Valuing Benefits to Inform a Clinical Trial in Pharmacy

Do Differences in Utility Measures at Baseline Affect the Effectiveness of the Intervention?

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Abstract

Background The generic health-related quality-of-life (HR-QOL) utility measures the EQ-5D and SF-6D are both commonly used to inform healthcare policy developments. However, their application to pharmacy practice is limited and the optimal method to inform policy developments is unknown.

Objectives Our objective was to test the sensitivity of the EQ-5D and SF-6D within pharmacy when measuring whether changes in health status or other co-variables at baseline affect the effectiveness of the intervention at follow-up. A further objective was to consider the implications of the findings for pharmacy research and policy.

Methods The EQ-5D and SF-6D utility measures were employed within a randomized controlled trial (RCT) of community pharmacy-led medicines management for patients with coronary heart disease. The intervention covered a baseline visit with the potential for follow-up. Simultaneous quantile regression assessed the impact of the intervention on both EQ-5D and SF-6D measures at follow-up, controlling for baseline health, appropriateness of treatment, personal characteristics and self-reported satisfaction.

Results No statistically significant difference in HR-QOL across the intervention and control groups at follow-up was reported for either measure. Increased health gain was however associated with the baseline utility score (with the EQ-5D more sensitive for those in worse health) and the appropriateness of treatment, but not patient characteristics or self-reported satisfaction.

Conclusion Neither generic measure detected a gain in HR-QOL as a result of the introduction of an innovative pharmacy-based service. This finding supports other work

in the area of pharmacy, where health gains have not changed following interventions. Disease-specific utility measures should be investigated as an alternative to generic approaches such as the EQ-5D and SF-6D. Given that the RCT found an increase in self-reported satisfaction, broader measures of benefit that value patient experiences, such as contingent valuation and discrete-choice experiments, should also be considered in pharmacy.

Key Points for Decision Makers

- Neither the EQ-5D nor the SF-6D found a significant effect of the intervention on health at follow-up, regardless of the health outcome quantiles considered
- The sensitivity of both the EQ-5D and the SF-6D was related to baseline utility score and appropriate treatment only
- Disease-specific utility measures should be considered in pharmacy
- Valuation methods such as discrete-choice experiments and contingent valuation, which go beyond health outcomes and value patient experiences, should be applied within pharmacy

1 Introduction

Health economic measures of value are essential to inform policy regarding the efficient use of scarce healthcare resources. A major challenge is how to value benefits across a range of conditions and patient groups and to produce a single summary measure of benefit (or utility score). The commonly used approach integrates survival and health-related quality of life (HR-QOL) into a single measure: the QALY.^[1] Here the number of life-years gained is adjusted for quality of life, using utility weights. Several generic utility measures are available, including: the Quality of Well-Being (QWB) scale, the Health Utilities Index (HUI) versions 1, 2 and 3, the 15 dimensions (15-D) instrument, the EQ-5D, and the SF-6D.^[2-7] Two of the most widely used are the EQ-5D and the SF-6D.

QALYs are recognized to be the main valuation technique for policy decision making in many countries. For example, they are recommended by bodies such as the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the Australian Medical Services Advisory Committee (MSAC).^[8-12] QALYs are also commonly employed in randomized controlled trials (RCTs) when comparing alternative health technologies and procedures.^[13]

Over recent years, a number of studies have compared the performance of the EQ-5D and the SF-6D across a range of diseases and population groups.^[14-43] For the majority of

cases (24 of 30 papers, 80 %), poor agreement between utility measures was found. There is recognition that alternative measures might produce differences in the number of QALYs, leading to different cost-effectiveness outcomes.^[44] Different reasons for disparities between utility measures have been identified, including: variation in the descriptive system (i.e. compared with the EQ-5D, the SF-6D has more dimensions [six vs. five] and more levels [four to six vs. three]); variation in the methods used to derive the utility values attached to each health state (time trade-off for the EQ-5D vs. standard gamble for the SF-6D); and in the SF-6D's explicit inclusion of the items 'vitality' and 'functioning', which are not explicitly included in EQ-5D.^[19,22]

