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Quality of life and alcoholic cirrhosis of the liver: an economic approach

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Introduction

This paper reports a pilot study for a larger economic evaluation into the treatment of alcoholic cirrhosis of the liver (ACL). The project began as part of an MSc Health Economics project as a small study to test various methods of utility measurement in patients with ACL. This pilot study is part of a proposed larger trial into a treatment for ACL known as S-Adenosylmethionine (SAMe). This is a multi national trial which incorporates an economic evaluation alongside a traditional clinical trial. The estimates of the utility values obtained in this study maybe used in a decision model as part of the larger economic evaluation based on the trial.

The aim is for the results from this pilot study to be reported in a medical journal in the area of hepatology to illustrate the concepts of utility measurement to clinicians. Therefore, this paper is presented in the format of a clinical journal article and one piece of advice we would like to receive is whether the paper would be suitable for such an audience.

Cirrhosis of the liver is a common, and increasing, cause of death internationally [1, 2]. The symptoms of alcoholic cirrhosis of the liver (ACL) can have a huge impact on quality of life by restricting normal functioning [3, 4]. In a chronic disease, such as ACL, where no treatment can offer a complete cure, quality of life may be seen as the primary outcome of treatment. There is also growing recognition, in health care evaluations, of the importance of complementing traditional, clinical endpoints (such as mortality, morbidity and biomedical indicators) with patient-reported outcomes [5] Despite this, there have been no studies conducted on quality of life in ACL patients specifically. Studies have been conducted on patients with the general condition of cirrhosis of the liver [3] and post liver transplant patients [6].

Quality of life is essentially multi-dimensional, instruments to assess it being conveniently divided into ‘generic’ and ‘specific’. Generic instruments are designed to ‘capture a very broad range of aspects of health status’ [7] and therefore to be applicable across a wide range of disease groups as well as to healthy individuals. They can also be useful in conditions where no disease-specific instrument is available. In addition, they may detect unexpected and non-specific effects of any intervention, whether positive (e.g. enhanced energy levels) or negative (e.g. drug side-effects), which would be missed by a very focused disease-specific instrument [8-10]. However, the development of a widely applicable generic instrument may result in the omission or minimisation of content and/or detail that would be relevant to certain disease groups. By forgoing such detail, the generic instrument may lose relevance and may be less responsive to change in a particular disease group or following a specific intervention [5]. Disease-specific instruments, on the other hand, are developed to assess the effect of one particular condition on health status or quality of life and to ameliorate some of the problems of generic instruments [11]. It is now generally argued that a combination of disease-specific and generic instruments should be used. Moreover, for economic

evaluations, such measures should incorporate the strength of patients' or society's preferences for the different health states of concern.

To date, the studies in ACL have used generic, indirect methods of assessing quality of life such as the SF-36 or the EQ-5D whereby patients rate their health which is then scored using a 'tariff' derived from another sample, usually of the general population. There have been no studies which attempt direct measurement of the values that patients with ACL attach to health states associated with ACL. The aims of this paper are to describe a particular method of measuring such values, known as utility assessment, and report on a pilot study aimed at deriving such 'utilities'. Results from the use of this more specific approach are compared with patients' assessments of quality of life through the two generic measures referred to above. In the following section, the concept of health state utilities is described in more detail, focusing on how such utilities feed into the construction of a particularly useful outcome measure for economic evaluation, and, thus, resource allocation, the quality adjusted life year (QALY). The methods and results from the study aimed at deriving utilities for the main classifications of ACL are reported before discussing the policy and research implications of the project.

