179)	0.795 (0.205)	0.881 (0.166)	0.917 (0.138)	0.928 (0.133)	0.211**
	CVS	0.825 (0.195)	0.870 (0.204)	0.934 (0.135)	0.958 (0.983)	0.962 (0.991)	0.110**
	UKVS	0.713 (0.226)	0.788 (0.248)	0.882 (0.182)	0.920 (0.144)	0.930 (0.143)	0.217**
	EVS-CVS	-0.108**	-0.075**	-0.053**	-0.041**	-0.034**	
	EVS-UKVS	0.004**	0.007**	-0.001**	-0.003**	-0.002**	
	UKVS- CVS	-0.112**	-0.082**	-0.052**	-0.038**	-0.032**	
BELGIUM	**EVS**	0.727 (0.222)	0.772 (0.157)	0.873 (0.152)	0.891 (0.142)	0.892 (0.152)	0.165**
	CVS	0.705 (0.235)	0.748 (0.162)	0.859 (0.168)	0.878 (0.156)	0.880 (0.155)	0.175**
	UKVS	0.715 (0.284)	0.782 (0.184)	0.881 (0.161)	0.900 (0.144)	0.900 (0.156	0.185**
	EVS- CVS	0.022**	0.024**	0.014**	0.013**	0.012**	
	EVS-UKVS	0.012**	-0.010**	-0.008**	-0.009**	-0.071**	
	UKVS- CVS	0.010**	0.034**	0.022**	0.022**	0.020**	
FINLAND	**EVS**	0.669 (0.230)	0.798 (0.174)	0.878 (0.165)	0.924 (0.139)	0.933 (0.136)	0.264**
	CVS	0.665 (0.193)	0.766 (0.182)	0.858 (0.185)	0.911 (0.158)	0.922 (0.155)	0.257**
	UKVS	0.652 (0.281)	0.801 (0.187)	0.881 (0.171)	0.927 (0.135)	0.937 (0.132)	0.285**
	EVS- CVS	0.004**	0.032**	0.020**	0.013**	0.011**	
	EVS-UKVS	0.017	-0.003**	-0.003**	-0.003**	-0.004**	
	UKVS-CVS	-0.013	0.035**	0.023**	0.016**	0.015**	

**** Significantly different at 5% level***

***** Significantly different at 1% level Wilcoxon signed rank test***

Table 3: Agreement between UKVS EVS and CVS

Country	Preference Weights	Baseline	Week 1	Week 2	Week 3	Week 4

Wales	EVS & CVS	0.9790 **	0.9821**	0.9839**	0.9821**	0.9787**
England	EVS & CVS	0.9788**	0.9824**	0.9798**	0.9827**	0.9803**
Netherlands	EVS & CVS	0.9666**	0.9735**	0.9647**	0.9683**	0.9680**
	EVS & UKVS	0.9970**	0.9973**	0.9981**	0.9988**	0.9990**
	UKVS & CVS	0.9629**	0.9678**	0.9849**	0.9912**	0.9947**
Spain	EVS & CVS	0.9727**	0.9845**	0.9904**	0.9910**	0.9906**
	EVS & UKVS	0.9973**	0.9984**	0.9993**	0.9997**	0.9997**
	UKVS & CVS	0.9636**	0.9811**	0.9954**	0.9964**	0.9963**
Germany	EVS & CVS	0.9200**	0.9210**	0.8876**	0.8697**	0.8813**
	EVS & UKVS	0.9987**	0.9998**	1.0000**	1.0000**	1.0000**
	UKVS & CVS	0.9155**	0.9799**	0.9895**	0.9936**	0.9967**
Belgium	EVS & CVS	0.9964**	0.9957**	0.9982**	0.9983**	0.9985**
	EVS & UKVS	0.9979**	0.9997**	0.9993**	0.9997**	0.9994**
	UKVS & CVS	0.9940**	0.9911**	0.9970**	0.9982**	0.9984**
Finland	EVS & CVS	0.9294**	0.9441**	0.9588**	0.9718**	0.9695**
	EVS & UKVS	0.9987**	1.000**	0.9996**	1.0000**	1.000**
	UKVS & CVS	0.9677**	0.9776**	0.9887**	0.9949**	0.9957**

