Appendix H

Review of health related quality of life evidence in the TLoC population

The aim of this review is to summarise the available evidence on health-related quality of life (HRQoL) that could be used within the economic model to determine the cost-effectiveness of the various diagnostic tests. In order to estimate the cost-effectiveness of a health care intervention, such as a diagnostic test, it is necessary to determine not only how the intervention will affect patient outcomes, such as diagnosis of the underlying condition and subsequent treatment, but also how this will impact on the health-related quality of life of the individual and their life-expectancy. There are many different generic and disease specific tools that can be used to measure HRQoL, but preference based measures which estimate the health utility are useful when conducting an economic analysis as they can be used to estimate QALYs. In this review we have focused on generic quality of life instruments that provide a preference based measure of health utility such as the EQ-5D or direct measures of utility such as the time-trade-off or standard-gamble approaches. Papers reporting non-preference based measures were to be included in the review on the proviso that they were only to be considered if there was a lack of evidence on preference based utility scores. For the epilepsy population there is a large quality of life evidence base much of which focuses on non–preference based and disease specific instruments, so we have restricted our search in this population to preference based measures only. The outcomes we were interested in were mean utility in patients with TLoC (or patients with a specific condition that causes TLoC), utility compared to population norms, utility according to frequency of episodes and utility according to treatment or clinical response to treatment.

In order to identify relevant studies, a health economics filter was applied to the main literature search (see appendix C for details). This filter was designed to select economic evaluations in addition to papers on HRQoL and resource use. Of the 616 papers identified, by the search, 11 papers were considered to have potentially relevant HRQoL data based on their titles and abstract. The main literature search had been designed to restrict papers on epilepsy to those that considered the misdiagnosis of epilepsy in order to

increase the specificity of the search. Therefore a separate search was conducted combing the quality of life part of the health economics filter with a patient filter for epilepsy. This was restricted to 2002 as literature searches for quality of life studies up to 2002 were conducted for the NICE appraisal of newer epilepsy drugs in adults [HTA 2005;9(15)]. This search identified 616 papers, of which 18 full text papers were ordered. We also searched the NHS EED database, the Harvard Preference Scores database and relevant NICE Technology Appraisals and HTA reports to find health utility data that has been used in existing published economic evaluations. The reference lists of relevant published reviews were also checked for any studies that may have been missed by the searches. In total 52 full text papers were ordered, 29 of which were potentially relevant HRQoL studies. The rest were reviews or cost-utility studies that were ordered in order to check their reference lists. Of the 29 potential HRQoL papers, 4 papers were excluded. Erdogan 2003 was excluded as not all patients within the sample had experienced TLoC. Rose 1999 and Van Dijk 2007 were excluded as they were validation studies using samples also presented elsewhere and Balabanov 2006 was excluded as QALYs appear to have been calculated using outcomes from a non-preference based tool (QOLIE-31).

Of the 25 included papers, 9 reported only non-preference based scores and were not considered further as there were papers available reporting preference based measures which could be used to inform the economic model. The Sheldon 1998 study reported that it used the EuroQol tool, which can be used to derive a preference based utility score, but it appears from the paper that they used the “EuroQol thermometer” which is non preference based visual analogue tool included within the EuroQol tool to measure HRQoL. Rose 2000 also reported that they used the EuroQol tool, but they also appear not to have reported any preference based utility scores. The other seven papers reported SF-36 scores which are not preference based.

Preference based utility measures

Sixteen papers used generic preference based measures of health utility with some papers reporting multiple preference based measures (Groeneveld

2007, Langfitt 2006, Stavem 2001, Forbes 2003). The EQ-5D instrument was reported by 11 papers, HUI-II or HUI-III was reported by 5 papers, SF-6D by 1 paper, time-trade off by 4 papers and the 15-D and standard gamble technique by 1 paper each. One study (Langfitt 2006) used 5 different methods to measure utility in the same population and demonstrated that the mean utility varied from 0.610 to 0.816 between these methods