Utility assessment and QALYs

In the health context, 'utility' is an estimate of how good or bad a health state is. Thus different degrees of impairment would be weighted (or given a utility value) between 0 and 1, where 0 is assumed to be equated to 'being dead' and 1 is equated with 'full/normal health'. These weights can be used to 'quality adjust' survival gains or remaining years of life, hence the term 'QALY'. QALYs are the product of life years and the quality of those life years. Therefore, two years in a health state valued at 0.5 would be equivalent to one QALY, the same as one year spent in a health state valued at 1.0. This is useful because, if time in different health states can be empirically assessed and it is feasible to value those different health states on the 0-1 scale, then, using QALYs, the impact of different treatments can be compared on a common unit of assessment which encompasses both quality and length of life [12].

QALYs can be illustrated using a hypothetical time profile of a patient with ACL (Figure 1). This hypothetical profile is of a patient with fifteen years to live who, at diagnosis, is classified as a Child-Pugh A cirrhotic. Following the solid line in the Figure, for two years s/he continues in a Child-Pugh A classification, which is assumed here to have a utility value of 0.9 – that is, not quite as good as full health. His/her health then deteriorates to a Child-Pugh B classification for the remaining 13 years with a corresponding utility value of 0.7 assumed for each of those years. This gives a total of 10.9 QALYs ([2*0.9] + [13*0.7]). Imagine a drug which altered the profile so that a patient was kept at Child-Pugh A level for longer, thus following the dotted line between years 2 and 10, after which s/he deteriorates to Child-Pugh B for five years, joining the solid line again. With the same utilities of 0.9 and 0.7 (respectively) attached to the years in each of those states, this would yield a total of 12.5 QALYs, or a gain of 1.6 QALYs over the original (without drug) profile.

QALYs are used in health care resource allocation through comparison of the cost per QALY gained by different treatments, thus aiding judgements about how best to spend limited budgets to achieve maximum health (or QALY) gains. For example, all else being equal, and assuming a fixed clinical budget, if a treatment had a cost per QALY of £1,000 whilst another had a cost per QALY of, say, £50,000, resources would be moved out of the latter and into the former, thus increasing the number of overall QALYs produced from the budget.

For illustrative purposes, the utility values used in the above example were assumed. The next question is how to estimate such values empirically. These 'quality adjustment' components of the QALY can be derived by a number of different techniques [13]. The objectives of this study were to estimate such weights from a sample of patients with ACL using, first, two 'off-the-shelf' measures, the EQ-5D and the SF-36, to obtain general measures of quality of life, and second, a more direct measure known as the standard gamble [13]. These instruments were used to rate individuals' own health. The standard gamble was also used to place values on three separate health state descriptions, each representing one of the three Child-Pugh classifications commonly used to monitor disease progression in this patient group [14].

So far in the literature, utilities have been estimated only for patients with the general condition 'cirrhosis of the liver' [3]. Estimation of utilities by Child-Pugh classification will allow treatments within the ACL area to be compared in terms of QALYs gained, and for such information to be used for purposes of resource allocation as described above. This is the first study to use direct methods of preference elicitation to show how people affected by ACL value the health states they are in or are likely to go through.

Method

Study sample

The patients used in this study were drawn from a hospital ward and an outpatient clinic in the same hospital in north-east England. Patients with ACL who attended the outpatient clinic for routine follow-up between August 2003 and April 2004 were approached for questioning. Local ethical committee approval for the study was obtained. Patients who were admitted to the ward with ACL were examined by a doctor before their suitability for questioning was determined. Prior to attending the outpatient clinic, each potentially suitable patient had been sent a letter from the doctor asking them to participate in the study, along with an information sheet informing them of the study details and what they would be required to do. Written consent to participate was obtained by the interviewer prior to the start of the interview for both inpatients and outpatients.

Questionnaire

A questionnaire was devised for each participant in the study to complete which would allow for indirect elicitation of a utility score reflecting their current health status. The questionnaire comprised two tools, the EQ-5D and SF-36,

used to measure quality of life. Pre-defined utility values, from previous surveys of the general population, are available for the EQ-5D. The EQ-5D questions ask people to rate their health status along five broad dimensions and on a visual analogue (thermometer) scale (VAS) from 0-1, again with 1 representing full health and 0 death [15, 16, 25]. The SF-36 comprises a series of 36 questions based across eight dimensions incorporating both mental and physical components [17]. Demographic questions were included so as to allow for a description of the sample. The Child-Pugh classification of each respondent was also noted by the interviewer from information received from the consultant (CPD).