When selecting the appropriate health outcome utility measure, consideration should be given to the method likely to be the most sensitive to the health change. Thus, the preferred measure will be dependent on the condition and setting.^[19] In pharmacy practice research, whilst there is an awareness of the importance of carrying out a comprehensive assessment of the benefits that patients derive from pharmacy interventions to better inform policy decision making, there has been limited application of health economic outcome utility measures, including QALYs, to new community pharmacy services to date.^[45] To our knowledge, only five RCTs valuing alternative pharmacist-based services have compared QALYs across treatment groups.^[46-53] A key and consistent finding from all these trials is that the innovative services provided by community pharmacists did not improve health-related outcomes, as measured by the EQ-5D or the SF-36, although Etemad and Hay^[54] reported pharmacist-based

interventions being cost effective when using life-year saved (not adjusted for quality) as the measure of benefit.

More research is needed to investigate whether the EQ-5D or the SF-6D is the more sensitive utility measure when exploring the effectiveness of pharmacist-delivered interventions. As the EQ-5D and SF-6D cover different domains (see the possible reasons for disparities between the utility measures reported previously in this section), one of them might be more sensitive to health change when valuing new pharmacy services.^[19,22] There might also be a difference in the sensitivity of the utility measures according to the health status of the patient. It could be hypothesized that different utility measures capture the effect of the intervention at different parts of the distribution, discriminating between subgroups of patients in worse or better health.

This paper contributes to the literature in a number of ways. Firstly, we compare the sensitivity of the EQ-5D and SF-6D between treatment groups within the MEDMAN (community pharmacy-led MEDicines MANagement) RCT (see more on the MEDMAN trial in the Methods section)^[46], investigating the effect of baseline patient health status on sensitivity. Secondly, we employ a relatively novel econometric approach, simultaneous quantile regression. The commonly used ordinary least squares (OLS) regression approach has shown that whilst intervention patients within the MEDMAN trial reported an increase in satisfaction, this was not associated with any increase in their EQ-5D utility score.^[46,52] The OLS regression approach assesses how the mean of the dependent variable varies with changes in the independent variables (co-variates).

Simultaneous quantile regression allows further investigation across quantiles of the EQ-5D and SF-6D distributions i.e. estimating the dependent variable, conditional on the values of the co-variates, at different quantiles simultaneously.^[55] We develop this analysis by testing whether changes in health status or other co-variates at baseline affect the effectiveness of the intervention at follow-up. In the next two sections, the methods and results are presented. In the last section, the results are discussed, with future areas for research highlighted.

2 Methods

2.1 The Data

The MEDMAN study was a large RCT designed to evaluate the introduction of a pharmacy-led medicines management service for patients with coronary heart disease (CHD) involving 58 community pharmacies in nine NHS areas of England.^[46] Patients in the treatment group had a consultation with the community pharmacist to discuss and review their medicines. In addition, the consultation also covered lifestyle issues such as smoking and diet. Follow-up consultations were arranged by the pharmacist if required. A total of 1,493 patients (980 treatment group, 513 control group) with a history of CHD (previous myocardial infarction [MI], angina, coronary artery bypass graft [CABG] and/or angioplasty) participated in the trial.

Within the trial, data were collected at baseline and 12 months on: HR-QOL, using the SF-36 and EQ-5D; the appropriateness of treatment; and self-reported satisfaction. SF-6D utility values were derived from the SF-36.^[6] A measure of appropriate treatment was

developed, summarizing the different components of treatment (on target for: aspirin-related treatment, lipid and blood pressure management, smoking cessation, physical activity, diet, and body mass index [BMI]) within a single score.^[58] A measure for self-reported satisfaction was developed and validated.^[59] Information was also collected on the age and gender of respondents.