**** Significantly different at 5% level***

***** Significantly different at 1% level***

TABLE 4: Relationship between EQ-5D scores medical investigations and antibiotic prescribing

	Investigations					***Antibiotics***				
Wales		**N**	**UKVS**	**EVS**	**CVS**		**N**	**UKVS**	**EVS**	**CVS**
	No	179		0.718	0.674	No	51		0.735	0.728
	Yes	2		0.883	0.738	Yes	130		0.682	0.654
	Difference			-0.165	-0.064	Difference			0.053	0.074
England										
	No	159		0.740	0.738	No	63		0.762	0.769
	Yes	9		0.721	0.716	Yes	105		0.725	0.718
	Difference			0.019	0.022	Difference			0.037	0.051
Netherlands			**UKVS**	**EVS**	**CVS**			**UKVS**	**EVS**	**CVS**
	No	186	0.711	0.718	0.761	No	113	0.763	0.759	0.799
	Yes	9	0.895	0.883	0.912	Yes	82	0.622	0.683	0.729
	Difference		-0.184*	-0.165*	0.151*	Difference		0.141*	0.076*	0.070
Spain	**Spain**					**Spain**				
	No	309	0.722	0.732	0.732	No	225	0.709	0.723	0.725
	Yes	39	0.714	0.718	0.710	Yes	93	0.756	0.750	0.743
	Difference		0.008	0.014	0.022	Difference		-0.047	-0.027	-0.018
Germany										
	No	140	0.709	0.712	0.824	No	120	0.711	0.716	0.826
	Yes	41	0.727	0.760	0.825	Yes	61	0.716	0.720	0.822
	Difference		-0.018	-0.048	-0.001	Difference		-0.005	-0.004	0.004

Belgium										
	No	156	0.715	0.726	0.703	No	120	0.720	0.729	0.706
	Yes	8	0.713	0.754	0.740	Yes	44	0.701	0.721	0.701
	Difference		0.002	-0.028	-0.037	Difference		0.019	0.008	0.005
Finland										
	No	67	0.695	0.702	0.696	No	51	0.665	0.682	0.682
	Yes	23	0.526	0.573	0.574	Yes	39	0.634	0.652	0.643
	Difference		0.169*	0.129*	0.122*	Difference		0.031	0.030	0.039

**** Significantly different at 5% level***

***** Significantly different at 1% level Mann Whitney test***

TABLE 5 Relationship between EQ-5D scores and severity scores at baseline

	EVS		**UKVS**		**CVS**	
	Patient	Clinician	Patient	Clinician	Patient	Clinician
Wales	-0.005**	-0.006**	-0.007**	-0.007**	-0.007**	-0.007**
England	-0.006**	-0.005**	-0.007**	-0.006**	-0.007**	-0.006**
Netherlands	-0.006**	-0.005**	-0.007**	-0.006**	-0.006**	-0.005**
Spain	-0.003**	-0.003**	-0.004**	-0.004**	-0.003**	-0.004**
Germany	-0.005**	-0.004**	-0.006**	-0.005**	-0.005**	-0.004**
Belgium	-0.004**	-0.004**	-0.006**	-0.005**	-0.005**	-0.004**
Finland	-0.008**	-0.009**	-0.009**	-0110**	-0.007**	-0.008**

**** Significantly different at 5% level***

***** Significantly different at 1% level***

TABLE 6 Known Group Validity of EQ-5D using the CVS, EVS and UKVS

		Headache				***Interference***				**Disturbed sleep**		
Wales	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	78		0.722	0.704	58		0.811	0.808	63		0.751	0.742
Yes	103		0.678	0.654	123		0.645	0.615	118		0.668	0.639
Difference			0.044	0.508			0.166*	0.193*			0.083*	0.103*
Z			1.182	1.211			4.554	4.564			2.496	2.601
Relative precision			0.976[a]				0.997[a]				0.960[a]	
England	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	72		0.764	0.774	37		0.845	0.851	75		0.787	0.798
Yes	96		0.719	0.707	130		0.707	0.703	93		0.709	0.699
Difference			0.446	0.067			0.137*	0.148*			0.078*	0.099*
Z			1.155	1.257			4.332	4.327			2.517	2.645
Relative precision			0.919[a]				1.001[a]				0.952[a]	
Netherlands	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	79	0.795	0.787	0.824	53	0.845	0.839	0.863	88	0.800	0.790	0.830
Yes	116	0.663	0.681	0.728	142	0.668	0.680	0.730	107	0.675	0.691	0.735
Difference		0.132*	0.106*	0.096*		0.122*	0.160*	0.133*		0.125*	0.099*	0.095*
Z		3.462	3.329	3.124		4.713	4.662	3.940		2.950	2.753	2.504
Relative		1.040[b]	1.066[a]	0.902[c]		1.196[b]	1.183[a]	0.836[c]		1.178[b]	1.099[a]	0.849[c]

