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EEPRU

Economic Evaluation of Health and Social Care Interventions Policy Research Unit

RESEARCH REPORT

Supporting the routine collection of patient reported outcome measures in the National Clinical Audits for assessing cost-effectiveness

Work Package 1

What patient reported outcome measures should be used in the 13 health conditions specified in the 2013/14 National Clinical Audit programme?

APPENDIX D, EPILEPSY

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The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 7 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

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Acronym	Definition
A&E	Accident and emergency
AE	Adverse events
AMED	Allied and Alternative Medicine
AMSTAR	Assessing the quality of systematic reviews
CG	Clinical guideline
CHQ	Child health questionnaire
CHQ-CF87	Child health questionnaire child form 87
CHQ-PF50	Child health questionnaire parent form 50
CHU-9D	Child Health Utility 9D
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMH	Composite mental health subscale of ESI-55
CPH	Composite physical health subscale of ESI-55
DH	Department of Health
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
ELDQOL	Epilepsy and Learning Disabilities Quality of life Scale
EQ-5D	EuroQol 5 dimensions
EQ-5D-VAS	EuroQol 5 dimensions visual analogue scale
ESI-55	The epilepsy surgery inventory
ESI-CRF	Epilepsy surgery inventory composite role function subscale
FR	Future research
GRC	Global rating of change
HADS	Hospital anxiety and depression scale
HR	Hazard ratio
HRQoL	Health related quality of life
HRQoLCE	Health related quality of life in children with epilepsy
HS	Health states
HTA(s)	Health technology assessment(s)
HUI	Health Utility Index
HUI2	Health Utility Index mark 2
HUI3	Health Utility Index mark 3
ICC	Intraclass correlation coefficient
ICND	Impact of Childhood Neurological Disability Scale
IPES	Impact of Paediatric Epilepsy scale
IPEF	Impact of Paediatric Epilepsy on the Family
KGV	Known group validity
MFQ	Mood and Feeling questionnaire
MOS	Medical outcomes study
MTAs	Multiple technology assessments
NCA	National Clinical Audit
NHP	Nottingham Health Profile
NHS	National Health Service
NHSSS	National hospital seizure severity score
PedsQoL™	Paediatric quality of life inventory™
PR	Potential recommendations
PR	Parent/carer report

PREMs	Patient Reported Experience Measures
PROM(s)	patient reported outcome measure(s)
QALYs	Quality adjusted life years
QOLAS	The quality of life assessment schedule
QOLCE	Quality of Life For Children with Epilepsy
QOLIE-31	Quality of life in epilepsy -31
QOLIE-89	Quality of life in epilepsy -89
QOLIE-AD-48	Quality of Life Inventory for Adolescents with Epilepsy
Q-TWIST	Quality-adjusted time without symptoms or toxicity
QVCE	HRQoL questionnaire for Brazilian children with epilepsy
R&D	Research and development
RCT	Randomised controlled trial
SCARED	Screen for Child Anxiety Related Emotional Disorders
SD	Standard deviation
SDQ	Strengths and Difficulties Questionnaire
SF-12	Short form-12
SF-36	Short form-36
SF-6D	Short form-6D
SIGLE	System for Information on Grey Literature in Europe
SIP	Sickness Impact Profile
SRM	Standardised response mean
STA	Single technology assessment
TA	Technology Appraisal
VAS	Visual analogue scale
WHOQOL-BREF	WHO quality of life - BREF
WP	Work package

1. BACKGROUND

The Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) was approached by Jason Cox (Research and Development (R&D) Division) to prepare a programme of research to support the appropriateness of, and use of, patient reported outcome measures (PROMs) collected for the National Clinical Audit (NCA). The EEPRU programme was informed by a R&D template prepared by Simon Bennett, Steve Fairman and Keith Willett at National Health Service (NHS) England.

The purpose of introducing PROMs into the NCA programme is to be able to 1) compare performance between providers and commissioners in the NHS, 2) compare the cost-effectiveness of alternative providers in delivering the specific services (i.e. linking outcomes and resource use), and 3) assess the cost-effectiveness of alternative interventions and other changes in the NHS. The intention is to introduce PROMs across a range of conditions over the next 3 years commencing with 13 conditions in the 2014/15 NCA programme.

The agreed research programme consists of 3 concurrent work packages (WP) as described in the document submitted to the Department of Health (DH) (8th November 2013). The current document provides details on the objectives, methodology and results for Work Package 1 (WP1): to determine what PROMS should be used in the 13 health conditions specified in the 2014/15 NCA programme.

2. OVERVIEW

WP1 is split into three separate components consisting of:

- WP1.1 To examine whether the EuroQol-5D (EQ-5D) is appropriate in the 13 health conditions specified in the 2013/14 NCA programme.
- WP1.2 To identify what measure could be used when the EQ-5D is not appropriate in the 13 health conditions, taking into account that the proposed measure would be used to generate preference-based utility measures (either directly through existing preference-based weights, or indirectly through existing mapping functions suitable for the proposed measure).
- WP1.3 To identify the evidence required to address questions of cost-effectiveness using the NCA data.

Each component consists of a series of reviews of the literature.

This Appendix provides the detailed results for the condition epilepsy and should be read in conjunction with both the main report and the methods/search strategy appendices.

3. METHOD

The full detailed methodology used is provided in Appendix A and B, including the search strategy, selection criteria for studies included, and data extraction etc. In summary, a review of the literature was undertaken to assess the appropriateness of the EQ-5D in terms of classic psychometric criteria (WP1.1); where the EQ-5D was not considered appropriate, additional searches were undertaken to identify alternative measures (WP1.2); and finally, existing health technology appriasials were reviewed and data requirements were compared with variables currently collected in the epilepsy audit (WP1.3).

3.1 **Psychometric properties** (WP1.1)

Assessments reported in the included studies were categorised according to the following definitions:

Acceptability

Data relating to how acceptable the measure was to the person completing it, expressed as the proportion of completed surveys, or the proportion of missing data.

Reliability

There are two main definitions for reliability, a) the degree to which a measure reproduces the same results in an unchanged population and b) the degree to which a measure reproduces the same results when completed by different assessors (e.g. patient and proxy report). In both cases, reliability can be assessed by re-testing, and calculating the correlations or difference between tests. In case a) the comparison may be between the same populations separated by time, where no change in health state was observed (as compared to using an alternative condition specific or generic measure). In case b) the measure may be completed by multiple people (proxies) on the patient's behalf and their responses compared with those of the patient. Where the outcome measure is specifically designed for self-report by patients, this test of reliability may be expected to produce less agreement.

Construct validity

This is an assessment of how well an instrument measures what it intends to measure. Two main definitions are used in this review.

a) Known group validity, where estimates for groups that are known to differ in a concept of interest are compared either qualitatively or statistically. The known groups may be defined using other measures, according to clinical categorisation.

b) Convergent validity assesses the extent to which a measure correlates with other measures of the same or similar concepts. Correlation coefficients were considered low if <0.3, moderate if between 0.3 and 0.5, and strong when >0.5.

Responsiveness

a) Change over time. This is an assessment of whether measurements using the instrument can detect a change over time, where a change is expected. This may be before and after an intervention, or through progression of a disease. Evidence was considered to be good where a t-test was significant, though weaker evidence to support responsiveness was considered where there was a change in the expected direction, but was not statistically significant or not tested. Effect size and standardised response mean were also acceptable assessments of responsiveness.

b) Ceiling and floor effects were also considered to be indicators of responsiveness. Assessments of ceiling effects include the proportion of patients who score full health within a group of patients with known health detriments. A ceiling or floor effect can affect the sensitivity of the measure in detecting changes over time in patients at the extremes of the measure (for example those with severe disease activity and those with just minor symptoms of the condition).

