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DEMENTIA: CHALLENGES IN APPLYING THE QALY MODEL

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Summary

This paper explores the aspects of health care decision making that make use of QALY data, examines (using the available literature) the methods used to measure and value health, focusing on Alzheimer's disease (AD), and reviews the issues for health care decision making when health related quality of life (HRQoL) and utility data are required to support resource allocation in AD.

Abstract

The quality adjusted life year (QALY) model is based, amongst other things, on the premise that HRQoL is measurable on a single index scale. The QALY maximisation rule, often advocated by health economists, defines the objective of the health care system as the maximisation of the number of QALYs gained. Alzheimer's disease (AD) poses many challenges in applying the QALY model and the maximisation rule. Quality of life is multidimensional, for example, as AD progresses, cognitive problems give way to behavioural problems and apparent emotional distress gives way to loss of insight and sense of self. The burden of AD shifts from patient to carer thus requiring that the carer's health and quality of life be taken account of in the overall assessment of the QALY. Currently available health utility scales do not encompass many of the health related quality of life (HRQoL) domains relevant to AD patients and their carers and so could underestimate the value of halting AD progression. The shorter life expectancy of AD patients further reduces the scope for maximising QALYs. These factors are multiplicative and challenge the premise that with current methods "all QALYs are equal".

1. Introduction

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive degenerative disorder of the central nervous system. After onset the sufferer faces increasing cognitive impairment over time. Sufferers become increasingly unable to care for themselves and correspondingly the burden on their carers increases. The onset of AD is highly linked to age with few cases occurring before the age of 60, but with as many as 1 in 7 people over the age of 80 suffering from the disease. The ageing population means the number of cases will increase. Due to the high prevalence and debilitating nature of the disease the associated costs are high. Recent estimates have suggested the cost of AD to the UK is between £5.4 and £5.8 billion. However, estimates such as this miss a major

component of the burden of the disease, the significant impact on the health related quality of life (HRQoL) of sufferers and, most importantly, the impact on the carers of people with AD.

Policy decision makers in the UK have a preference for health utility and cost utility analyses to support decisions on resource allocation to health care interventions. However, these analyses are often done without establishing the validity or relevance of the utility measure to the disease in question. Thus there is the potential for a mismatch between the aspects of treatment that are valued by patients and society and what the instrument measures or values.

This situation is particularly important for diseases like AD where the progression of the disease is characterized by changes in the relative importance of different impairments over time. For example, cognition may dominate in the early stages but behavioural problems may dominate later on. In addition, the relative impact of the burden of the disease generally shifts from patient to carer as the disease worsens. With the gradual loss of cognition and associated insight, the assessment of patient HRQoL, especially emotional well-being or distress, is difficult to measure.

The definition of the value of an intervention and its assessment are not straightforward in AD. The methods used to derive utility values and societal preferences to capture the impact on a person who has AD to generate quality adjusted life years (QALYs) may not be adequate in AD.

Health Care Decision Making Using QALYs

The QALY was developed to combine the attributes of length of life and quality of life into a single index measure. The number of QALYs relating to a health outcome are expressed as the value 'Q' given to a particular health state multiplied by the value of 'T', the time spent in that health state, multiplied by the size of the group.

Health economists have often asserted that resources should be directed towards interventions that yield low-cost QALYs and away from interventions that yield high-cost QALYs, thus implying that one objective of the health care system should be to maximise the number of QALYs gained. This allocation rule embodies the equity principle that a QALY is considered to have the same value across all individuals.

Harris (1) suggests that QALYs discriminate against the disabled. For example: suppose an intervention adds one year's life expectancy for an able-bodied individual. This intervention will result in a health gain of approximately 1 QALY. If the same intervention adds a year's life expectancy for a patient with disability, this will result in a health gain of less than 1 QALY. If decisions are made using cost per QALY thresholds, it suggests that the health care decision maker is willing to pay more for extending the life of an able-bodied individual than for a disabled person.

It could also be argued that in diseases where there is no cure and interventions can only alleviate symptoms or reduce the rate of progression, the potential to gain QALYs is limited, and hence the cost per QALY for these interventions is likely to be high. This contrasts with interventions for acute diseases, where an individual has the potential to return to full health.

Whilst the goal of allocating resources informed by QALY information is laudable, the user of the information should be aware of the underlying assumptions and measurement difficulties inherent in estimating the 'Q' in QALY. Beyond these general cautions, when deriving QALY data it is also important to appreciate that certain chronic conditions and some acute illnesses do not lend themselves readily to deriving QALY data.

2. Objectives

1. To describe AD and its progression in clinical and humanistic terms for both patients and caregivers.

2. Identify the methods for measurement and valuation of AD reported in the literature.
3. Evaluate the ability of the instruments identified to capture the impact of AD on patient and carer HRQoL.
4. Identify areas for further research to fill gaps in HRQoL and utility assessment in AD.