precision												
Spain	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	159	0.754	0.757	0.758	183	0.780	0.778	0.779	124	0.787	0.787	0.788
Yes	188	0.696	0.709	0.707	164	0.658	0.678	0.676	224	0.684	0.698	0.697
Difference		0.057*	0.048*	0.050*		0.122*	0.101*	0.103*		0.103*	0.089*	0.091*
Z		3.254	3.092	3.291		5.363	5.348	5.617		5.445	5.358	5.303
Relative precision		1.052[b]	0.940[a]	1.011[c]		1.003[b]	0.925[a]	1.047[c]		1.016[b]	1.010[a]	0.974[c]
Germany	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	56	0.749	0.748	0.851	40	0.791	0.795	0.877	60	0.764	0.767	0.861
Yes	125	0.697	0.704	0.813	141	0.690	0.695	0.809	121	0.690	0.695	0.808
Difference		0.052	0.044	0.037*		0.100*	0.010*	0.068*		0.075*	0.072*	0.053*
Z		1.768	1.819	2.054		4.785	4.874	3.678		3.057	3.107	2.783
Relative precision		0.971[b]	0.886[a]	1.162[c]		0.982[b]	1.325[a]	0.769[c]		0.984[b]	1.116[a]	0.910[c]
Belgium	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	77	0.739	0.752	0.732	34	0.780	0.771	0.749	58	0.753	0.769	0.748
Yes	86	0.695	0.705	0.682	129	0.697	0.715	0.693	106	0.696	0.706	0.683
Difference		0.044	0.047	0.049		0.083	0.056	0.056		0.058*	0.063*	0.065*
Z		1.037	1.011	0.954		1.103	0.948	0.956		0.975	1.004	1.022
Relative precision		1.037[b]	1.011[a]	0.954[c]		1.103[b]	0.948[a]	0.956[c]		0.975[b]	1.004[a]	1.022[c]
Finland	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	30	0.705	0.718	0.725	37	0.736	0.736	0.731	28	0.709	0.723	0.737
Yes	60	0.626	0.645	0.635	53	0.593	0.622	0.618	62	0.626	0.644	0.632
Difference		0.079*	0.073*	0.090*		0.142*	0.114*	0.113*		0.082*	0.079*	0.105*
Z		2.179	2.162	2.430		2.809	2.759	2.908		2.193	2.193	2.474
Relative precision		1.008[b]	0.890[a]	1.115[c]		1.018[b]	0.949[a]	1.035[c]		1[b]	0.886[a]	1.128[c]

**** Significantly different at 5% level Mann Whitney test***

[a] EVS vs CVS [b] UKVS vs EVS [c] CVS vs UKVS

TABLE 7 Known Group Validity of EQ-5D using the CVS, EVS and UKVS

		Heart				***Diabetic***			**Respiratory**			
Wales	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**	**N**	**UKVS**	**EVS**	**CVS**
No	164		0.696	0.673	167		0.695	0.672	141		0.715	0691
Yes	17		0.706	0.694	14		0.723	0.708	40		0.631	0.618
Difference			-0.011	-0.021			-0.028	-0.035			0.084	0.074
z			-0.377	-0.432			-0.198	-0.328			2.009	1.798
Relative precision			0.873[a]				0.604[a]				1.117[a]	
England	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	156		0.732	0.729	161		0.740	0.739	137		0.757	0.755
Yes	12		0.822	0.838	7		0.706	0.687	31		0.647	0.648
Difference			-0.090	-0.109			0.034	0.052			0.110*	0.107*
Z			-1.538	-1.515			0.059	0.108			2.630	2.656
Relative precision			1.015[a]				0.546[a]				0.990[a]	