3.2 **Alternative measures** (WP1.2)

As the epilepsy audit includes paediatrics and the EQ-5D is not designed for use in this population, alternative instruments were reviewed. This entailed a review of existing guidelines (section 4.2.1), and a review of primary studies (section 4.2.2) relating to the four prespecified paediatric measures (EQ-5D-Y, Child Health Utility 9D (CHU-9D), health utility index mark 2 (HUI2), Paediatric quality of life inventory^{TM} (PedsQL)(1-4)), as detailed in section 3.2, Appendix A.

3.3 **Evidence required for economic evaluations** (WP1.3)

The existing Health Technology Assessments (HTAs) were reviewed alongside the variables currently collected in the NCA to determine if clinical or PROM data routinely collected in the NCAs would

suffice to address questions of cost-effectiveness, and to identify any gaps in the evidence that would be required to compare providers, or the cost-effectiveness of interventions or policies.

4. RESULTS FOR EPILEPSY

4.1 Evidence of appropriateness of EQ-5D in epilepsy (WP1.1)

The epilepsy NCA is in paediatrics, consequently the EQ-5D, which is recommended for adults, is potentially not relevant for this population. However, evidence from studies in adults will provide a useful indicator of the appropriateness of the EQ-5D in a younger population. For example, if the EQ-5D is found to be inappropriate in adults, it is very unlikely to be appropriate in paediatrics. The literature describing the appropriateness of the EQ-5D in adults with epilepsy is reviewed below. A summary of the literature on measures for paediatrics with epilepsy is provided in section 4.2.

4.1.1 Selection of systematic review

No selection was required as only one review was identified.(5) This review was an update of a previous review from the same group.(6)

4.1.2 Structured abstract for Davies et al. 2009(5)

Purpose of review

The review aimed to assess the evidence of PROMs for people with epilepsy, in order to provide recommendations of the potential use of PROMs in epilepsy in large-scale populations, as an update of a previous review. The previous review reported evidence for a number of PROMs: EQ-5D; Health Utilities Index (HUI); Nottingham Health Profile (NHP); Quality-adjusted time without symptoms or toxicity (Q-TWIST); Short form-36 (SF-36); Short form-12 (SF-12); Sickness Impact Profile (SIP). The update provided additional evidence for the EQ-5D and the SF-36, and evidence for the performance of the short form-6D (SF-6D) (derived from the SF-36); and WHO quality of life - BREF (WHOQOL-BREF). Only results pertaining to the EQ-5D (and the associated comparator used in each analysis) are reported here. It was not always clear if the results related to EQ-5D preference based index, the EQ-5D visual analogue scale (EQ-5D-VAS), or both.

Methods of the review

Search and study selection: The following sources were searched: The PROM Bibliography (developed by the Oxford PROMS group) which includes 12,000 records relating to published instrument evaluations found on the following electronic databases: Allied and Alternative Medicine

(AMED), Biological Abstracts, British Nursing Index, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Econlit, EMBASE, Medline, PAIS International, PsycInfo, System for Information on Grey Literature in Europe (SIGLE), and Sociological Abstracts); scanning the reference lists of key articles; checking instrument websites; hand searching of titles of key epilepsy journals (2006 to 2008). In the 2009 update, PubMed records for 'epilepsy' and known instrument names from the 2006 review were also searched. Studies were included if they provided evidence of measurement and/or practical properties for multi-item instruments assessing aspects of health status or health related quality of life (HRQoL) in patients with epilepsy. Studies in adolescents and children were excluded.[1] Two reviewers assessed each citation retrieved.

Data extraction and synthesis: it was not clear whether data extraction was validated by a second reviewer. A standardised form was used. Methods of analysis and synthesis were described as being "based on weighing up for each of the instruments considered in detail: the volume of available evidence, the quality of studies and, ultimately, the overall extent of positive and supportive evidence of measurement properties and feasibility."(pg 19, Fitzpatrick 2006).(6) In both the 2006 and 2009 report, a multidisciplinary expert panel discussed the evidence and drew conclusions, which were then considered, alongside the evidence, by the authors of the report to draw overall conclusions. Psychometric qualities considered by the authors were defined as follows: 1) reliability, whether measurement is accurate over time, 2) validity, whether an instrument measures what it is intended to measure in different setting, including face and content validity, and construct validity, 3) responsiveness, as assessed by distribution-based and anchor-based approaches, and considering precision, floor and ceiling effects, 4) acceptability, how willing or able participants are to complete a measurement instrument, and 5) practicality, the time and cost of administration.

Results of the review

The review provides a narrative evaluation of the performance of the EQ-5D for use in adult patients with epilepsy. Very little data was provided from the included studies. In the previous review, 3 studies were identified. Evaluation of these studies demonstrated mainly negative evidence regarding the appropriateness of the EQ-5D in patients with epilepsy. Three further studies were identified in the update.(7-9) Again, data from the individual studies were not reported.

[1] The inclusion criteria used in the update of this review (Davies et al. 2009) was relaxed to include samples of all ages. Data for children and adolescents were reported in a separate chapter. Here, these results are considered in Section 5.1.2, as the analysis methodology differed considerably from that of the review of adults, and no evidence relating to the EQ-5D was reported in the chapter.

Responsiveness and known group validity were demonstrated by Selai et al.(7) according to anti-epileptic drug type and seizure frequency in patients receiving adjunctive therapy (respectively), and by Xu et al, who demonstrated that the EQ-5D was able to discriminate between patients with epilepsy experiencing sleep disturbances and those with no sleep disturbance.(8) However, Langfitt et al found that the responsiveness of the EQ-5D when considering seizure control was inferior to other generic, preference-based measures such as the Health Utility Index-3 (HUI3) and SF-6D. Langfitt et al also reported some ceiling effects with 34% of patients with epilepsy scoring full health on the EQ-5D index.

Review authors' conclusions

The review authors concluded that there are some concerns about the psychometric properties of the EQ-5D, especially in terms of ceiling effects. The expert panel favoured the SF-6D. However, the authors of the review recommended the EQ-5D for use in epilepsy, in combination with the condition-specific measure, the quality of life in epilepsy -31 (QOLIE-31). Some of the reasons cited by the authors for their final recommendation of the EQ-5D (rather than the SF-6D favoured by the expert panel) related to an avoidance of overlap with the SF-6D, as the QOLIE-31 includes SF-6D items.

4.1.3 Assessment of the review in relation to objectives of work package 1.1

Relevance of review question: The aim of Davies 2009(5) is convergent with the aims of WP1.1.

Assessment of review quality: A summary of the quality assessment is shown in Table A1 in the Appendix. The quality assessment does not provide sufficient assurance of the quality of the review. Whilst two reviewers assessed the retrieved papers for relevance, there was insufficient detail reported within the review to enable an assessment of other quality criteria. Quality assessment of individual studies does not appear to have been conducted in a formal sense, or documented, though some consideration of study quality appears to have been integrated into the consideration of the evidence by the review group. In addition, no data from individual studies were reported. It is therefore unclear whether the evidence in the individual studies adequately supported the authors' conclusions.

Acceptability of the search: The Oxford PROMS bibliography was the primary database that was searched for studies. Other search techniques were applied (e.g. hand searching of journals and

instrument website search) and supplementary named instrument searches in PubMed also added to the evidence base. Whilst there is some uncertainty about the methods used in that the Oxford PROMS bibliography is relied upon heavily rather than direct searching of bibliographic databases, the EEPRU review team considered the search was unlikely to have missed studies.

Acceptability of the study selection: The inclusion/exclusion criteria were not well described and it is therefore difficult to evaluate how well these met the objectives of work package 1.1. However, given the convergent aims of the review, it would seem likely that study selection is appropriate.

Adequacy of available data and synthesis: It was difficult to assess the strength of the existing evidence as data from individual studies was not reported, and no details of quality assessment were provided. Therefore, it is not possible to evaluate the robustness of the findings, or how conclusive they are. The review reports an overall appraisal of the content validity, construct validity and responsiveness of the EQ-5D. Whilst the authors state that the quality of studies was considered in the 2006 report, this was not clear in the 2009 update.