Population

None of the papers included an unselected TLoC population. Two papers were in patients receiving treatment for arrhythmias (Groeneveld 2007 and Lopez-Jimenez 2002), one was in patients receiving treatment to prevent recurrent vasovagal syncope (Mitton 1999) and the remainder were in people with epilepsy. The majority of the papers which included people with epilepsy focused on secondary or tertiary care populations with medically refractory epilepsy. Two papers (Stavem 1998 and Stavem 2001) describe a secondary care population but were considered by the authors to be representative of the epilepsy population within the community due to a lack of alternative community based services in the area. In Mittmann 1999, people self-reporting epilepsy diagnosed by a health care practitioner were selected from a large (17,626) community dwelling general population sample. In Xu 2006 the cohort was a community based sample of people with stable epilepsy taking more than 2 AEDS. The SANAD trial (Marson 2007a and 2007b) recruited patients with 2 or more seizures in the previous year which included newly diagnosed patients (82.1%) and those switching therapy after failure of a previous monotherapy and those who had experienced a period of remission followed by relapse after treatment withdrawal.

Mean utility and utility compared to population norms

No papers compared preference based utility scores for patients with TLoC against those of the general population, or against the utility of people with other chronic health conditions. The utility values for each population and any reported subgroups are summarised in the Table below. Lopez-Jimenez 2002 reports a mean utility of 0.76 (sd 0.06) in people receiving a pacemaker for bradycardia as measured by the TTO. Groeneveld 2007 reports a median

utility of 0.84 for adults who had previously received an ICD (both primary and secondary prevention) as measured by the EQ-5D, with higher scores reported using the HUI-III (0.85 & 0.88 for secondary and primary prevention subgroups). There was a wide range of utility values reported in the epilepsy population (0.40 to 0.96), with variations in utility reported according to the frequency of episodes (see below), the presence of drug related side-effects and the presence of comorbidities. Langfitt 2006 reported utilities varying from 0.610 to 0.816 when using 5 difference preference-based utility measures in the same populations. Stavem 1998 reported values ranging from 0.89 to 0.92 when using three different measures in the same population.

Utility according to frequency of episodes

Forbes 2003 and Messori 1998 reported lower utility for those more frequent episodes. On the other hand Stavem 1998 found no significant association between utility and seizure activity during the previous year although all three of these studies included less than 100 participants. Stavem 2001 found that seizures in the previous year was associated with a lower utility score (0.07, $p<0.001$ for EQ-5D) in 397 people with epilepsy.

Change in utility in response to treatment.

Two studies reported the change in utility following implantation of a pacemaker. Lopez-Jimenez 2002 reported utility gains of 0.165 (SD=0.4, $p=0.0001$) at 3 months which was independent of the pacing mode to which patients were randomised. The utility then appeared to remain stable at further follow-up (9mths and 18mths). Mitton 1999 used EQ-5D utility scores to estimate a 10-year QALY gain of 0.69 (discounted at 5%) for patients with vasovagal syncope who received a pacemaker. A constant utility gain of 0.085 would be consistent with this 10-year QALY gain estimate.

In the epilepsy population, Weibe 2001 reported that changes of 0.2 or 0.3 are needed to establish a real difference in utility, as measured by the HUI-III, at the 90% and 95% confidence limits, although this was based on a small sample of only 40 patients with medically refractory epilepsy. Weibe 2002 reported mean changes of 0.15 (95%CI 0.1 to 0.21) using HUI-III for patients achieving the “minimally important change” on a global rating scale of change

(3 point on scale of 1 to 7). Selai 2002 & 2005 report that in patients with medically refractory epilepsy (continued seizures after treatment with 1 or more AEDs), only the patients who were seizure free following a change in epilepsy treatment experienced a significant increase in their health status (difference from baseline of 0.09) whilst a reduction of more than 50% was not sufficient to significantly increase health status. Selai 2000 found a trend towards improved health status, that was not statistically significant, in 22 patients who achieved a 75% or greater reduction in seizures following surgery. In the SANAD trial, there was a significant utility gain of around 0.07, in both arms for patients experiencing a 12 mth remission during the 2 year follow-up and a significant utility loss of 0.03 in one arm and 0.04 in the other, for those experiencing a treatment failure. Langfitt 2006 showed mean changes from baseline in patients who were seizure free after evaluation for epilepsy surgery (72% had surgery) varying from 0.01 to 0.10 depending on the instrument used with a gain of 0.09 (sd 0.31, n=33) using the EQ-5D with the UK tariff.