Interview

The questionnaire was followed by a short interview at which the respondent was asked to rank 6 health states. Three of the health states were designed to reflect the symptoms and characteristics of Child-Pugh A, B and C classes. These three health states were derived from the Chronic Liver Disease Questionnaire [18], a review of the literature [3, 4, 6, 19-21] and expert knowledge from a hepatologist (CPD). They were labelled states X, Y and Z with state X approximating to Child-Pugh A cirrhosis, state Y approximating to Child-Pugh B cirrhosis and state Z to Child-Pugh C cirrhosis – see Appendix. The fourth health state was 'own health today', the respondent being asked to think about how they were feeling at the time of interview. The fifth health state was full health while the sixth state was immediate death.

Respondents were then asked four standard gamble questions to value the three health states associated with ACL and their 'own health today'. This section of the interview was conducted using a visual aid known as a chance board [22]. The chance board presents a choice between the certainty of being in an impaired health state (one of states X, Y or Z) for certain and a gamble. The gamble involves a probability (p) of returning to full health and a corresponding probability (1-p) of immediate death. This choice, Choice A, is illustrated in Figure 2, but its display on a chance board makes the exercise less cognitively demanding for the respondents. Choice B represents the certain outcome of remaining in the given health state (X, Y or Z) for the rest of his/her life. Within Choice A, the probabilities of returning to full health or immediate death were altered using a ping pong strategy [22]. This is where the probabilities are alternated back and forth between a high value of p (e.g. 0.9) and a low value (e.g. 0.1), continually narrowing the difference between the high and low values until the individual cannot choose between Choice A and Choice B. The ping-pong method was used to avoid any framing effects or anchoring bias [22, 23]. The use of probabilities means that each health state can be placed on a scale ranging from 0 (immediate death) to 1 (full health), where the utility value placed on the health state in question is given by the probability at which the patient cannot choose between A and B (or is 'indifferent' between A and B).

Analysis

The data collected during the interview and from the questionnaire were entered onto an SPSS database [24] to be analysed. The questionnaire was analysed in two parts. From people's assessments of their health on five

dimensions, and the corresponding utility scores from a survey of the general population of the UK [25], the mean EQ-5D tariff score was calculated, as was the mean of the VAS score. Summary statistics of the domain scores of the SF-36 and the mental component score (MCS) and the physical component score (PCS) were produced for the sample as a whole [26]. The rankings of the health states by the respondents were analysed to discover the percentage of respondents who had ranked the three ACL health states in the 'correct order' – in other words, indicating that they preferred the least severe health state (health state X, which is associated with a Child-Pugh A classification) over the others and so on. The mean standard gamble scores for each of the three ACL health states and the respondents' own health states were calculated. To test for consistency, mean values for the health states were compared with their 'natural' ordering with the expectation that health state X (representing Child-Pugh A) would be valued closer to 1 (i.e. full health) than either Y (Child-Pugh B) or Z (Child-Pugh C). Furthermore, values of own health from people of different Child-Pugh classifications can also be compared in a similar fashion. Finally, the utility values produced for own health were compared with the tariff values obtained from the EQ-5D questions and the VAS score.

Results

The sample comprised 20 respondents, 13 men and 7 women. 19 people gave their ages; the mean age being around 51 years, with a range from 29 to 78. Half of the patients were unable to work because of their illness. The respondents were categorised by Child-Pugh class; 9 were Child-Pugh A, 7 Child-Pugh B and 4 Child-Pugh C.