In conclusion: the methods employed in the review required some remedial action. The searches were thought to be adequate, and the inclusion criteria appeared to be consistent with those of WP1.1. However, the data extraction and synthesis were not detailed enough to allow a thorough understanding of the psychometric properties of the EQ-5D in this population. As such, all studies were re-considered for inclusion, an update search conducted, and a detailed data extraction and narrative synthesis of these studies performed.

4.1.4 Update and reanalysis of Davies et al.(5)

Davies et al. included six studies in total across the two reviews. Reconsideration of these studies revealed that two citations were parallel publications from one study.(7;10) A further parallel publication for the same study, which was referenced in both the parallel publications(7;10) was referred to for additional data.(11) As such, a total of five studies were available for analysis, reported across seven publications.(7-13) Study characteristics and results are tabulated in the Appendix (Tables A2 to A5).

The update search retrieved 37 titles. None of these studies met the inclusion criteria, and all were excluded from the update.

Of the five included studies, two were conducted in the USA(8;9) and the remaining three were conducted in the UK.(7;10;11;13;14) (Table A2) Two studies did not report which EQ-5D tariff they used (13;14) whilst the other three used the UK tariff (Table A4).(7-9)

Three studies recruited patients who were experiencing seizures despite medication(7;9;12) and in the case of Selai et al. these patients were undergoing evaluation for surgery.(12) The remaining two studies recruited a more general population of people with epilepsy (Table A2).(8;13) However, the worst mean EQ-5D at baseline was reported in Xu et al. at 0.64 (standard deviation (SD) 0.35)(8) and the best in Selai et al. at 0.85 (SD 0.1772).(7) Mean ages were similar across studies, ranging from 32.8(12) to 46 years.(13) All studies were conducted in adults (Table A3).

Three studies were cross sectional(7;8;13) and two studies were time series(9;12), one of which was a psychometric study.(9) The other four studies all aimed to assess the impact of epilepsy on quality of life, but did not have a psychometric focus.(7;8;12;13) Study size ranged from 22(12) to 289 participants with epilepsy.(13) Missing data was not reported in three studies(7;8;13) and was something of a problem in the other two studies, with both having >20% missing data (Table A3).(9;12)

Construct validity (Known group): Five studies reported results that provide some support for the construct validity of the EQ-5D.(7-11;13) However, formal statistical tests were not always performed. Xu et al. compared mean EQ-5D scores for those diagnosed with and without sleep disturbance, and found the expected difference for the sub-groups, as was observed in both the QOLIE and Medical outcomes study (MOS) measures (EQ-5D: 0.49 vs. 0.71 $p<0.001$; MOS: 46.8 vs. 31.1 $p<0.001$).(8) Langfitt et al. used the national hospital seizure severity score (NHSSS) to measure severity and control of seizures. They found the EQ-5D index was sensitive to seizure severity ($F=12.18$, $p<0.05$), as were other generic measures (HUI2, HUI3, SF-6D, $F>4.0$, $p<0.05$), and the condition specific measure, quality of life in epilepsy -89 (QOLIE-89) ($F>0.04$, $p<0.05$). They also reported all generic tools had a similar strength of association to seizure control (F: 0.06 to 5.60), and were generally insensitive.(9) Selai et al. considered the mean EQ-5D index for different frequencies of seizure per month, and whilst a formal statistical comparison for all categories was not performed, a trend of increasing mean EQ-5D scores for sub-groups with decreasing frequency of seizures was observed (Table A5.(7;10;11) In addition, there was a significant difference (p-value not reported) in the mean EQ-5D index when comparing those who achieved ≥50% reduction in seizures at the end of the study to those who didn't.(7) Trueman & Duthie et al. presented data (but

no formal statistical test) of mean hospital anxiety and depression scale (HADS) scores for patients scoring no problem, some problems and severe problems in the EQ-5D anxiety/depression dimension, and found the trend in mean HADS scores for the sub-group with epilepsy was in the expected direction.(13)

Construct validity (convergent): Langfitt et al.(9) reported results relating to convergent validity. Analysis of the EQ-5D dimensions showed that usual activity and pain/discomfort were significantly correlated with seizure severity ($p<0.05$), and mobility was significantly correlated with seizure control ($p<0.05$). However all correlations between the other dimensions and either comorbid conditions or the two seizure variables (severity and control) were very small and not statistically significant ($p>0.05$).

Responsiveness (change over time): Selai et al. (2000) compared patients pre- and post-surgery. The EQ-5D (index) improved post-surgery, as did scores in each dimension, but the changes were not statistically significant (index), or were not tested (dimensions). The quality of life assessment schedule (QOLAS) and the composite mental health (CMH) and composite physical health (CPH) subscales of the epilepsy surgery inventory (ESI-55) did detect a statistically significant improvement post-surgery, whilst the composite role functional subscale did not (ESI-CRF). Selai et al. (2005) compared the difference in mean EQ-5D index from baseline to follow-up (after treatment) for groups of patients according to whether they achieved seizure reduction. No formal statistical analysis was performed, but changes in means were positive for those who achieved ≥50% reduction in seizures, and negative for those who didn't.(7) Interestingly, results from an earlier report(10) of the same study were interpreted as negative evidence for the responsiveness of the EQ-5D.(15) Specifically, these results related to the change in the EQ-5D in response to treatment only being positive in two treatment groups out of five. The later report of this study(7) gave a more in-depth assessment of responsiveness, and included the analysis of seizure reduction described above. Langfitt showed the EQ-5D index was also able to detect a change (as observed in the change in QOLIE-89) in sub-groups who reported being either much better or much worse on the global rating of change (GRC).(9) However, when assessing the change in mean EQ-5D in patients who were free from seizures for two years, the magnitude of change was substantially smaller than expected relative to those observed for the QOLIE-89 measure.(9)

Responsiveness (ceiling effect): There is some evidence of a ceiling effect with 34% of patients in one study scoring full health compared to 10% on other generic measures (SF-6D and HUI).(9)

4.1.5 Conclusion of appropriateness of EQ-5D in epilepsy

The evidence base assessing the psychometric properties of the EQ-5D in adults with epilepsy on the whole is positive albeit limited. There is some evidence of a ceiling effect compared to other generic measures (SF-6D and HUI).(9) Support for construct validity was relatively good with evidence the EQ-5D was able to detect differences in sub-groups categorised by seizure frequency,(11) and the NHSSS,(88) despite the correlations between the EQ-5D and both the severity and control of seizures being small.(9) While there was also no correlation between responses on the EQ-5D health dimensions and presence of comorbidity in one study,(9) Trueman and Duthie reported a relationship between the EQ-5D anxiety/depression health dimension and HADS scores.(13) There was also evidence to suggest the EQ-5D was able to detect changes in HRQoL over time in patients sub-grouped by achievement of seizure reductions,(7) or improvement or deterioration on the GRC.(9) However, one study suggested the magnitude of change in mean EQ-5D was smaller than might have been expected based on changes in the QOLIE-89 measure,(9) and in another study improvements in EQ-5D scores were not statistically significant in patients pre- versus post- surgery, where other measures were.(12)

In conclusion, this evidence suggests that the EQ-5D may not be the most appropriate measure in adults, though it may be regarded as adequate. However, the EQ-5D is not relevant for paediatrics, the subject of the epilepsy NCA.