3. Methods

Literature Search and Strategy

A structured literature review was performed. The databases Medline, Embase, Healthstar, PsycInfo and OLGAs were searched. The searches were limited to English language articles after 1995. The search terms included were: Alzheimer's disease, dementia, disease progression, physical function, cognitive function, clinical impact, functional impact, behaviour problems, health status, health related quality of life, quality of life, carer burden, cost-utility, QALY, HYE, utility, valuation, EQ5D, HUI, QWB, 15-D. The bibliography of located references was searched for additional articles of interest. This resulted in substantial extra literature. In addition, a search for grey literature was conducted.

Papers were selected on the basis of abstracts and then reviewed. For the purposes of this paper, reference to quality of life refers to HRQoL, as defined by Revicki (2). This concept incorporates all the factors that impact upon an individual's health, including dimensions such as physical, sensory, cognitive, social and emotional functioning as well as experience of pain and the ability to care for oneself. Literature that reviewed or used instruments that did not conform to the definition of HRQoL were not included in this review.

The remaining literature was carefully reviewed and synthesised to identify a conceptual model of HRQoL for AD. The HRQoL and utility methods and instruments used to measure the impact of AD on patients and carers were summarised. The HRQoL instruments and utility assessment methods and instruments were evaluated against current best practice in HRQoL and utility measurement and against the conceptual model of HRQoL in AD. The final stage was to identify any gaps in evaluation of HRQoL and utility assessment in AD and identify areas for further research.

4. Results

The Clinical Aspects of Alzheimer's Disease

AD is typified by a chronic, unremitting decline of capacity and ability in cognitive, personality/behaviour and motor domains, leading to premature death. In general the time from onset of symptoms to diagnosis is about three years, and the average time from diagnosis to institutionalisation is around two years. Once institutionalised, the mean time to death is about 3.5 years. Overall disease duration from onset of symptoms is approximately 8.5 years (3, 4, 5).

During the progression of AD, there appears to be a hierarchical decline in function but not cognition (3). Various cognitive abilities are affected at different stages of AD and display dissimilar rates of deterioration in different patients (3). Some studies have suggested that deterioration in AD, as measured by annual changes in cognitive scales, does not occur at a consistent rate, but rather is slower for mildly and severely demented patients, and faster for moderately demented patients (6). Despite these findings, the literature carries general estimates of the expected rate of decline using various instruments (7)(8).

The apparent course of the disease can be affected by the individual. For example, someone with high verbal abilities, IQ and education may be able to compensate for some aspects of early disease. However, those with complex and demanding jobs may be seriously affected by even

slight declines in memory or language ability. Similar slight declines may not have an impact on job performance in someone with very routine work (3, 9, 10).

Disease Staging

Several staging methods have been developed, one of the most common descriptions used by physicians categorises AD as mild, moderate or severe (10,11). Mild disease is often not obvious to those who do not know the patient and may be denied by both patient and caregiver. Moderate disease is obvious to strangers and interferes with daily activities (3, 10).

Clinical Dementia Rating (CDR) system (12) is a global evaluation instrument that stages patients according to the severity of dementia measured over several domains. Table A1 in the Appendix summarises information on the clinical course and staging of AD and shows how different aspects of the disease are highlighted in different stages.

Morbidity of Alzheimer's Disease

Some investigators have found that AD patients have an average of about 2.9 medical diagnoses each, compared with 5.2 diagnoses for matched, non-demented subjects. It may not be the case that AD patients have fewer morbidities, rather, it may reflect the difficulty of making a diagnosis of AD if other confounding medical conditions are present. AD patients probably also under-report symptoms, and diseases may present with atypical features because of difficulties in communication (3).

The following are examples of co-morbid conditions and consequences associated with AD:

- Poor judgement predisposes to vehicle and household accidents (10)
- Motor co-ordination diminishes, accidents and falls become more common, often with associated fractures (3,10)
- Poor diet may lead to malnutrition and wasting, associated with an increased incidence of infections (3,10)
- Urinary and faecal incontinence may lead to urinary tract infections (13,7)
- Impairment of the swallow reflex is associated with choking and aspiration pneumonia (3,10)
- Faecal impaction is common (3,10)
- Depression is found more often in the AD population than in the general population, with some studies reporting a prevalence of up to 50% (3,10).

Mortality Due to Alzheimer's Disease

AD shortens life expectancy compared with the general population. AD patients typically survive for seven to eight years after diagnosis, although extremes of two and twenty years are known (3). Patients with early onset of the disease have an average post diagnosis survival of 6.8 years, contrasted with 21.5 years in matched controls. Patients with late onset AD have an average survival of 5.1 years, compared with 9.6 years in matched controls (3).

Mortality due to AD is greatly underestimated because the death certificate rarely attributes AD as the cause of death. AD is an underlying indirect cause of death in many patients, the most common direct causes being pneumonia, tracheal aspiration, pulmonary embolism and septicaemia from UTI or pneumonia (3).