2.2 Outcome and Patients Co-Variates: Raw Statistics

Descriptive statistics for all variables were reported for baseline and follow-up according to treatment group (intervention or control). Differences across groups were tested using Wilcoxon and McNemar's tests as appropriate. Medians (interquartile range [IQR]) for skewed continuous data and percentages for categorical data are presented. For the SF-6D and EQ-5D, following standard practice, five quantiles were considered: quantile 25 (Q25) [25th percentile]; Q50 (50th percentile, or median); Q75 (75th percentile); and two outer quantiles (Q10 [10th percentile] and Q90 [90th percentile]).^[57]

2.3 Simultaneous Quantile Regression Modelling

Simultaneous quantile regression modelling was used to determine the effect of co-variates (i.e. 'age', 'gender', 'appropriate treatment base score', 'satisfaction score', 'treatment', 'utility base score') simultaneously at the five quantiles for both EQ-5D and SF-6D distributions.^[31] When modelling the effect of a co-variate on utility scores in a specific quantile, all observations in the sample are included and observations are weighted according to whether the estimated residual is greater or less than zero, with weights depending on the specific quantile being estimated. A priori hypotheses about

these effects are shown in the Appendix (Online Resource), and were based on both a priori expectations and existing literature. For example, it has been shown that, for patients with CHD, younger people are more likely to report smaller changes in utility score than older people and women are less likely to report an improved utility score than men.^[60] It is also known that an increased appropriateness of treatment and satisfaction score is associated with an increased reported utility score in CHD patients (see the Appendix [Online Resource]).^[61-62]

Previous work using an OLS regression model did not show any statistically significant difference in utility measure according to the treatment received using the EQ-5D (i.e. intervention or control group)^[46]. However, ‘treatment’ was included in the simultaneous quantile regression model as a co-variate since we wanted to investigate the sensitivity of either the EQ-5D or the SF-6D utility measure between groups when looking across quantiles of their distribution. For all other co-variables, a forward stepwise approach was adopted, starting with no variables in the model, trying out the variables one by one and including them if they were ‘statistically significant’.^[57] Such a strategy has been argued to be the most straightforward for variable selection, as its application has been reported as simple, intuitive and effective, and is commonly used when approaching complex modelling problems, as presented within the machine learning literature.^[63] Co-variables were included if they were significant at the 95 % level.

The EQ-5D and SF-6D utility measures were considered separately, and no direct comparison was made between them at quantile level. Only the general change in utility across the different quantiles was reported and compared between utility measures.

Data for the regressions were for individuals who had paired values for both EQ-5D and SF-6D utility scores across time. EQ-5D and SF-6D utility scores at baseline and follow-up were standardized before the models were produced, by subtracting the population mean from an individual raw utility score and then dividing the difference by the population standard deviation.

3 Results

3.1 Response Rates

A total of 558 subjects in the intervention and 299 subjects in the control were included in the analysis.

3.2 Outcomes and Patient Co-Variates: Raw Statistics

Similar EQ-5D and SF-6D utility scores were reported for both groups at both time points (see Table 1). Follow-up and baseline data reported comparable patient characteristics across groups, although at follow-up the treatment subjects were more satisfied, and reported an increased ‘appropriate treatment base score’ compared with baseline ($p < 0.01$).

3.3 Simultaneous Quantile Regression Modelling

Using forward stepwise regression, the age, gender, satisfaction score and treatment co-variates were not significant at the 95 % level. Appropriate treatment base score and utility base score were significant at the 95 % level and included in the final model. Whilst the treatment co-variate was not significant at 95 % for any quantile, it was included in the final model to test whether changes in appropriate treatment and utility at baseline affect the effectiveness of the intervention at follow-up across quantiles. Table 2 reports the final EQ-5D and SF-6D simultaneous regression models estimated.

The statistically significant EQ-5D and SF-6D utility base score indicates a significant association between baseline and follow-up health (all p values ≤ 0.01). The positive signs indicate that the better the health at baseline, the better it was at follow-up. The strength of association (described by the magnitude of the coefficient) varied between quantiles for the EQ-5D, with the association stronger at the lower quantiles. For the SF-6D, the association was similar across quintiles. For example, for the EQ-5D, the coefficient of 0.88 for Q25 implies that when the EQ-5D health score at baseline increases by 0.50, the EQ-5D health score at follow-up increases by 0.44 (0.88×0.50). In comparison, for Q75, the lower coefficient of 0.56 implies a lower increase of $0.56 \times 0.50 = 0.28$ in response to a baseline increase of 0.5. For the SF-6D, the coefficient of 0.74 for Q25 implies that when the SF-6D health score at baseline increases by 0.50, the SF-6D health score at follow-up increases by 0.37 (0.74×0.50). Similarly, a utility base score of 0.71 for Q75 implies an increase of $0.71 \times 0.50 = 0.36$ in the health score at follow-up when the health score at baseline increases by 0.5.