4.2 **Alternative measures in epilepsy** (WP1.2)

4.2.1 Other measures for epilepsy

Six documents were identified by the initial searches. Three documents were from the Royal College of Paediatrics and Child Health, describing the methodology used in the Epilepsy 12 NCA reviewed below (Section 5.4), and thus were excluded from further analysis. Two documents were research guidelines from the EMA, which were produced by an expert panel with a stakeholder consultation period.(16;17) One document was superseded by the other and as PROMS were not discussed these documents were excluded from further analyses or review. It is worth noting that they recommended the primary efficacy outcome should be seizure frequency, measured over a defined period, with responders classified according to the percentage decrease in frequency.(17)

The final document was the Oxford PROM group review that is discussed above in section 3.1. In addition to reviewing measures in adults, this review also considered which outcome measures

should be used in children with epilepsy.(5) The authors noted that few measures had been used in or developed for this patient group, and that there was little development in the field. They cited two epilepsy-specific PROMs specifically developed for paediatric populations: the Health-Related Quality of Life in Children with Epilepsy (HRQoLCE),(18) and the Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD-48).(98) While acknowledging there were many paediatric-specific generic PROMs, the authors did not conduct an independent review of the literature themseleves. They instead relied on the conclusions reported by Eiser and Morse (19) that only three of the generic measures (CHQ,(20) PedsQL,(4) HUI2 (3)) satisfied even very basic psychometric criteria.(19) However, the primary studies used by Eiser to inform this conclusion were not explicitly cited and only summary results of psychometric properties (i.e. assessed or not) were presented.

4.2.2 Other measures for paediatrics with epilepsy

As the results of the reviews did not provide conclusive evidence to support the use of a particular measure, an additional search was conducted with the aim of identifying literature describing the psychometric properties of measures suitable for this population.

Results of searches: The searches identified 141 unique references. After consideration of titles and abstracts, the full-text papers of 28 studies of potential relevance to the review were obtained. Of these, 23 did not meet the inclusion criteria for the review and were excluded (detailed reasons provided in Table A6).

Of the remaining five studies, two were retained as they were systematic reviews which included a section on paediatric measures in epilepsy.(21;22) The remaining three studies presented data which could be used to examine the psychometric properties of the PedsQL measure in paediatrics with epilepsy. No studies were identified in this population for the other three paediatric generic preference-based measures (EQ-5D-Y, CHU-9D, HUI2). The results reported in these five articles were collated and are summarised below, augmented with any relevant evidence reported in Eiser and Morse 2001, and the Oxford PROM review.(5;19)

Results of review: Cowen 2004 conducted a systematic literature review of subjective impact measures for use in children and adolescents with epilepsy and identified five HRQoL measures (Table A7). Waters 2009, described QoL instruments, found through a systematic search, for children and adolescents with neurodisabilities including three generic and five epilepsy-specific measures.(21) Both reviews were poorly reported when assessed using the relevant Assessing the

quality of systematic reviews (AMSTAR) criteria, with failures to report robust methods of data extraction and study selection being key issues. Davis et al. cited the two epilepsy-specific questionnaires (HRQoLCE, QOLIE-AD-48)(5) and Eiser et al. the three generic measures (CHQ, PedsQL, HUI2) (19) described in the Oxford Proms review.(5) Brunklaus 2011, used two epilepsy-specific (Impact of Peadiatric Epilepsy Scale (IPES), Epilepsy and Learning Disabilities Quality of Life Questionnaire (ELDQOL)) and one generic measure (PedsQL) in their study in paediatrics with Dravet syndrome (an epileptic encephalopathy with defined genetic etiology). Modi 2010 used the PedsQL in children who had had a single seizure or were newly diagnosed and untreated.(23) Stevanovic 2011 used two anxiety / depression measures (Screen for Child Anxiety Related Emotional Disorders (SCARED), Mood and Feeling questionnaire (MFQ)), and the PedsQL to evaluate the effects of anxiety and depression in children and adolescents with epilepsy.(24) A brief comparison of the measures used and the psychometric properties of the measures reported within the studies are provided below, sub-grouped into epilepsy-specific measures and generic measures. Not all these measures are PROMs, and the clinician reported measures (generally used as comparator for other measures, or to define severity-based subgroups) are included for completion.

Condition-specific measures used in paediatrics with epilepsy

Eight condition-specific measures that had been used in paediatrics with epilepsy were identified: the ELDQOL,(25-28), HRQoLCE,(18) the Impact of Childhood Neurological Disability Scale (ICND),(29;30) the Impact of Paediatric Epilepsy on the Family (IPEF),(29) The Quality of Life For Children with Epilepsy (QOLCE),(31;32) The QOLIE-AD-48(33), The HRQoL questionnaire for Brazilian children with epilepsy (QVCE-50),(34) The Strengths and Difficulties Questionnaire (SDQ).(35;36)

Epilepsy and Learning Disabilities Quality of life Scale (ELDQOL)(25-28) used in Cowan 2004 and Brunklaus 2011.

The ELDQOL was developed for use in children (2-18 years) with severe epilepsy and learning difficulties, and is completed by either a parent or main caregiver. It covers seizure severity and control, mood behaviour disturbance, overall quality of life, overall health and side effects of treatments. No details of the scoring mechanism were provided. It has been reported to have a modest test-retest coefficient (r=0.67-0.87) and internal consistency (α=0.71-0.84), but as it is relatively long, Espie et al. suggested it was more suited to provide an overview than to be used as an outcome measure. Consequently it is not considered for inclusion in the NCA.(37;38)

The HRQoL in Children with Epilepsy measure (HRQoLCE)(18) was used in Cowan 2004, and referred to in Waters 2009, and Davies 2009.(5;21;22)

The HRQoLCE consists of a parent/proxy questionnaire and a self-report questionnaire and was developed for use in older children (8-15 years) with epilepsy. The 25 item measure covers five domains: interpersonal⁄social consequences; worries and concerns mostly in daily life experiences; intrapersonal⁄emotional issues; secrecy and concealment of epilepsy; and quest for normality.

Reliability: Test-retest reliability over a two week period for the self-report (parent-proxy) measure was 0.59 (0.60) although it was not clear if the condition was stable during this period. The correlation between subscales ranged from 0.26 to 0.52.(21)

Construct validity (convergent): Convergent validity was demonstrated by examining the associations with a number of clinical criteria, including health-care use and seizure severity, special educational needs, anti-epilepsy drug toxicity, number of anti-epilepsy drugs taken, number of close friends, extracurricular activities. The results showed that both the self-report and parent-proxy scores were significantly correlated with the majority of these variables.(22) Internal consistency of above 0.70 was reported on all subscales apart from the quest for normality subscale (Cronbach's α=0.63) and the parent-proxy subscale of present worries (Cronbach's α=0.64).

Responsiveness: The development study for the HRQoLCE reported adequate scaling properties with no significant floor or ceiling effects for any of the subscales, and with scores being normally distributed.(18)

In summary, the evidence reviewed for the HRQoLCE is limited, it does not describe health related quality of life and thus its usefulness in economic evaluations is very restricted. Consequently this measure is not recommended for inclusion in the NCA.

The Impact of Paediatric Epilepsy on the Family (IPEF)(29) used in Waters 2009 and Brunklaus 2011

As the name indicates, the IPEF[2] was constructed to evaluate the impact of epilepsy on both the family's and child's HRQoL (2 to >15 years). Completed by the parent, 11 items cover the child's overall health, relationships, social life, academics, self-esteem, family activities, and the parents' hopes for their child's future. Each item is scored on a four-point likert scale (0=epilepsy does not affect the area; 3=epilepsy greatly affects the area) and summed to give the total IPEF total score

[2] Although Brunklaus refer to this measure as the Impact of Paediatric Epilepsy Scale (IPES), it is the same measure referred to in Waters as the IPEF.

with low scores indicative of lower epilepsy related HRQoL. There is an additional numeric scale (range 0-6) of the child's overall quality of life where the maximum value indicates excellent quality of life. It was reported that these items may tap into a single factor based on high internal consistency (coefficient 0.92),(39) but no additional results of alternative psychometric assessments are provided. This measure does not have a self-report version thus is not considered a candidate measure for the NCA.

The Impact of Childhood Neurological Disability Scale (ICND),(29;30) used in Cowan 2004.
The ICND is suitable for children (12-18 years) and is completed by a parent. The measure is an expansion of the IPEF and includes additional questions relating to cognition, behaviour and physical/neurological disability. In addition to the 4 point scales used for each of the 11 questions in each area, there is a six point scale single overall quality of life item. Reliability and validity has been evaluated on a sample of children with epilepsy (n=68) and a sample of children with epilepsy and comorbidities (n=29).(22)

Reliability: Satisfactory (intraclass correlation coefficient (ICC)=0.89) test-retest reliability (using an interval of 1-3 weeks) was reported.