Humanistic Aspects of AD: Conceptual and Measurement Issues

HRQoL in AD

Assessing HRQoL in AD poses unique challenges. Not only are there challenges of defining HRQoL in a disease with increasing problems with cognition, and the loss of a sense of personal identity (14), but the practical issues around making assessment of HRQoL in people with AD provide a considerable challenge. However it is important to measure HRQoL, as more therapies become available. Whilst these may not always have a clinically significant effect on clinical measures of disease progression, they may impact mood, engagement in activities and self awareness, all of which would effect HRQoL.

The Conceptual Framework of Alzheimer's Disease

Most conceptual frameworks of HRQoL probably contain many of the domains relevant to older adults as well as younger ones. The precise definition of the domains may differ for older adults because of their changing role and living conditions and the greater variation in health. For example, physical function may need to be defined in terms of more basic functions such as getting in and out of a chair or climbing a few steps (1). The validity of HRQoL measures developed for general populations need to be confirmed in the AD population. The first steps in this process is to define a conceptual model for AD.

Table 1 presents the domains suggested for dementia specific HRQoL taken from Brod and Stewart (15).

Table 1: Dementia Specific HRQoL

DOMAIN	DEFINITION
Aesthetics	Enjoying/appreciating beauty, nature and surroundings
Positive Affect	Experiencing humour, feeling happy, cheerful, content, hopeful
Negative Affect	Experiencing worry, frustration, depression, anxiety, sadness, loneliness, fear irritability, nervousness embarrassment, anger
Self Esteem	Feeling accomplished, confident or satisfied with self, able to make own decisions
Feelings of belonging	Feeling lovable and liked, useful

Selai's (16) summarises issues from qualitative interviews with a sample of people with mild to moderate dementia (n= 14). The issues deemed important for HRQoL in dementia, reported from patient on self and carer on patient, were grouped into the following domains:

- Physical health,
- Psychological health
- Social life
- Family life
- Work/main activity
- Cognitive problems

In 1997 Whitehouse (17) reported that the Alzheimer's Advisory Panel of the US Department of Health and Human Services was developing a conceptual model in which the dimensions of HRQoL appear on one axis and stages of disease on another. As the disease progresses, the loss of ability to perform simple tasks such as self-care become more prevalent as do behavioural and physical problems which finally lead to nursing home placement. The distinct stages of AD can have differing impacts on HRQoL. The conceptual models found describe only mild and mild to moderate AD and Whitehouse's paper makes only general statements about HRQoL and AD in all stages.

Mild AD is characterised predominantly by cognitive symptoms and loss of ability to perform complex tasks and functional independence. At the mild state there is disruption predominantly to complex tasks and patients experience intermittent distress as they become aware of the increasing impact of the disease. This stage of the disease is still consistent with the consensual approach to the meaning and measurement of HRQoL. Patients can be assessed by questionnaire, and their responses will reflect their HRQoL. The challenges of identifying relevant domains of HRQoL and measurement relate to the appropriate choice of instrument to capture the impact of AD symptoms at this stage and the reliability of results due to loss of memory relating to recent experiences and events and lack of understanding of the task itself.

At the moderate stage, there is increasing disruption to simple activities. Any apparent lack of distress at this moderate stage could lead to the inference that patients' HRQoL actually improves on the domain of mental functioning. This might be the view if a proxy answered an HRQoL questionnaire appropriate to the moderate stage. However, a lack of distress at this stage may not be due to improvement in mental functioning but, because mental functioning has deteriorated, it may be that it is no longer as relevant a criterion for HRQoL as it is for the mild patient. The reason for the apparent lack of distress might be because the capacity for distress has disappeared along with a decrease in self-concept, or, a decrease in 'personhood' (14).

AD patients in the moderate stage of disease begin to challenge the consensual definition and measurement of HRQoL – that the patients functions, phenomenologically, as a person. However, Whitehouse et al (17) maintain that intact cognition is not necessary for HRQoL. Emotional well-being can still result from a variety of sources such as relationships activity and human touch all of which are experienced by AD patients.

The later, more severe stage of AD, is marked by the initiation of problem behaviours, such as wandering and incontinence. This severe stage is economically important because these problem behaviours can initiate transfer to institutional care. Wandering and other problem behaviours may result in poor health if they put the patient at risk of harm, but of themselves they do not constitute any deterioration in the patients HRQoL. The patient remains active and activity is a positively valued attribute of HRQoL. What problem behaviours may amount to, however, is a deterioration of the caregiver's HRQoL.

Brod (15) suggests that negative behaviours such as wandering and shouting can serve as examples that such objective manifestations of dementia are not considered part of HRQoL (for the patient) as the meanings of the behaviours are unclear. Ronch (18) suggests that these negative behaviours may even be 'problem solving behaviours' for the patient. In the same paper Ronch also suggests that what the observer sees as simple memory loss can be the result of multi-level emotional and cognitive experiences.