Appropriate treatment base score was statistically significant for: Q10 and Q90 for both utility measures, Q25 for the EQ-5D, and Q50 and Q75 for the SF-6D only. The positive sign indicates that the more appropriate the treatment was at baseline, the better the health was at follow-up. The size of the effect varied across quantiles. For example, for Q25 for the EQ-5D utility measure, the appropriate treatment base score showed a significant gain in health at follow-up—the appropriate treatment base score of 0.07 implies that when the appropriate treatment base score increases by 0.50, health at follow-up (EQ-5D follow-up) increases by 0.04 (0.07×0.50). For example, for the SF-6D, the appropriate treatment base score showed a significant gain in health at follow-up for Q75—when the appropriate treatment base score increases by 0.50, the health at follow-up (SF-6D follow-up) increases by 0.04 (0.07×0.50).

For Q10 and Q25, the significant negative ‘constant’ shows, everything else constant, a relatively low health status at follow-up. For Q75 (EQ-5D only) and Q90 (both EQ-5D and SF-6D utility measures), a significant positive ‘constant’ indicates an improvement in health at follow-up. In other words, those subjects in worse health at baseline deteriorated further with time, whilst subjects in better health improved. For the EQ-5D (Q25), the health at follow-up deteriorates by 0.52, whilst for Q75 the health at follow-up increases by 0.40. For the SF-6D (Q25), the health at follow-up deteriorates by 0.69.

4 Discussion

This paper tested the sensitivity of the EQ-5D and SF-6D utility measures between treatment groups over time. The application was an RCT investigating an innovative

pharmacy practice service. Using the SF-6D or the EQ-5D utility measure, no significant effect of the intervention on health was found across quantiles, though the strength of association between baseline and follow-up utility scores varied at different parts of the distribution (EQ-5D only). Increased appropriateness of treatment was associated with a health improvement for both the EQ-5D and the SF-6D, regardless of treatment group. Age, gender and self-reported satisfaction did not impact on the health status at follow-up. Neither utility measure supported the introduction of the new community pharmacist-based medicine management service.

We applied the relatively novel simultaneous quantile modelling approach and used the forward stepwise approach to identify variables included in the model.^[31,55] Use of the forward stepwise approach requires the selection of variables to test for inclusion. Clearly there is potential for misspecification, although the selection of variables was based on a priori expectations and evidence from existing literature.

There are a number of possible reasons that may explain the lack of a treatment effect within the MEDMAN trial. Both the EQ-5D and the SF-6D are generic measures of utility. Disease-specific utility measures are known to be more sensitive to change in outcomes.^[64] A recent review of the literature looking at generic and disease-specific utility measures used in the assessment of HR-QOL in CHD recommended use of both generic and disease-specific utility measures.^[65] An example of a disease-specific descriptive measure discussed by Cepeda-Valery et al.^[65], and recently used to derive utility values for the calculation of QALYs, is the Seattle Angina Questionnaire

(SAQ).^[66] It might be that CHD domains, such as patient physical limitations caused by angina, frequency of angina, angina stability (recent changes in their symptoms), satisfaction with treatment and disease perception, are more sensitive when valuing the effectiveness of the MEDMAN trial intervention. Future research in pharmacy should consider using disease-specific utility measures.