Construct validity (convergent): Comparing with data on other measures such as family function, parenting stress, self-concept and loneliness, children with high ICND scores also scored highly on parenting stress and emotional problems. Cowan reported satisfactory item convergent validity, and excellent internal consistency (α=0.97), but did not provide any additional details.

Construct validity (known group): The ICND total score was shown to discriminate between children with more severe epilepsy and comorbidities and was highly significantly negatively correlated with the quality of life scores used for comparison.

Cowan concluded that while the brevity of the ICND contributes to weaknesses in several psychometric properties, its brevity also makes it clinically attractive and suggested that it could be useful to identify potentially problematic issues for patients with epilepsy. The authors cautioned against using the measure in intervention outcome studies, presumably due to lack of evidence.

It is not thought that this measure was designed to capture all aspects of HRQoL (even when used in conjunction with the IPEF). It is only suitable for adolescents, and does not have a self-report version, thus it is not considered a candidate for inclusion in the NCA.

The Quality of Life For Children with Epilepsy (QOLCE)(31;32) used in Cowan 2004 and Waters 2009. The QOLCE was designed to assess a variety of age-relevant domains and is completed by parents of children (age 4-18 years) with refractory epilepsy with average intellectual abilities. The measure consists of two parts. The first uses 56 items assessing seizure description and 31 items assessing medication side effects. The second uses 77 (79 reported in Waters)(21) items assessing subjective impact of epilepsy. The items are merged to provide five main domains (physical function, cognitive function, emotional well-being, social function, behavioural function) and an overall quality of life scale. Responses for all items are transformed linearly onto a 0-100 point scale.

Reliability: While internal reliability was reported as satisfactory (Cronbach's α ranging from 0.72 to 0.93) by Cowan,(22) Waters stated these were limited to the characteristics of the sample tested and also reported high internal consistency in six subscales were indicative of item redundancy (correlation ranges 0.07 to 0.84).(21) Both studies indicated that test-retest properties of the QOLCE had not been analysed.

Construct validity (known group): The measure was reported to discriminate by age at epilepsy onset, seizure frequency and number of anti-epileptic drugs.(31) However, Cowan advocated caution regarding these results in all eligible populations as there is no evidence regarding the psychometric properties of the QOLCE with children with learning disabilities.

Construct validity (convergent): Item convergent and discriminant validity was established (no additional information provided). All of the QOLCE subscales (except depression, self-esteem, attention, and behaviour) were negatively correlated with severity (assessed using severity of seizures), and a significant inverse relationship was observed between the number of anti-epileptic drugs taken over the previous 6 months and the QOLCE subscale of memory and language. Two generic measures of child health were used to assess convergent validity using correlation coefficients between theoretically similar and dissimilar constructs between the QOLCE and these scales (assumed acceptable although actual results not provided in Cowan).

Responsiveness: Ceiling effects were reported for the social activities (17.5%) and stigma (32.5%) subscales within the domains.

Epilepsy and learning difficulties often co-exist. Comparing the measure in parents of children with average intelligence (n = 64) and those of children with mild to moderate learning disability (n = 30), intellectual disability independently depressed scores on the QOLCE, indicating it may not be appropriate in all populations.

In summary, both Cowan and Waters warned that small sample sizes used in the psychometric analyses may have limited the apparent quality of the QOLCE's psychometric properties. Cowan also stated that no examination of the possible existence of age effects had been reported even though the QOLCE was intended for use with a large age range. There is sufficient negative evidence to raise concerns regarding its appropriateness and a review of all literature on this measure would be required before it could be recommended for use in the NCA.

The Quality of Life Inventory for Adolescents with Epilepsy (QOLIE-AD-48)(33) used in Cowan 2004, Waters 2009, and Davis 2009.
The QOLIE-AD-48 is a self-report measure for adolescents (11-17 years) of average intelligence with epilepsy. The measure consists of 48 items (rated on 5 point scale) describing eight subscales (epilepsy impact, memory/concentration, attitudes towards epilepsy, physical functioning, stigma, social support, school behaviour, health perceptions), and a total summary score.

Reliability: While test-retest reliability for the summary score over a 4 week period was good (0.83), it was not clear if respondents' epilepsy was stable over this period; this is assumed to be the case.(22)

Construct validity (known group): The QOLIE-AD-48 was able to discriminate between groups differing in seizure severity (known group validity).

Construct validity (convergent): Construct validity (convergent) for the summary score was reported to be good (Cronbach's α=0.74) and with the exception of the health perception subscale (Cronbach's α=0.52) good for the other subscales (Cronbach's α range: 0.73 to 0.94).(22) Cowan reported issues with the factor analyses (convergent) reported on the measure, questioning its reliability in external data. Correlations of between 0.65 and 0.54 were reported between the QOLIE-

AD-48 and measures of self-efficacy and self-esteem respectively.(40) In addition a greater overall subjective impact of epilepsy was more likely to be reported in those with more severe epilepsy and more symptoms of neurotoxicity, those living in households with lower socio-economic status and older adolescents.(40)

Responsivenesss: No floor or ceiling effects were detected with responses on all subscales covering the full range (0-100),(22) although items in two subscales were potentially redundant.(21) The results of a regression analysis (dependent variable being the 'overall HRQoL'), suggested the main explanatory variables were age, seizure severity, neurotoxicity of the anti-epileptic drugs and socio-economic status.(33)

In summary while the QOLIE-AD-48 has been reported as meeting many of the psychometric criteria necessary for a robust instrument, it is restricted to use with adolescents without learning difficulties, does not have a self-report version, and further investigation of the construct validity in larger populations has been recommended.(22)

The HRQoL questionnaire for Brazilian children with epilepsy (QVCE-50)(34) used in Waters 2009
The QVCE-50 is a Portuguse instrument completed by the care giver (age range not provided) designed to measure quality of life. The measure includes 50 items covering four domains (psychological health, physical health, cognitive educational issues, and social and family relationships), indicating it will provide a mix of objective functional and subjective health perceptions. This measure is not appropriate for inclusion in the NCA and is described here for completion only.

The Strengths and Difficulties Questionnaire (SDQ)(35;36) used in Brunklaus 2011

The SDQ is completed by the parent/ care giver, and provides information on psychosocial attributes of children (age 3 to 16). The measure consists of 25 items with each attribute rated using 'not true', 'somewhat true', or 'certainly true'. The SDQ total score is obtained using four scales (emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems) with 5 items in each scale. Higher values on the SDQ total score indicate greater difficulties. Brunklause stated good validity and reliability had been reported but provided no additional details relating to this.(35;36) It is not thought that this measure covers all aspects of HRQoL, it does not have a self-report version, and is not considered a candidate for inclusion in the NCA.

Generic- measures used in paediatrics with epilepsy

Child Health Questionnaire (CHQ)(20) used in Waters 2009, and Eiser 2001.

Originally designed by Landgraf in the 1990's, the CHQ is designed to measure wellbeing, functional health status, and health outcomes in children (4-19 years) and is a widely used and accepted measure. The parent/proxy (CHQ-PF50)(21) is the most widely used version while the Child health questionnaire child form 87 (CHQ-CF87) is completed by adolescents (age 10-19 years).(19) The questionnaire includes 50 items covering the following domains: behaviour, bodily pain, general health, mental health, physical functioning, parent impact-time, parent impact-emotional, role-emotional ⁄ behavioural, role-physical, and self-esteem. There are two overall summary scores: physical and psychosocial (range 0-100 with 100 being better health). Neither Waters nor Eiser presented analyses exploring the psychometric properties of the measure in children with epilepsy.