The issues described above suggest that value judgements are very much to the fore when reviewing the impact of AD on patient and in building a conceptual model of HRQoL in AD.

HRQoL Measurement in AD Patients and Caregivers

A UK Health Technology Assessment (UK HTA) report evaluated use of patient based outcome measures (including HRQoL instruments and multi-attribute utility scales (MAUS)) in clinical trials (19). Criteria for evaluation of patient based outcome measures stated are:

- Appropriateness
- Reliability
- Validity
- Responsiveness
- Precision
- Interpretability
- Acceptability
- Feasibility

This review of available instruments for use in AD uses these criteria, paying particular attention to validity – whether the instrument measures what it purports to measure and the constructs relevant to AD and its stages.

Rabins et al, in a recently published paper, report a USA based cross sectional study using the ADRQoL instrument in moderate AD patients, cared for in a specialist assisted living/nursing home environment (20). The total ADRQoL score was significantly correlated with the clinical indicators of AD, such as cognitive impairment, physical symptoms and depression. A ceiling effect was observed, and a number of plausible reasons suggested. There were also some inconsistent results and the type of care offered in the study setting was very specialised. There is no other reported validation of this instrument. The ADRQoL does not meet the criteria outlined in the HTA report, though it may prove to be valid in mild and mild/moderate AD patients.

Brod et al have developed the D-QoL (21). As yet in the early stages of development, the D-QoL is designed so that the mild to moderately demented individual can complete it without resort to a proxy. The instrument does not meet the HTA report requirements thus far but is a promising development for this group of patients, particularly if it does rise to the challenge of patient self completion. The instrument is not designed for severe AD.

Selai et al (22) have taken a different approach to the measurement of HRQoL and adapted the Quality of Life Assessment Schedule (QOLAS) for AD. This approach yields both quantitative and qualitative data. The main advantage of the QOLAS is that each respondent can identify the items of importance to his own HRQoL. It is an interviewer administered instrument. The QOLAS was tested in people with mild to moderate dementia (mostly AD dementia) alongside a range of other measures to test the psychometric properties of the instrument. The results suggested that these patients could rate their own HRQoL and that the QOLAS was reliable and valid in this group of patients. It is a promising method, but as yet does not meet the UK HTA criteria.

Logsdon et al (23) report the development of a 13-item interviewer administered HRQoL instrument for AD – the QoL-AD. The instrument was tested in a population of 77 community based (USA) AD patients with probable or possible AD (i.e. mild). Of the caregivers, 95% lived together. The caregiver and person with AD both complete the questionnaire, but the focus of HRQoL measurement is the person with AD. A composite score derived from both patient and carer responses can be calculated or the instrument can yield a ‘stand alone’ score for a patient completed or carer as proxy response. In this study the patient and caregiver reports are related, but different. Depressed caregivers gave the patients HRQoL a lower rating than non-depressed caregivers. This study reports the QoL-AD as valid and reliable and confirms that research is continuing that will look at the performance of the instrument over time, the impact of interventions and the effect of patient/carer relationships on HRQoL.

A review of the HRQoL literature in AD (up to 1997) was undertaken by Walker and Salek et al (24, 25). The review covered both HRQoL, some functional and health status measures and utility instruments used in surveys of AD patients and carers, and in intervention studies. The instruments were reviewed and rated for validity, reliability and sensitivity, with none achieving their highest possible rating (comprehensive validation in a large sample producing good results using an acceptable methodology). None of the instruments reviewed by Walker and Salek appear to meet the UK HTA criteria apart from the SIP which Salek reports as valid, reliable and sensitive in a single study. In one small study, which used a widely used generic HRQoL instrument, the Short Form –36, in mild to severe AD patients, there was limited evidence to suggest that it was appropriate in AD. These two instruments, whilst broad ranging in evaluation of HRQoL, have limited ability to specifically tap into the constructs of HRQoL summarised in this review.

Broadly speaking the findings of this review support the issues reported by other authors, summarised above. Salek concludes that some instruments are ‘promising’ in the measurement

of HRQoL in people with AD. The sickness impact profile (SIP) excluding the work subscale is valid (according to his and the HTA definition) in a mild AD population.

Table 2 below provides a summary of the HRQoL domains and relationship with AD stages suggested by the literature.

The more heterogeneous the samples used for measuring HRQoL in AD, the more difficult it is to select a single instrument that will take account of the full range of functioning likely to be exhibited and the stage of the disease. Ceiling effects can also occur when using measures of self-care in an active non-frail older population. Floor effects can be encountered when using an instrument in a frail population. These effects will also depend on the levels within the domains of the HRQoL instrument.