The mean EQ-5D tariff value and VAS scores produced from the questionnaires (Table 1) show that, at a group level, respondents value their health more highly through the VAS section than through the EQ-5D questions. Thus, it seems that respondents value their health more highly, in the VAS, than do members of the general population, through the EQ-5D tariff. This is not uncommon amongst people with a chronic disease and may be related to adaptation to their health status. However, it may also be that those who have not experienced the health state cannot conceive what it is like and think it is much worse than it is in reality.

The respondents' SF-36 scores for all eight domains, the MCS and the PCS are shown in Table 2. For the SF-36 domain scores the highest score was for the mental health domain (63.89) and the lowest was the general health domain (44.04). The PCS was lower than the MCS indicating this sample of ACL patients were more limited in their usual physical activities.

Ten people in the sample completed the ranking exercise. The 'correct' ranking order was to rank health state X above health state Y and to rank this above health state Z. The ranking of 'own health today' was excluded from this section of the analysis. When asked to rank the three ACL health states directly, all ten respondents ranked states X, Y and Z in the 'correct order'.

However, only two peoples' standard gamble valuations of the three states placed them in the 'correct' order. Five people gave two of the states the same value, two people valued all three of the states the same and two people valued the states incorrectly, i.e. a more severe state was valued higher on the 0-1 scale than a less severe state. One person only valued states Y and Z and eight people did not complete the standard gamble component of the exercise. For those outpatients who did not complete the standard gamble exercise the main reason was due to lack of time to complete the exercise and the questionnaire. For a small number of inpatients who had difficulty completing the questionnaire it was decided by the interviewer not to continue onto the standard gamble exercise.

The scores that were obtained, using standard gamble, for each health state during the interview period represent the directly derived utility values of those states. The utility values of the four health states that were used in the interview are presented in Table 3. At an aggregate level, the mean utilities are in line with expectations, with State X (Child-Pugh A cirrhosis) valued highest and State Z (Child-Pugh C cirrhosis) valued the lowest. Thus, at the group level, the results appear to make sense.

The utility values individuals placed on their own health depended upon disease status (see Table 4) and again follow a logical pattern, with those who are healthier, according to Child-Pugh classification, rating their own health higher.

The utility values for the respondents' own health were different for each of the valuation techniques used. The mean utility value for 'own health' elicited using the standard gamble was higher than the mean utility value elicited by applying the tariff to the responses to the individual EQ-5D and to the values stated in the EQ-5D VAS (see Table 5). Once again, the results make sense in that, not only will patients value their health higher than the general public, but also the VAS tends to lead to a lower value for a given health state as it does not involve any notion of sacrifice as embodied in the standard gamble in which respondents are faced with a probability of death if they select the gamble as opposed to the impaired health state for certain [27].

Discussion

From assessment of their own health, the mean EQ-5D tariff value of the sample as a whole for their current health status was 0.6159 and that from the VAS score was 0.71. This is not surprising, as, firstly, patients with chronic conditions are likely to value their own health more highly than members of the general public (from whom the EQ-5D tariff is derived) and, secondly, the EQ-5D tariff allows for negative scores (i.e. scores worse than death) not permitted with the VAS. A Child-Pugh C patient interviewed on the ward valued their health worse than death with the tariff value based on their responses to the first five items producing a utility value of -0.59.
On the SF-36, scores on mental health components of the questionnaire were higher than those for the physical components. This compares with the

literature which reports physical problems as more likely to affect the quality of life of patients with ACL rather than mental problems [4].