As the literature searches were not designed to identify evidence for this measure, and no evidence was found on the psychometric properties, additional searches and a review of all evidence on the measure used in epilepsy would be required before it could be recommended for inclusion in the NCA.

Health Utility Index Mark 2 (HUI2) (3) used in Eiser 2001

The HUI2 was originally designed for use in children with cancer and is now used as a paediatric generic measure.(41) The instrument covers six dimensions: sensation, mobility, emotion, cognition, self-care, pain with 3-5 levels on each question. A fertility dimension was originally used in the version developed for cancer but was subsequently dropped from the generic version. In addition to the six dimensions, there is a UK preference-based tariff which can be used to generate utility values

for use in economic evaluations.(42) No literature describing the psychometric properties of this measure are reported in Eiser et al.

As the literature searches included terms to identify evidence of the HUI2 in paediatrics with epilepsy, it is unlikely that there is evidence describing the psychometric properties of this measure in this population. Consequently it cannot be recommended for inclusion in the NCA without additional research (see recommendations below).

*KIDSCREEN (43)*used in Waters 2009

The KIDSCREEN-10 is a generic measure designed to measure the HRQoL of healthy and chronically ill children (8 to 18 years). Either self-completed or completed by the parent/caregiver, the domains include: physical well-being, psychological well-being, social support and peers, and financial resources. The inter-subscale correlations range from poor to fair (0.1 to 0.62) demonstrating the relative independence of the domains. Good test–retest reliability (r=0.73) and internal consistency (0.82) have been reported.(43)

It is not believed that this measure is widely used in epilepsy and a full systematic search would be required to identify all available evidence before it could be recommended for use in the epilepsy NCA.

The Paediatric Quality of Life Inventory (PedsQL(4)) used in Waters 2009, Eiser 2001, Brunklaus 2011, Modi 2010, Stevanovic 2011

The PedsQL, a generic measure of HRQoL, has been reported as being one of the most thoroughly developed measures available.(19) It takes 4 minutes to complete and is either self-completed (5-18 years), or completed by a parent/caregiver (2-18 years). The measure covers 23 items describing four domains: emotional (5 items), social (5 items), physical (8 items), and school (5 items). Items are answered on a five-point Likert scale (0 = ‘‘never a problem’’ to 4 = ‘‘almost always a problem’’). The scores from these are used to derive summary scores in physical health (8 items) and psychosocial health (15 items) and an overall total score. These are all standardised (0-100) where higher scores indicate better HRQoL. In addition to the PedsQL core instrument, a new module for epilepsy is currently being developed. However, this will not be available for a couple of years.(44)[personal communication, J Varni, June 2014]

Reliability: The PedsQL Generic Core Scale total score has adequate internal consistency reliabilities for both the proxy-report (α=0.70 to 0.89) and self-report (α=0.54 to 0.86),(45) and between 0.68 to 0.90 in a second study.(23) There were some differences in the ability of the measure to discriminate between different levels of severity of anxiety and depression when comparing the child and parent responses, though this is possibly to be expected.(24)

Construct validity (known group): The PedsQL total and sub-scores have been shown to differ (construct, known group validity) between healthy children (n=665) and children with Dravet syndrome (n=158, p<0.001), (46) and across age categories (e.g. 2-3, 4-5, 6-9, 10-14, >15 years) in the Dravet sample with mean HRQoL scores decreasing as age increased (p<0.001 for all comparisons).(46) The total number of comorbidites was associated with lower HRQoL for all subscales and total score (p<0.05), and there was also significant differences in mean scores when compared to PedsQL normative data (p<0.05).(23) In a different study, using both self-report and parent-proxy data, the PedsQL was able to differentiate between severity of depression or anxiety disorders in children with epilepsy (n=60).(24)

Responsiveness: Comparing children who had a history of a single seizure (n=53) with newly diagnosed untreated children (n=56), no significant differences was found in any of the mean subscales (p>0.05) for the patient–proxy reports.(23) While the authors suggested these results indicated that the PedsQL may not be sensitive to change due to treatment of epilepsy, it is unclear why a change was expected based on the evidence reported in the article.(23)

Summary and conclusion of review of literature on paediatrics with epilepsy

Although limited, the evidence suggests the EQ-5D is adequate for adults, inferring the youth version is worth considering for paediatrics. However, the EQ-5D-Y is only suitable for older children and no evidence was identified on its appropriateness in paediatrics with epilepsy. The evidence identified which could be used to compare PROMs in this population was limited. The searches, although limited in scope due to the time constraints of the project, did not identify any evidence which could be used to generate quality adjusted life years (QALYs) directly from PROMs in this population. The most likely candidate measures for inclusion in the epilepsy NCA are the QOLIE-AD-48 and the PedsQL^{TM} v4. Based on the evidence reviewed, the target age group, and alternative responder versions, the PedsQL^{TM} is recommended over QOLIE-AD-48 measure (Table 1). However, research is required to generate an associated preference-based tariff for the PedsQL^{TM} (or a mapping function

to one of the alternative preference-based generic measures) which could be used to generate utility values for use in cost-effectiveness evaluations.

Table 1: Summary of evidence on PROMs for epilepsy

Measure (N)	Target Age (years)	Target Responder	Acceptability	Reliability	Construct (KGV; Convergent)	Responsiveness (Change over time; Ceiling effects)
Adults						
EQ-5D (5)	-	-	No evidence	No evidence	Good; Good	Mixed; Poor
Adequate but the evidence on the different psychometric properties is very limited (n studies =5) Is not appropriate for paediatrics with epilepsy.						
Paediatrics						
QOLIE-AD-48 (3)	11-17	SR	No evidence	Good	Good; Mixed	No evidence; Good
Adequate but evidence is limited (n= 3 studies and not all properties tested) Would require a systematic literature review to identify additional evidence. Cannot be used to generate QALYs and only appropriate for adolescents.						
PedsQL (5)	2-18	SR;PR	No evidence	Good	Good; No evidence	Unclear; no evidence
Acceptable (n studies = 5) but cannot be used to generate QALYs						
PedsQL epilepsy module Currently under development but could be considered in the future						

KGV = known group validity; CE=ceiling effect; n = number, SR=self-report, PR=Parent/carer-report

4.3 Evidence for economic evaluations in epilepsy (WP1.3)

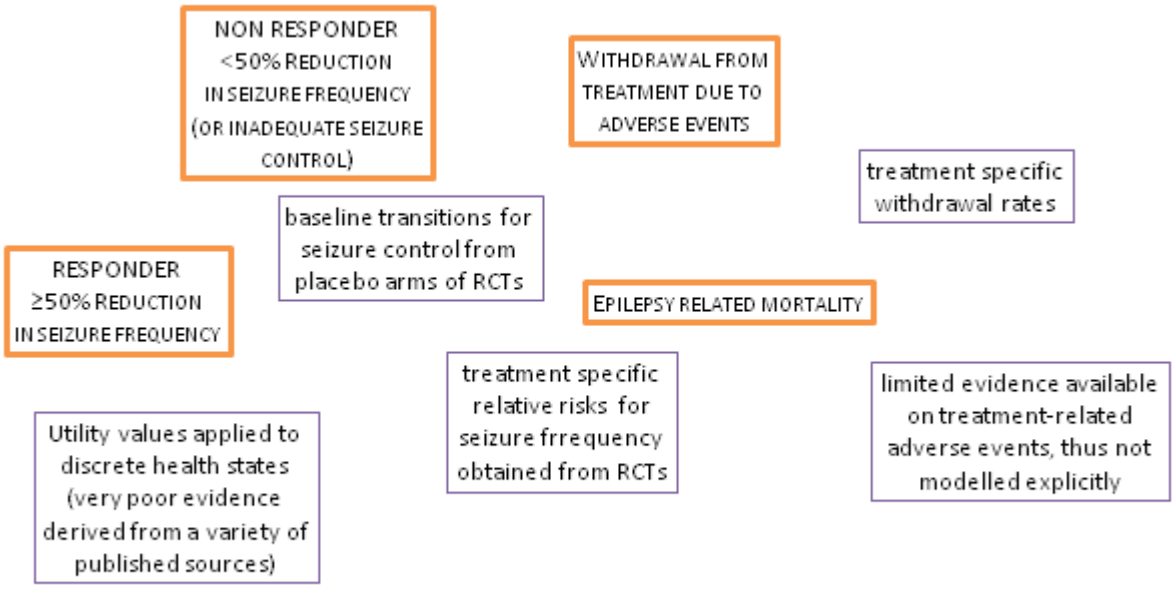
4.3.1 Cost-effectiveness modelling approach used in recent HTAs in epilepsy