Limited numbers of follow-up visits (about 91 % of the intervention patients had only one visit with the pharmacist; see Scott et al.^[52]) might have compromised the ability of the intervention to influence the trial outcomes. The limited follow-up period is also a limitation: a longer period of time may have been needed to fully experience the health benefits of the treatment. It is also possible that GPs optimized patient care before the start of the trial, reducing opportunities for community pharmacists to detect patients not being treated according to the agreed guidelines. Other possibilities for a lack of treatment effect include a non-representative sample of respondents with suitable data for the analysis presenting (the majority of intervention patients not completing the 12-month follow-up survey may have included subjects with experience of an effective intervention) and a possible Hawthorne effect (an increase in outcomes from control patients because of their participation in the MEDMAN trial).^[67]

However, a major limitation of this trial, in common with many trials, is that the value of factors beyond health outcomes (measured by QALYs) was not considered. Other RCTs in pharmacy practice that used the EQ-5D utility measure in their evaluations have also failed to demonstrate QALY changes resulting from the pharmacy intervention.^[47-49]

Identification of this as a major limitation is supported by the finding from the MEDMAN trial that patients who experienced the intervention were more satisfied—so there was increased benefit! But the QALY approach did not value this benefit. An approach put forward in the economics literature to go beyond the QALY and value broader measures of utility, such as the patient experience (which may be proxied through patient satisfaction, but not valued), is willingness to pay (WTP).^[68] WTP is based on the premise that the maximum amount of money an individual is willing to pay for a commodity is an indication to them of the value of that commodity.^[69] In contrast to satisfaction surveys, WTP can be used to derive a single measure of utility or benefits.^[1,68-71] Different approaches for estimating WTP are available, such as contingent valuation (CV) or discrete-choice experiment (DCE). They have been extensively applied to pharmacy and a few examples are reported elsewhere.^[72-76]

Future research could employ WTP approaches to revisit the economic evaluation of alternative pharmacist-based interventions and integrate WTP estimates into a cost-benefit framework.^[54,70]

5 Conclusion

The sensitivity of the EQ-5D and SF-6D have been explored as part of an evaluation of a new community pharmacy-based medicines management service. Simultaneous quantile regression modelling provided information on differences in health outcomes across five quantiles. Neither utility measure found a significant effect of the treatment intervention on health at follow-up. However, health gains were associated with baseline utility score

and appropriate treatment only. Furthermore, the sensitivity of the baseline utility score was related to health quantiles for the EQ-5D, with sensitivity higher for lower quantiles (worse health). Neither the EQ-5D nor the SF-6D explained observed changes in satisfaction scores across trial groups. Both disease-specific utility measures and broader measures of utility such as CV and DCE, which take account of patient experiences, should be further explored when informing pharmacy policy.

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Table 1 Outcomes and patient co-variables: raw statistics

Parameter	Intervention			Control		
	Baseline	Follow-up	<i>p</i> value	Baseline	Follow-up	<i>p</i> value
Cut-off points or quantiles						
EQ-5D ^a			0.36			0.10
Q10	0.36	0.31		0.36	0.36	
Q25	0.62	0.66		0.66	0.66	
Q50, median	0.73	0.73		0.73	0.73	
Q75	0.80	0.92		0.85	1.00	
Q90	1.00	1.00		1.00	1.00	
SF-6D ^a			0.87			0.96
Q10	0.52	0.52		0.53	0.53	
Q25	0.59	0.58		0.59	0.59	
Q50, median	0.71	0.70		0.71	0.70	
Q75	0.82	0.83		0.83	0.86	
Q90	0.89	0.89		0.90	0.93	
Co-variables						
Treatment [% (<i>n</i>)]	100 (558)	100 (558)				
Age ^a [median (IQR)]	69 (56–80)	69 (56–80)	0.98	69 (57–80)	69 (57–80)	0.97
Female ^b [% (<i>n</i>)]	24.2 (135)	24.2 (135)	1	30.9 (72)	30.9 (72)	1
Appropriate treatment	4.0 (4–5)	5.0 (4–6)	≤0.01	4.0 (4–5)	4.5 (4–5)	0.46
base score ^a [median (IQR)]						
Satisfaction score ^a	43.0 (36–49)	45.0 (40–53)	≤0.01	42.0 (36–49)	44.0 (38–49)	0.11
[median (IQR)]						

IQR interquartile range, *Q* quantile

^a For both groups, differences across time were tested using Wilcoxon test

^b For both groups, differences across time were tested using McNemar's test

Table 2 Simultaneous quantile regression model: differences in utility score between groups at follow-up