Netherlands	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	172	0.717	0.725	0.766	180	0.709	0.717	0.762	145	0.722	0.728	0.771
Yes	23	0.730	0.731	0.785	15	0.816	0.815	0.836	50	0.710	0.717	0.760
Difference		-0.013	-0.006	-0.020		-0.107	-0.098	-0.075		0.011	0.011	0.011
Z		0.589	0.530	0.204		-1.411	-1.455	-1.281		0.505	0.557	0.340
Relative precision		1.111[b]	2.598[a]	0.346[c]		0.970[b]	1.136[a]	0.908[c]		0.907[b]	1.638[a]	0.673[c]
Spain	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	322	0.720	0.729	0.728	331	0.712	0.721	0.762	303	0.709	0.721	0.722
Yes	26	0.736	0.747	0.746	17	0.904	0.897	0.922	45	0.803	0.791	0.784
Difference		-0.016	-0.018	-0.017		-0.192*	-0.18*	-0.161*		-0.094*	-0.696*	-0.062
Z		-0.169	-0.217	-0.454		-3.903	-3.931	-3.943		-2.310	-2.368	-1.936
Relative precision		0.779[b]	0.478[a]	2.686[c]		0.993[b]	0.997[a]	1.010[c]		0.976[b]	1.223[a]	0.838[c]
Germany	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	170	0.711	0.717	0.822	172	0.712	0.715	0.763	155	0.713	0.718	0.824
Yes	11	0.740	0.728	0.859	9	0.739	0.756	0.794	26	0.711	0.714	0.828
Difference		-0.028	-0.012	-0.037		-0.028	-0.040	-0.031		0.003	0.004	-0.004
Z		-0.149	-0.217	-0.299		-1.099	-1.126	-0.543		0.474	0.452	0.128
Relative precision		0.687[b]	0.726[a]	2.007[c]		0.976[b]	2.074[a]	0.494[c]		1.049[b]	3.531[a]	0.270[c]
Belgium	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	155	0.709	0.723	0.700	158	0.713	0.726	0.760	130	0.730	0.741	0.719
Yes	9	0.823	0.808	0.791	6	0.805	0.792	0.831	34	0.653	0.670	0.647
Difference		-0.114	-0.086	-0.090		-0.090	-0.066	-0.071		0.077	0.071	0.073
Z		-1.016	-1.033	-1.084		-0.396	-0.396	-0.437		1.688	1.804	1.877
Relative precision		0.984[b]	0.953[a]	1.067[c]		1[b]	0.837[a]	1.194[c]		0.936[b]	0.961[a]	1.112[c]
Finland	**N**	**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**		**UKVS**	**EVS**	**CVS**
No	87	0.654	0.670	0.665	87	0.658	0.675	0.729	80	0.638	0.695	0.662
Yes	3	0.608	0.642	0.656	3	0.484	0.496	0.584	10	0.763	0.747	0.685
Difference		0.046	0.028	0.009		0.173	0.179	0.145		-0.124	-0.087	-0.023
Z		-0.261	-0.307	-0.375		0.988	1.056	0.852		-1.018	-1.018	-0.824
Relative precision		0.850[b]	0.819[a]	1.437[c]		0.936[b]	1.239[a]	0.862[c]		1[b]	1.235[a]	0.809[c]

**** Significantly different at 5% level Mann Whitney test***

[a] EVS vs CVS [b] UKVS vs EVS [c] CVS vs UKVS

TABLE 8: **Difference between EQ-5Dscores at baseline and week 4 with UKVS, EVS and CVS**

	Wales	**England**	**Netherlands**	**Spain**	**Germany**	**Belgium**	**Finland**
UKVS			0.186	0.217	0.217	0.185	0.285
EVS	0.130	0.157	0.177	0.202	0.211	0.165	0.264
CVS	0.146	0.156	0.154	0.200	0.110	0.175	0.257
EVS-UKVS			-0.010*	-0.014**	-0.006**	-0.021**	-0.020**
EVS-CVS	-0.015	-0.004**	-0.023**	0.002**	0.073**	-0.010**	0.007
UKVS-CVS			0.032**	0.016**	0.080**	0.011	0.028

** Significantly different at 5% level*

*** Significantly different at 1% level Wilcoxon signed rank test*

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