Three Technology Appraisals (TA) relating to epilepsy were identified from the searches and one clinical guideline (CG) was identified from the reference lists. Two of the multiple technology assessments (MTAs) were superseded by the CG and thus excluded from the review.(47;48) The remaining Single Technology Appraisal (STA) examined the clinical and cost-effectiveness of a pharmaceutical intervention in adults with partial refractory epilepsy (10).(49) The CG compared interventions in primary and secondary care for both adults and children.(50)

The STA used a decision tree with four discrete health states (seizure free, responder (≥50% reduction in seizures), non-responder (<50% reduction in seizures), withdrawal (due to adverse events (AEs)) as described in Figure 1.(49) Baseline transitions for the health states were derived from placebo arms of clinical studies, and treatment effects were modelled by applying relative risks (RRs) (obtained from clinical studies) to the baseline transitions. The CG used a Markov model with four discrete health states (seizure, reduction in seizure frequency, inadequate seizure control,

epilepsy related mortality).(50) Again both the baseline and active treatment health state transitions were derived from published clinical studies.

Figure 1: Modelling approach used in epilepsy HTAs



Orange framed boxes with uppercase text describe potential health states, blue framed boxes with lower case text describe the clinical evidence used in the economic models.

Both studies quality adjusted survival by assigning mean utility values to the discrete health states and EQ-5D data (or proxy values) were sourced from the literature in both cases.(49;50) It is worth noting that a) the results of the searches for preference-based utilities indicated that the volume of evidence in this patient group was sparse, particularly in paediatrics, and b) it was reported that utilities were a major driver of the cost-effectiveness results.(49)

Table 2: Summary of existing models used in epilepsy TAs

Model method, clinical effect	Method used to model utilities
STA (TA232): Epilepsy (partial) - retigabine (adjuvant); 2011	
Decision tree 4 discrete health states: seizure free, ≥ 50% reduction in seizures (responder), < 50% reduction in seizures (non-responder), withdrawal (due to AEs). Effectiveness: applied RRs to baseline transitions (derived from placebo arms) for: seizure free, response (see above), withdrawal (due to AE), withdrawal for any reason Source: RCTs used for clinical effect	Utility: EQ-5D; mean values assigned to discrete HS Source: published literature AEs: not modelled explicitly as side effects of treatments assumed to mitigate withdrawal (due to AEs)
CG (CG137): The Epilepsies. Diagnosis and management of the epilepsies in adults and children in primary and secondary care; 2012	
Markov models 4 discrete health states: seizure, reduction in seizure frequency, inadequate seizure control, epilepsy related mortality. Effectiveness: baseline transitions (probabilities derived from survival curves) from RCT data; effects for active interventions applied to baseline transitions using HRs Source: RCTs used for clinical effect	Utility: proxy EQ-5D elicited from clinicians; mean values assigned to discrete HS Source: published literature[b] AEs: assumed transient and disappeared on treatment cessation (no disutility)

HS: health states; AE: Adverse Events; STA: Single Technology Appraisal; CG: Clinical Guideline; TA: Technology Appraisal; RCT: randomised controlled trial; HR: Hazard ratios

[b] NB the evaluation for children used values elicited from paediatric neurology experts who ranked 6 epilepsy related health states and classified these using the EQ-5D descriptor

The health states used in the HTAs are informed by the clinical effectiveness evidence which is typically reported as differences in rates of responders (as measured by reduction in seizure rates) in this population. The health states appear crude (seizure free, responder, non responder and withdrawal) when considering the full clinical pathway for paediatrics with epilepsy. It is possible that the conceptual model could be further developed to cover the full spectrum of disease and interventions for epilepsy, including hospitalisations, visits to accident and emergency departments (A&E), surgical interventions etc. This would require additional evidence including a measure of severity, in addition to the changes in frequency of seizures and adverse events associated with treatment. It is likely that even if the design of the economic model was expanded to include these additional health states, the approach taken to model HRQoL would remain the same with mean values assigned to the individual health states.

In summary, the following evidence would be required to compare providers or the cost-effectiveness of interventions for epilepsy:

- Seizure frequency (repeatedly measured over time)
- Seizure severity
- Pharmaceutical interventions (type of intervention, concomitant medications, 'response' rates, withdrawal rates, adverse events)
- Surgical rates (type of intervention, success rate, post-surgical complication, length of stay)[3]
- HRQoL data (collected alongside seizures if possible, and before and after surgical interventions)
- Death rates (seizure and surgical related, all cause)

The majority of this evidence would need to be linked through timings of collection.

4.3.2 Fields collected in the epilepsy NCA

The epilepsy NCA collects information on and from paediatrics with a diagnosis of epilepsy and the corresponding health services provided. The fields in the NCA are collected via three questionnaires, a Clinical proforma, a Service proforma, and a patient questionnaire.(51) All questions in the Clinical and Service audits are mandatory for inclusion of the patient in the audit (Table A9). The former includes questions relating to the diagnosis, nature and frequency of epilepsy episodes at initial assessment and at 12 month after the first assessment; the type of investigations and professionals involved; and the number of pharmaceutical treatments used. The latter obtains information on the type of epilepsy services provided, and the number and type of consultants within the audit unit on a specific day within the audit period. The patient questionnaire collects information of both patients' and parent/carers' experiences of the health services provided (Table A10). There is currently no PROM or clinical measure included in the patient questionnaire.

4.3.3 Comparing fields in epilepsy NCA with variables and methods used in existing HTAs

The existing HTA models are constructed around the number of seizures, the reduction in numbers of seizures (response) due to treatment, withdrawal from treatment due to AEs, and HRQoL scores categorised by current health status. The fields in the current NCA provide insufficient detailed mandatory information to examine changes in frequency of seizures, the epilepsy medications taken (and duration), or withdrawal due to AEs or non-response. The epilepsy Patient questionnaire does not currently collect HRQoL information, concentrating on patient reported experience measures

[3] If appropriate for the epilepsy NCA

(PREMs), and the mandatory fields do not include a surrogate measure which could be used to estimate proxy utility values. The evidence used in the existing economic models indicates there is very little appropriate published evidence which could be used. Consequently it will not be possible to source robust values from the literature. It is not clear if surgical interventions and associated information might be considered for collection in future audits but this is evidence that would be useful for comparing providers or the cost-effectiveness of alternative policies.

While it is currently not possible to compare the cost-effectiveness of interventions in epilepsy using the audit data, it may be possible to compare performance across units, stratified for example by the type of services provided, using the mandatory annual aggregate number of seizures. It is not known if there are plans to expand the audit to include additional fields or if there are any ongoing studies relating to PROMs in this area.[personal communication, Calvin Down, Project Manager, 13th May 2014]

4.4 Recommendations for epilepsy

The results from the paediatric review suggest the PedsQL is an appropriate measure for paediatrics with epilepsy, but it cannot currently be used to generate utility values. The results of the review of existing cost-effectiveness HTA models indicated that the evidence base of existing preference-based data in patients with epilepsy was extremely sparse, particularly in paediatrics, and that economic models are sensitive to the utility values used (Section 4.3). Finally, the current epilepsy NCA does not provide sufficient mandatory information to compare providers or the cost-effectiveness of interventions as used in general clinical practice. The issues and corresponding potential recommendations (PR) and areas for future research (FR) are discussed below. All suggested future research areas are indicative and would require a discussion and detailed proposal if required.