Whitehouse's review (17) lists six questions (based on the evaluated literature published since 1997) that are critical to making progress in the area of HRQoL assessment in AD:-

1. How do we conceptualise the HRQoL of patients with dementia as they progress from the pre-symptomatic stage to the terminal state?
2. What characteristics of patients permit them to participate in a dialogue concerning their own HRQoL?
3. What are the characteristics of instruments that could be used to assess the subjective aspects of HRQoL in patients with dementia?
4. Do HRQoL measures offer us anything additional to the sum of measures of cognition, behaviour and function already available?
5. Can we validate HRQoL measures in dementia by comparing patient judgements with caregiver and external rater valuations? Is HRQoL an emergent concept that needs separate assessment?
6. How should we conduct cost-utility analysis in chronic progressive diseases? What are the appropriate reference groups?

In the context of the literature currently available (late 2000) these questions appear to be unanswered.

STAGE OF AD	CLINICAL MANIFESTATIONS	SUGGESTED HRQOL DOMAINS	HRQOL INSTRUMENT	HRQOL DATA SOURCE
	<ul style="list-style-type: none"> Mild impairment of function at home Needs prompting for personal care 	<ul style="list-style-type: none"> Situation Memory Family Marriage Friends Self Ability to chores Ability to do things for fun Money Life as a whole 		
(Mild to moderate)	<ul style="list-style-type: none"> Severe memory loss Severe problems with time relationships Problems with disorientation to place Severely impaired in handling problems Social judgement impaired 	<ul style="list-style-type: none"> Aesthetics Positive Affect Negative Affect Self esteem Feelings of belonging 	D-QoL	Brod and Stewart
	<ul style="list-style-type: none"> No independent function outside home Only simple chores preserved Requires assistance in dressing, hygiene etc. 	<ul style="list-style-type: none"> Physical health Psychological health Social life Family life Work/main activity Cognitive problems 	QOLAS	Selai
Severe	<ul style="list-style-type: none"> Severe impairment of memory and all cognitive functions Unstable effects on cognitive function, vision and language Loss of ability to care for self Very reduced mobility 	<ul style="list-style-type: none"> None described 	None	

HRQoL and the Carers of AD Patients

Kane (26) addresses the issue of appropriate outcomes in AD. He emphasises the importance of treatment outcomes in terms of alleviation of caregiver burden. Kane also raises an issue that should be borne in mind when evaluating HRQoL of carers - the state of mind that carers may develop. Denial of resentment, a sense of being irreplaceable, a strong sense of social duty and the obligation to give a socially desirable response may all serve to confound the results of HRQoL and caregiver burden assessment.

The caregiver's quality of life is important, and requires assessment. Caregiver's have their own health burdens that are increased by the stress of care giving. However, the caregiver is affected in different ways by mild, moderate, or severe patients. At the mild stage, caregiver distress will result primarily from empathy with the patient. At the moderate stage, caregiver burden will increase in the form of a number of additional activities that need to be performed during the day. At the severe stage, caregiver burden takes a qualitatively different form because there is no time during the 24 hours when the caregiver can be 'off-duty'. Thus, the shift from moderate to severe may reflect only gradual deterioration in the patient's HRQoL but a much more abrupt shift to the caregiver.

Surprisingly very little HRQoL research in AD carers appears in the literature. The domains of HRQoL relevant to caregivers as assessed by two reviews are summarised in Table 3.

Table 3: HRQoL Impact on Caregivers

Domains	STUDIES	
	Korczyn (27)	Hollister and Gruber (28)
Social Isolation		Depression and dysphoria
Verbal abuse and physical aggression by the patient		Increasing need to provide more care
Sleeplessness		Loss of personal time
Loss of independence		Growing social isolation
Financial burden		Significant financial difficulties

The Assessment of Utility in AD Patients and their Carers

The difficulties described in measurement of HRQoL in AD are equally evident in deriving a single utility index (the 'Q' in QALY) to calculate QALYs for people with AD. The methods and instruments used need to be valid in an AD population and need to address the stage specific aspect of quality of life together with the conceptual and measurement issues and the impact on the carer.

Lawton's review of HRQoL measurement in AD (29) rejects the notion that HRQoL can be reduced to a single construct or index and argues for profile scores generated from multidimensional instruments.

Chisholm et al (30) in their review of QALYs and mental health care discuss the difficult challenge of capturing the impact of HRQoL (for all the reasons described above) on people who have mental health problems or dementia. The review also makes the point that successful treatment of someone with such disorders will confer benefits on carers by improving their HRQoL and averting costs in caring for people. He also suggests that these important third party benefits should be specified, otherwise some interventions might be systematically under-valued.

Brazier and Deverill (31) review and summarise the existing MAUS used to derive 'Q.' It is clear that the individual MAUS have varying attributes and can vary in their suitability for different diseases. The HUI and the EQ-5D are the only MAUS that are true preference based instruments suitable for use in economic evaluation and QALY calculation.

Table 4 (next page) consolidates the domains identified for the various stages of AD and compares them with the HRQoL domains captured by the MAUS described below.