In the QALY literature, it is not uncommon to find inconsistencies in ordering of health states at the level of individual respondents [28]. Despite such inconsistencies, at the group level the valuations of X, Y and Z were in the 'correct' order with X (0.64) valued higher than Y (0.58) which was valued higher than Z (0.43). Similarly, the valuations of 'own health' were as expected, with Child-Pugh A patients valuing their health higher than Child-Pugh B and C patients. One discrepancy here is that Child-Pugh A patients value their health at close to 0.8, unlike the sample as a whole who valued state X (representing Child-Pugh A) at 0.64. This raises the question of whose values are to count in such exercises (especially if the values are for purposes of resource allocation) and the need to obtain more accurate estimates from larger samples of patients. It may also raise issues about the development of the health state descriptors used for the standard gamble exercise. Further piloting of these descriptors may be useful to establish how people with Child-Pugh A, B and C cirrhosis would describe their health in contrast to the descriptions provided by the hepatologist. At an individual respondent level there were two patients who valued health states X, Y, Z and their own health with the same value. This may have been because the respondent did not fully understand the standard gamble exercise. When comparing the utility values of own health elicited from the EQ-5D and the standard gamble, the standard gamble values came out higher (0.7125 against 0.6159), again likely due to respondents rating ACL higher than members of the public. This raises the question of which method would be used to derive the utility values in a clinical trial.

The results of this study must be treated with caution if they are to be used in making judgements about further care of patients with ACL as the small sample size may not be representative of the population of ACL patients. This small sample size may be further diminished as, during the course of this study, it became obvious that many of the patients who were interviewed on the hospital ward were unsuitable for inclusion with the most severely ill patients unable to complete the questionnaire and the standard gamble exercise. In any future work with patients with ACL it may be appropriate to eliminate those who are most severely affected or to devise other methods for aiding them in such cognitively demanding tasks.

Nevertheless, given the emphasis placed on ACL in the Chief Medical Officer's recent report on the health of the nation, more emphasis will likely be placed on evaluating interventions in this area [29]. Given that 'value for money' is likely to be one criterion of such evaluations, and estimates of cost per QALY gained are accepted as the way of expressing this, it will be important to think about how patients value the different health states associated with ACL. Thus, despite the above caveats, it is important to recognise this study is the first to show how people with ACL value their own health and health states associated with ACL using direct methods of preference elicitation and that these values may form the basis for estimates

of the values attached to health states in future economic evaluations of interventions to alleviate the problems of ACL.

In addition to the issues raised above, we seek advice on whether, given that a decision analytic model based on the clinical trial would likely focus on movement between Child-Pugh states, is elicitation of values of these from patients appropriate, standard practise, etc?

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Table 1: EQ-5D Utility Score and VAS Score

	N	Minimum	Maximum	Mean
EQ-5DTariff Value	17	-0.59	1	0.6159
EQ-5D VAS	19	0.30	0.95	0.71

Table 2: SF-36 Domain Scores, Physical Component Summary Score and Mental Health Component Summary Score

	N	Minimum	Maximum	Mean
SF-36 - PHYSICAL FUNCTION SCALE SCORE	19	.00	100.00	59.1082
SF-36 - ROLE-PHYSICAL SCALE SCORE	19	.00	100.00	45.5044
SF-36 - BODILY PAIN SCALE SCORE	18	.00	100.00	56.6667
SF-36 - GENERAL HEALTH SCALE SCORE	18	10.00	77.00	44.0417
SF-36 - VITALITY SCALE SCORE	18	.00	87.50	49.6528
SF-36 - SOCIAL FUNCTION SCALE SCORE	18	.00	100.00	61.8056
SF-36 - ROLE-EMOTION SCALE SCORE	19	.00	100.00	53.0702
SF-36 - MENTAL HEALTH SCALE SCORE	18	30.00	85.00	63.8889
SF-36 - PHYSICAL HEALTH SCORE (UK DATA)	18	7.21	52.64	33.0844
SF-36 - MENTAL HEALTH SCORE (UK DATA)	18	28.38	59.66	44.4422
Valid N (listwise)	18			

Table 3: Standard Gamble Utility Values

	N	Mean	Std. Deviation
SG probabilty of state X	11	.6364	.27937
SG probability of state Y	12	.5833	.28471
SG probability of state Z	12	.4292	.28079
SG probability of own health	12	.7125	.28052
Valid N (listwise)	11		