First author, Year	*Setting*	*Study design*	*Population*	*Follow-up*	*Measures*
Lopez-Jimenez, 2002	USA, secondary care	RCT: Patients were randomised to one of two pacing modes.	407 patients aged over 65 receiving a pacemaker for bradycardia (sinus node dysfunction, AV block, carotid sinus hypersensitivity).	3, 9 and 18 mths	TTO: 0.76 (SD0.06) Improvement of 0.165 (SD=0.4, p=0.0001) from baseline to 3 mths. No sig change thereafter. No difference by randomisation SF-36 scores also reported
Groeneveld, 2007	USA, secondary care	Cross-sectional survey	120 adults who had previously received an ICD for prevention of sudden cardiac death. 45 cases were primary prevention and 75 were secondary prevention.	None	EQ-5D (median and IQR): Primary; 0.84 (0.77,100), secondary 0.84 (0.78,1.00). HUI-III (median and IQR): Primary 0.88 (0.72, 0.97), secondary 0.85 (0.72, 0.97) EQ-VAS and SF-12 also reported
Mitton, 1999	Canada, secondary care	Cohort	38 Patients receiving pacemaker for recurrent vasovagal syncope (>6 episodes before tile-testing or >1 recurrence in 6mths after testing), not all had positive tilt-test. Only 25 completed EQ-5D.	12 mths (SD 6.5 mths)	EQ-5D utility scores not stated. 10 year QALY gains of 0.69 calculated using EQ-5D utility (discounting 5%) EQ-VAS also reported
Forbes, 2003	UK, secondary care	Cross-sectional survey	42 patients with medically refractory epilepsy	None	EQ-5D: 0.848 (n=17) for <1& 0.681 for >1 (n=25) seizures per mth TTO also administered but utility values only reported for n=7
Langfitt, 2006	USA, secondary care	Cohort	165 adults with monthly consciousness impairing seizures for at least 2 years being assessed for surgery (72% had surgery after assessment)	3mths, 1 & 2 years	Baseline utilities: EQ-5D UK preferences: 0.762 (sd 0.262) EQ-5D US preferences: 0.816 (sd 0.184) HUI-2: 0.777 (sd 0.182) HUI-3: 0.610 (sd 0.298) SF-6D: 0.702 (sd 0.137) EQ-VAS also reported Mean change from baseline in patients who are seizure free at 2 year follow-up (n=33): 0.01 to 0.10 depending on instrument