The Health Utilities Index (HUI)

The HUI appears in the literature in two forms, reflecting the development of the instrument over time. The HUI II instrument has the following domains: Sensory, Mobility, Emotion, Cognition, Self care, Pain and Fertility. The domains in the HUI III are Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition and Pain.

In a study by Leon (32) a proxy version of the HUI II was used in a cross sectional study of 679 AD patients and caregivers. The AD patients in the study were categorised by disease stage and by location of care. The study reported the strongest relationship between greater AD disease severity and lower HRQoL for patient. This was not affected by the type of proxy (related carer or professional carer). The authors stated that the 'burden' on the caregiver varied according to a number of factors such as disease severity, setting and familial relationship, though the HRQoL and utility scores were not reported.

More detailed results from the HUI II data were reported separately by Neumann (33). Caregivers completed the questionnaire as a proxy for the patient and for themselves. The results for patients were reported as above and the authors note that the HUI II discriminated between stages and demonstrated a decrement in scores compared with general population age adjusted averages. The single attribute scores least sensitive to AD stage were emotion and pain. This is not surprising as they are the two attributes requiring the most subjectivity in proxy ratings. The caregivers' HUI II score was not influenced by patients' setting or disease stage. The scores were no different to age adjusted norms, which might suggest that the HUI II is unable to detect subtle but important changes. The authors emphasise the difficulties in measuring HRQoL in this area, but suggest researchers in the future evaluate the use of the HUI III, which has modified definitions of health attributes.

The Quality of Well-being Scale (QWB)

The QWB has three domains, Mobility, Physical Activity and Social Functioning and allows selection of the most undesirable symptoms from a range of 27 symptoms/problems. The proxy QWB questionnaire, used to measure the impact on HRQoL for 52 AD patients (with a range of categories of dementia) and their spouse-carer compared with matched control dyads were studied in the USA by Kerner (34). The QWB score was found to be strongly related to the measurement of patient's behavioural problems and the patient's dementia ratings. Good correlation was found with the Mattis Dementia rating scale. Patients with poorer cognitive functioning tended to have lower QWB scores. The weight applied to a choice of 'trouble thinking, learning or remembering' from the range of 27 undesirable symptoms is one of the lowest on the QWB system, and perhaps explains the correlation of the QWB score with cognition even though the instrument does not have a cognition domain. The authors conclude that the strength of the correlations was augmented by the fact that spouse-carers were used as proxies and thus better insight on behalf of the patients' 'state of being' resulted from the close and long term relationship.

The EuroQoL (EQ-5D)

Selai (22) reported the use of the EQ-5D as part of a larger study exploring HRQoL in people with dementia (principally AD). The EQ-5D was administered as a self-report and as a proxy questionnaire to 19 patients with mild to moderate AD who were capable of expressing themselves clearly. The EQ-5D was also given to the carers to complete as proxies. Qualitative data were collected as part of a larger study. An interesting note is made in the paper that these interviews revealed that the patients' psychiatric symptoms were not viewed as a problem for the patient, by the carer (most usually the spouse) but impacted the carers' HRQoL. The patient

Table 4: Comparison of HRQoL and Utility Instrument Domains

STAGE OF AD	HRQOL DOMAINS	UTILITY INSTRUMENT DOMAINS
AD Generally	<ul style="list-style-type: none"> • Loss of independence • Side effects of drugs • Incontinence • Social isolation • Paranoid reactions • Sleeplessness • Hallucinations and delusions • Depression • Social interaction • Awareness of Self • Feelings and mood • Enjoyment of activities • Response to surroundings 	<p>QWB: Mobility, physical activity, social functioning, 27 symptoms/problems (includes difficulty thinking)</p> <p>HUI2: Sensory, Mobility, Emotion, Cognitive, Self-care, Pain, Fertility</p> <p>HUI3: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition, Pain</p> <p>EQ-5D: Mobility, Self-care, Usual Activities, Pain/discomfort, Anxiety/depression</p>
Mild	<ul style="list-style-type: none"> • The ability to enjoy various aspects of life • Ability to perform household tasks • Extent of frustration or confusion • The extent to which a person can leave their immediate neighbourhood and travel on public transport • The ability to function in social settings • A need to define self-esteem in terms of embarrassment and self-consciousness. 	<p>QWB: Mobility, physical activity, social functioning 27 symptoms/problems (includes difficulty thinking)</p> <p>HUI2: Sensory, Mobility, Emotion, Cognitive, Self-care, Pain, Fertility</p> <p>HUI3: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition, Pain</p> <p>EQ-5D: Mobility, Self-care, Usual Activities, Pain/discomfort, Anxiety/depression</p>
(Mild to) moderate	<ul style="list-style-type: none"> • Aesthetics • Positive Affect • Negative Affect • Self esteem • Feelings of belonging 	<p>QWB: Mobility, physical activity, social functioning 27 symptoms/problems (includes difficulty thinking)</p> <p>HUI2: Sensory, Mobility, Emotion, Cognitive, Self-care, Pain, Fertility</p> <p>HUI3: Vision, Hearing, Speech, Ambulation, Dexterity, Emotion, Cognition, Pain</p> <p>EQ-5D: Mobility, Self-care, Usual Activities, Pain/discomfort, Anxiety/depression</p>

proxy agreement ranged from poor to moderate. It was noted that the EQ-5D did not have a domain for cognition. Comments on the performance of the five EQ-5D domains are summarised below:

- Mobility: Performed well as this is rarely a problem
- Self Care: Performed poorly and wording not helpful (implies washing and dressing but does not actually say so). Ceiling effect for both carer and patient when problems are reported by IDDD.
- Usual activities: Poor patient proxy agreement where qualitative data had shown good patient proxy agreement.
- Pain: Not normally a problem for AD patients and despite proxies not normally recognised at being good at scoring pain of others, there seemed to be good agreement.
- Anxiety/depression: Not a domain that is directly 'knowable' by others, though can be inferred, however there was moderate agreement.

Even though this study was preliminary it seems reasonable to conclude that it is not appropriate to use the EQ-5D to derive utilities even in this mild AD population, and probably even less appropriate in a more severely demented population.

Krabbe et al (35) reported the development of the EQ-5D by adding a sixth cognition domain to the EQ-5D (the EQ-5D+). The health states that included the 'cognitive ability' domain were valued by a convenience sample of university staff. The methods used were robust, but the work was recognised as preliminary. The EQ-5D+ classification system performed nearly as well as the EQ-5D and the authors suggest that the instrument benefits from this additional domain. However only a small number of valuations of a set of health states exist for the extended instrument EQ-5D+ and a utility algorithm does not exist for the EQ-5D+. Therefore the EQ-5D+ can not be applied as a utility instrument.

Drummond et al (36) devised an instrument, the Caregiver Quality of Life Instrument (CQLI) in order to make assessment of utilities in a study of a support programme for caregivers, compared with no intervention for carers of elderly people at home. The study population included carers of people with AD (over 60% in both groups). The instrument used the Time Trade Off (TTO) technique in order to generate the utility score to calculate QALYs for the two groups. The CQLI was not able to detect a statistically significant difference between the groups, but as it was not the primary outcome measure the sample size may not have been enough to be able to detect a difference.

The MAUIs are generic instruments designed to have a core set of domains common to all diseases in order that the utility scores and the QALYs calculated using them are comparable across diseases. Inevitably this means that unique aspects of some diseases, and notably AD, because of issues described by the authors featuring in this review, will not be captured by a MAUS.

Other Measurement Issues

Kane (26) addresses the issues of appropriate outcomes in AD. He identified complex problems around the fact that the proxy for HRQoL measurement is usually the major caregiver for the AD patient. Despite best intentions it is hard to unravel the real issues from the fact that caregivers and families have a big stake in determining outcomes for people with AD.

Gonzalez-Salvador's (37) report of the study using the ADRQoL was performed in a specialised centre devoted to the long term care of dementia patients, and this might affect the results. The paper reviews the aspects of setting and proxy measurement by professional carers that might influence measurement of HRQoL. It is suggested that in this type of setting the carers might be motivated to report higher HRQoL for the patients in their care. Given the high HRQoL scores and observed ceiling effect in the ADRQoL in this study it is sensible that any studies of HRQoL and utility in AD patients should take account of the influence of setting.

5. Discussion

This review has revealed a paucity of useful data to direct a researcher towards methods of measurement of HRQoL and utility in AD and the effect of AD on the HRQoL of the carer. Many of the instruments used in studies purporting to report HRQoL actually report functional status measurement. However, there is a small body of literature that has begun to identify the key issues around HRQoL measurement and to identify the themes and constructs that describe HRQoL for people in the early stages of AD. There is almost universal agreement that understanding what HRQoL is to the severe AD patient and the consequent measurement of HRQoL status verges on the impossible. Lawton (29) suggests that detailed observation by skilled and trained observers is the only way this can be done.

There is general agreement that HRQoL in AD has two important components, function and affect, but agreement is less strong beyond this point. It is clear that the nature of HRQoL for the AD patient shifts as the disease progresses, as does the impact of the disease on the carer, which will affect their HRQoL. One of the main questions still outstanding is from whose perspective the HRQoL is to be determined? As the burden of AD shifts from patient to carer as the disease progresses any intervention for the AD patient will affect the caregiver. Thus there is a patient versus carer tension, in terms of balancing the impact of interventions, which needs to be captured.

Walker and Salek (24,25) and Busschbach's (38) summary of HRQoL measurement in his review of methods for economic evaluations in AD (also published in 1997), suggest that the way forward for HRQoL is 'multi-assessment' in order to capture the different kinds of burdens imposed on patients and caregivers at different stages of the disease.