Cut-off points/ quantiles	Independent variables (or co-variables) included in the modelling ^a	EQ-5D ^b				SF-6D ^b			
		β	SE	95 % CI	<i>p</i> value	β	SE	95 % CI	<i>p</i> value
Q10	Constant	-1.44	0.33	-2.08, -0.79	≤ 0.01	-1.14	0.19	-1.51, -0.78	≤ 0.01
	Utility base score (β_1)	0.85	0.05	0.75, 0.94	≤ 0.01	0.61	0.05	0.52, 0.71	≤ 0.01
	Treatment (β_2)	0.00	0.18	-0.35, 0.35	1.00	-0.10	0.09	-0.27, 0.07	0.25
	Appropriate treatment base score (β_3)	0.18	0.06	0.06, 0.30	≤ 0.01	0.09	0.04	0.02, 0.16	0.02
	0.10 Pseudo R ²	0.3763				0.2682			
Q25	Constant	-0.52	0.13	-0.78, -0.27	≤ 0.01	-0.69	0.15	-0.99, -0.40	≤ 0.01
	Utility base score (β_1)	0.88	0.05	0.79, 0.97	≤ 0.01	0.74	0.04	0.66, 0.81	≤ 0.01
	Treatment (β_2)	0.01	0.06	-0.12, 0.14	0.89	0.01	0.07	-0.12, 0.14	0.88
	Appropriate treatment base score (β_3)	0.07	0.02	0.03, 0.12	≤ 0.01	0.06	0.03	-0.01, 0.13	0.08
	0.25 Pseudo R ²	0.3347				0.3259			
Q50	Constant	-0.04	0.04	-0.11, 0.04	0.31	-0.33	0.16	-0.65, 0.00	0.05
	Utility base score (β_1)	0.94	0.04	0.87, 1.01	≤ 0.01	0.83	0.03	0.76, 0.90	≤ 0.01
	Treatment (β_2)	0.00	0.03	-0.05, 0.05	1.00	0.01	0.07	-0.13, 0.16	0.88
	Appropriate treatment base score (β_3)	0.00	0.01	-0.02, 0.02	1.00	0.08	0.03	0.02, 0.14	≤ 0.01
	0.50 Pseudo R ²	0.347				0.3702			
Q75	Constant	0.40	0.07	0.26, 0.53	≤ 0.01	0.22	0.15	-0.06, 0.51	0.12
	Utility base score (β_1)	0.56	0.06	0.44, 0.68	≤ 0.01	0.71	0.03	0.64, 0.77	≤ 0.01
	Treatment (β_2)	0.00	0.00	0.00, 0.00	0.63	-0.06	0.08	-0.21, 0.09	0.44
	Appropriate treatment base score (β_3)	0.00	0.00	0.00, 0.00	0.34	0.07	0.03	0.01, 0.12	0.02
	0.75 Pseudo R ²	0.2704				0.3049			
Q90	Constant	0.55	0.10	0.35, 0.75	≤ 0.01	0.52	0.17	0.19, 0.85	≤ 0.01
	Utility base score (β_1)	0.31	0.04	0.24, 0.38	≤ 0.01	0.55	0.07	0.42, 0.68	≤ 0.01
	Treatment (β_2)	0.00	0.07	-0.14, 0.14	1.00	-0.01	0.07	-0.15, 0.13	0.87
	Appropriate treatment base score (β_3)	0.07	0.02	0.03, 0.11	≤ 0.01	0.09	0.04	0.02, 0.16	≤ 0.01
	0.90 Pseudo R ²	0.0615				0.1988			
<i>N</i>		720				720			

Q quantile, *SE* standard error

^a The final simultaneous quantile regression model estimated was: $Q_i(\text{EQ-5D or SF-6D}) = \text{Constant} + (\beta_1 \text{ Utility base score} \times \text{Utility base score}) + (\beta_2 \text{ Treatment} \times \text{Treatment}) + (\beta_3 \text{ Appropriate treatment base score} \times \text{Appropriate treatment base score})$ where: i indicates the specific cut-off point or quantile (i.e. Q10, Q25, Q50, Q75, or Q90), β_1 Utility base score, β_2 Treatment, β_3 Appropriate treatment base score and Constant are the coefficients and constant term specific to a particular quantile i

^b Dependent variable: utility score at follow-up

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