Table 4: Standard Gamble Utility Values of Own Health

Child-Pugh Classification	Mean Utility Value of Own Health
A (n=5)	0.79
B (n=6)	0.69
C (n=1)	0.45

Table 5: EQ-5D Utility Score, VAS Score and Standard Gamble Valuation of Own Health

	N	Minimum	Maximum	Mean
EQ-5D Tariff Score	17	-0.59	1	0.6159
EQ-5D VAS	19	0.30	0.95	0.71
Probability of own health	12	0.10	0.95	0.7125

Figure 1: Time Profile of Hypothetical ACL Patient

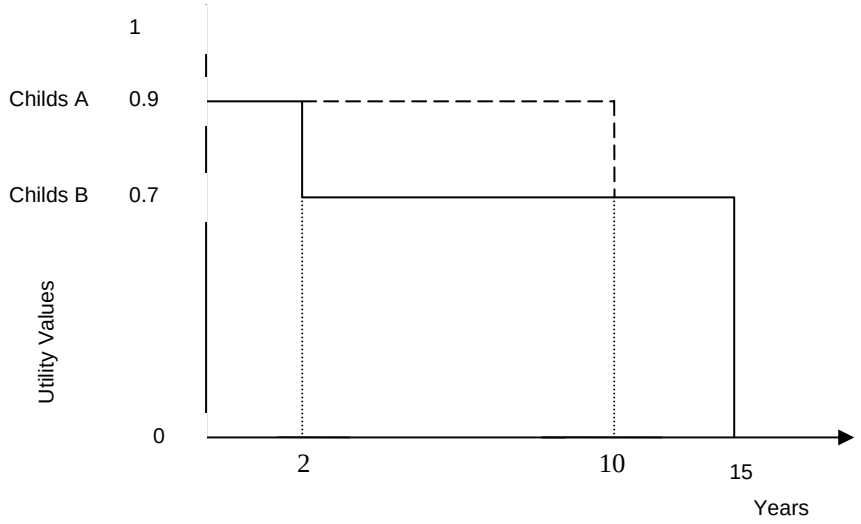
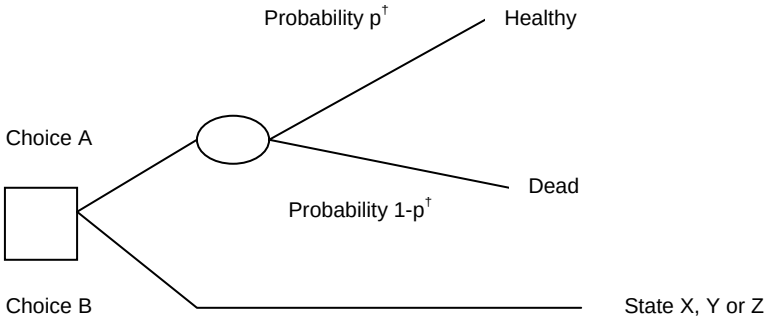


Figure 2: Standard Gamble



† Probabilities p and 1-p are varied until respondent cannot chose between A and B.

Appendix

Health State Descriptions

State X

- You will not develop jaundice
- You will feel tired some of the time
- You will not develop a swollen stomach
- You will not be troubled by itching
- A little bit of the time you will be worried about your condition getting worse

State Y

- Occasionally you will have jaundice
- You will feel tired a lot of the time
- Occasionally you will have swollen stomach
- Some of the time you will feel depressed about your condition
- You may become confused
- You may occasionally be admitted to hospital

State Z

- You will often have jaundice
- You will feel tired all of the time
- It is likely you will develop a swollen stomach
- You may be troubled by itching
- Some of the time you will be depressed about your condition
- You may become confused
- You are likely to spend several weeks a year in hospital
- You may vomit blood
- You may develop liver cancer

State O

- Your own health today