To move from measuring HRQoL in AD, and the complexity of the emerging picture, to measuring the 'Q' in QALY, is a challenge that seems not yet to have been met. There is, as in HRQoL measurement, an issue of different trade-offs between dimensions for both carer and patient at different times in the disease process. This is one of the aspects of AD that sets it apart from other diseases where QALYs have been derived, in which people get worse on the same dimensions over time. The instruments that have been used in AD patients are certainly measuring something, but as yet the evidence that the measurement captures 'Q' for AD patients at any stage of disease is unconvincing.

The QALY is designed to compare all interventions on the same scale. It seems that some diseases, such as AD, do badly out of this. This is less a criticism of QALYs but rather it reflects the important need to incorporate many other factors (such as equity) when making decisions about resource allocation in healthcare. The shorter life expectancy of AD patients reduces the scope for maximising QALYs. AD patients are very sick patients, for whom cure is not possible and social preferences are known to give greater priority to such patients (39).

There will always be trade-offs when using generic instruments such as MAUS, to ensure comparability between different diseases and completeness in being able to pick up every relevant piece of information. The MAUS reviewed here are designed to be generic, so inevitably do not encompass many of the HRQoL domains relevant to AD patients and carers and could underestimate the value of halting progression. Given current methodology the mismatch may be too great to allow use of MAUS and generation of QALYs in AD.

This view is endorsed by Chisholm (30), who accepts the merits of the principles and prioritisation that underlie the application of QALYs to health care decision making. However, he emphasises the technical challenges for deriving QALYs, the ethical qualms raised by the possibility that QALYs might discriminate against chronically ill and elderly people with mental health problems and the loss of information when dimensions of HRQoL are 'squeezed into a uni-dimensional straight jacket'. He suggests the necessary task is to inform decision making by bringing together all relevant data, rather than allowing the cost per QALY to drive the decision. He speaks for

mental health services in their entirety but it is relevant to dementia that he suggests that programme/disease specific utilities might be a better starting place for QALY generation.

6. Conclusions

Existing HRQoL and utility instruments only partially capture the complexity of a dementing illness, overlaid on an elderly population, whose disease and care visits itself profoundly on the carer. Busschbach (38) echoes the conclusions of Walker and Salek (24, 25) on the use of HRQoL and utility instruments, in AD.

“A multicriteria analysis seems more appropriate from a societal perspective in situations where the impact on caregivers is substantial”.

Both confirm the inadequacies in existing instruments and the care that is needed when considering use of an instrument. The need to validate a method for assessing HRQoL of both AD patients and their carers, at the same time, is vital. None of the ongoing research identified in this review seems to be responding to this need.

In order to meet the challenge of measuring utility to calculate QALYs for the different stages of AD and the impact on the carer it may be possible to use scenarios and profiles drawing on understanding of the disease stages and the conceptual model of HRQoL in AD proposed by Brod and Stewart. This approach has the potential to capture social preferences for the different stages of AD and the impact on the carer.

Capturing the impact of HRQoL alone has substantial challenges. Aspiring to derive a single index score ‘Q’ for AD, based on societal preferences, to provide health care decision makers with QALY data as an aid to decision making may be too challenging for the methodologies currently in use. If a QALY approach is taken to evaluate the cost-effectiveness of an intervention in AD, then different types of QALY calculation need to be taken at different stages of the disease. A single type of QALY assessment will not be valid.

Assessment of total value using MAUIs might under-estimate the baseline health state and fail to capture the full value of treatments. Incorporating a more accurate measurement of ‘Q’ into the QALY equation would perhaps improve the accuracy of the QALY value, but does not overcome the other issues (identified in this report) associated with using QALYs as an aid for priority setting. All the factors discussed are multiplicative and challenge the premise that with current methods ‘all QALYs are equal’.

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Appendix: Disease staging in AD
Table A1: CDR Disease Staging ⁽¹⁾

	HEALTHY (CDR 0)	QUESTIONABLE DEMENTIA (CDR 0.5)	MILD DEMENTIA (CDR 1)	MODERATE DEMENTIA (CDR 2)	SEVERE DEMENTIA (CDR 3)
MEMORY	No memory loss or slight inconsistent memory loss	Consistent slight forgetfulness; partial recollection of events; “benign” forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
ORIENTATION	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
JUDGMENT AND PROBLEM SOLVING	Solves everyday problems and business/financial affairs well; judgement good in relation to past performance	Slight impairment in solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgement usually maintained	Severely impaired in handling problems, similarities, differences; social judgement usually impaired	Unable to make judgements or solve problems
COMMUNITY AFFAIRS	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside home Appears well enough to be taken to functions outside the home	Appears too ill to be taken to functions outside the home
HOME AND HOBBIES	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
PERSONAL CARE	Fully capable of self care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