Marson 2007a &b	UK, NHS	RCT (Arm A comparing newer AEDs to carbamazepine and Arm B comparing newer AEDs to valproate)	1881 adult patients with 2 or more seizures in the previous year in whom treatment with a single AED represented the best therapeutic option. Included newly diagnosed patients (82.1%) and those switching therapy after remission or failure of a previous monotherapy. 1058 returned data at baseline and 2 years	1& 2 years	EQ-5D: Utility difference between those that did and didn't' achieve a 12 mth remission during the 2-year follow-up.0.07 (0.04-0.10) for arm A and 0.07 (0.04 – 0.9) for arm B Utility difference between those that did and didn't experience treatment failure by 2 year follow-up: -0.03 (-0.06 to -0.00) for arm A and -0.04 (-0.07 to -0.01) for arm B
Messori, 1998	Italy, secondary	Cross-sectional survey	81 patients with a diagnosis of refractory epilepsy who had been referred to outpatient clinic. Outcomes by the following categories; A: Presence of drug related side-effects (n=9), B:>=10 seizures per mth (n=12), C: 2-9 seizures per mth (n=30), D: <=1 per mth (n=15), E: No seizure in last year (n=15)	None	TTO: All patients, Mean 0.78 sd 0.19. A: 0.40 sd 0.07, B: 0.66 sd 0.08, C: 0.79 sd 0.13, D: 0.91 sd 0.09, E: 0.96 sd 0.04
Mittmann 1999	Canada, community dwelling general pop	Cross-sectional survey	17626 individuals of whom 116 reported having a diagnosis of epilepsy and 41 had epilepsy without any comorbidity	None	HUI-III (scored using HUI-II preferences) 0.78 sd 0.20 for epilepsy Age specific scores also reported 0.86 sd 0.14 for epilepsy without comorbidites
Selai 2000	UK, tertiary	Cohort	22 patients who had undergone surgery and achieved 75% or greater reduction in seizures. (subgroup of 145 evaluated and 40 who were followed up)	1 year	EQ-5D: Baseline 0.81, 1-year 0.91. No stat sig difference.
Selai 2002 and 2005	UK, teritary	Cohort	125 patient experiencing seizures despite treatment with one or more AEDs. Outcomes reported for the following categories: A: seizure freedom (n=11), B: >=50% reduction and <1 seizure per mth	3 & 6 mths	EQ-5D at 6 mths: All: Mean 0.8564 sd 0.1820 A: 0.9418 sd 0.0840, B: 0.8844 sd 0.1526, C: 0.9289 sd 0.0882, D: 0.8288 sd 0.2004, E 0.8377 sd 0.1972

			(n=16), C: >=50% reduction and >1 seizure per mth (n=9), D: <505 reduction (n=42), E: discontinued treatment (n=47)		Only those who were seizure free had sig improvement from baseline
Stavem 1998	Norway, secondary care (authors state that this is representative of community sample)	Cross-sectional	57 people with epilepsy who had attended a hospital outpatient service or been admitted for epilepsy in the previous 7 years. Epilepsy confirmed by medical record review. Original sample was 696 patients with confirmed diagnosis, 397 responded to questionnaire, 82 randomly selected and 57 completed study.	None	TTO: 0.92 (sd 0.11), n=57 SG: 0.93 (sd 0.11), n=57 15D: 0.89 (sd 0.09)., n=55 No sig difference associated with medication use or seizures during previous year EQ-VAS also reported
Stavem 2001	Norway, secondary (authors state that this is representative of community sample)	Cross-sectional	397 people with epilepsy who had attended a hospital outpatient service or been admitted for epilepsy in the previous 7 years. Epilepsy confirmed by medical record review. Original sample was 696 patients with confirmed diagnosis, 397 responded to questionnaire.	None	15-D: 0.88 (sd 0.12, n=348) EQ-5D; 0.81 (sd 0.23, n= 383) For both measures, scores were stat sig lower for patients with; seizures in the last year (0.07, p<0.001 for EQ-5D), neurological deficit, psychiatric comorbidity and those not working. But there was no sig difference for AED use.
Weibe 2002	Canada, secondary	Cohort	136 adults with medically refractory epilepsy being considered for surgery. Excluded PNES, learning disability, progressive CNS disorders, comorbidities precluding surgery	6 mths	HUI-III: 0.56 (sd 0.3, n=80) at base line and 0.61 (sd 0.3) at follow-up. Change of 0.05 (sd 0.3) Mean changes in HUI-III of 0.15 (95%CI 0.1 to 0.21) for those achieving the minimally important change of 3 on a global rating scale of change (1-7points) SF-36 also reported
Weibe 2001	Canada, secondary	Cohort	40 adults with stable temporal lobe epilepsy, being evaluated for surgery. Excluded learning disability, progressive CNS disorders, comorbidities precluding surgery	3 mths	HUI-III; 0.71 (sd 0.29) Changes to 0.25 to 0.3 required to establish real difference at 90% and 95% confidence limits respectively

Xu, 2006	USA, community base neurology practices	Cross-sectional	201 adults with partial-onset epilepsy taking 2 or more AED. Compared patients with and without sleep disturbances	None	EQ-5D; 0.64 (sd 0.35, n=200) 0.49 (sd 0.38, n=132) with sleep disturbance vs 0.71 (sd 0.31, n=132 without sleep disturbance)

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