Based on the evidence reviewed, the results for paediatrics with epilepsy suggest the PedsQL^{TM} is currently the most appropriate measure for this population and it is recommended that this is considered for inclusion in the epilepsy NCA (PR.1). Once available, PedsQL^{TM} epilepsy module may be worth considering as an adjunct to the core measure.

As discussed in the IBD section, until there is an associated preference-based tariff, the usefulness of the PedsQL™ for economic evaluations is limited. Until such a tariff is available, an alternative preference-based instrument will be needed. Again the EQ-5D-Y is recommended for adolescents and a measure such as the HUI2 or the CHU-9D for younger children (PR.2). As no evidence was identified which described the psychometric properties of these measures in paediatrics with epilepsy, these would need to be assessed in primary studies (FR.1).

The epilepsy audit does not currently collect sufficient detailed information which could be used to perform cost-effectiveness evaluations. Additional mandatory fields to capture the information required would increase the flexibility of secondary use of the data (PR.3). Formal detailed recommendations of which fields to include would require additional detailed inspection of the exact data collected in the current epilepsy audit (FR.2).

Table 3: Recommendations and associated future research for epilepsy

PR.1	*Include the PedsQL™ (and the PedsQL™ epilepsy module) in future epilepsy audits*
PR.2	*Include age related paediatric preference-based HRQoL instrument (e.g. CHU-9D, HUI2 and EQ-5D-Y) in future paediatric audits*
FR.1	*Assess the psychometric properties of the paediatric preference-based tools in epilepsy using data collected in the audit*
PR.3	*Include additional mandatory fields in the epilepsy audit severity and frequency of seizures, response to current treatment, and medications (and if applicable, evidence relating to surgical interventions), linked by time to HRQoL.*
FR.2	*Detailed analyses of fields currently collected in the epilepsy audit to identify recommendations for future mandatory fields*

5. SUMMARY

5.1 Summary of evidence used to inform the conclusions for WP1.1 and WP1.2

In summary, a review of evidence of PROMs provides evidence of reliability and known group validity for the PedsQL™ (5 studies) in paediatrics with epilepsy, but the strength of the evidence supporting sensitivity to changes over time was less evident (Table 4). While considered to be acceptable, additional validation is required to support the long term use of the PedsQL™ in this population. As with IBD, additional paediatric preference-based measures are recommended for use in paediatrics with epilepsy.

Table 4: Summary of evidence currently available for recommended measure(s)

Measure	N	Acceptability	Reliability	Construct		Responsiveness		Overall
				KGV	Convergent	Change over time	Ceiling Effect	
EQ-5D	5	NE	NE	Good	Good	Mixed	Poor	All evidence in adults. Not appropriate for paediatrics
PedsQL	5	NE	Good Good	NE	Unclear	NE		Acceptable
PedsQL epilepsy module		This measure is currently in development and it is unclear when it will be available						

N, number of studies used to inform conclusions; KGV: known group validity; NE, no evidence was identified; [a] consider the PedsQL epilepsy module as an adjunct to the core measure once available

5.2 Summary of evidence required for use in economic evaluations (WP1.3)

The existing patient questionnaire collects PREMs rather than PROMs and there is no existing variable within the current audit which could be used to map to a preference-based measure for use in economic evaluations. While the PREMs could be used to compare providers, their use in economic evaluations is limited. The review of existing economic evaluations identified that there was no suitable preference-based evidence in the literature for paediatrics with epilepsy. It is thought that the current audit contains insufficient detailed evidence on seizure frequency and severity, pharmaceutical interventions (and associated response, withdrawal rates and adverse events), surgical interventions and death rates to conduct formal economic evaluations with these data.

APPENDIX: EPILEPSY

The tables in this Appendix provide additional information for the reviews (WP1.1, 1.2 and 1.3) conducted for epilepsy.

Table A1: Quality assessment of the Davies et al. review of epilepsy (5)

Quality assessment criteria	**Compliance with criteria**
AMSTAR	
Was an a priori design provided?	Yes
Was there duplicate study selection and data extraction?	Yes, for study selection; unclear for data extraction.
Were the methods used to combine the findings of the studies appropriate?	Unclear - narrative synthesis conducted but no reported justification.
Was the scientific quality of the included studies assessed and documented?	Quality was considered in the weighing of the evidence, but not documented
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Unclear
Overall judgement of quality of review	Unclear - no quality assessment or justification for lack of statistical synthesis
Quality of the searches	Adequate – some lack of clarity, but unlikely to have missed studies.
Strength of the evidence	
Were the conclusions robust and conclusive?	
Quantity of the evidence	
Was there enough data to be confident that any additional data published subsequently would be very unlikely to change the conclusions drawn?	No, update required
Adequacy of data reported	
Did the review provide sufficient data to allow integration of an update/assessment of the methods used?	No, no data for individual studies reported
Did the review assess EQ-5D in a way compatible with the aims of work package 1.1?	Unclear – insufficient information provided, no individual data reported, only summaries of strength of evidence. Unclear of comparators for each study. Inclusion and exclusion criteria not described. No, age exclusion criteria does not match the population in the epilepsy NCA

Table A2: Characteristics of studies included in the systematic review for epilepsy

Study ref Author, Year	Country	Disease/treatment stage	Treatment (if any)	Study type (e.g. cross sectional, RCT, cohort)	Study objective
Langfitt 2006(9)	USA	All subjects had monthly, consciousness-impairing seizures for at least the past 2 years, despite trials of two or more anti-seizure medications. ≥18 years of age.	72% had surgery after assessment. The rest had insufficiently localized seizures or chose to rely on medical treatment only.	Time series within a larger observational study	To determine which instrument is the most appropriate for CUA of epilepsy care, using established psychometric criteria.
Selai 2000(12)	UK	Patients undergoing evaluation for definitive treatment for intractable epilepsy. Analysis is on the 22 patients who had surgery AND had ≥75% seizure reduction. Unclear age selection.	16 had left temporal lobe resection 4 had right temporal lobe resection 5 extra-temporal lobe resection. 22/25 who had surgery had ≥75% seizure reduction.	Time series	The aim of this work was to assess the health-related quality of life (HRQL) of patients pre and post surgical treatment for epilepsy.
Xu 2006(8)	USA	Adult patients with partial-onset epilepsy receiving stable polytherapy regimens. Patients had to have experienced at least one partial or complex partial seizure within the past 12 months.	Stable polytherapy regiments, at least two AEDs	Cross section	To examine the prevalence and impact of sleep disturbance in epilepsy.
Trueman & Duthie 1998(13)	UK	A sample with epilepsy, a sample without epilepsy, matched for patient characteristcs (age, sex, region of residence and social class). Unclear age selection.	NR	Cross section	A study was designed to assess the impact of epilepsy on health related quality of life in a large, general population study.
Selai 2005(7)	UK	Adult patients experiencing seizures despite treatment with one or more AEDs	Topiramate, lamotrigine, gabapentin, clobazam, vigabatrin	Observational study	To evaluate the impact of adjunctive treatment with an anti-epileptic drug on the health status of people with epilepsy and to investigate how seizure frequency affects their health.

CUA, cost utility analysis; AED, antiepileptic drug; NR, not reported.

Table A3: Participant characteristics of studies included in the systematic review for epilepsy

Study ref Author, Year	Number of participants recruited	Age in years mean (sd); range	Male %	Ethnicity %	Other characteristics %	Missing data (patients completing study) include reasons for non-completion if given
Langfitt 2006(9)	216 recruted 165 analysed, 140 had baseline data, 89 completed 2-year follow-up	N=165 37.4 (11.4)	47	NR	Temporal lobe surgery: 62 Extratemporal lobe surgery: 8 No surgery: 30 At 2 year follow-up Seizure-free: 45 Persisting seizures: 56	51 excluded due to missing data
Selai 2000(12)	40 interviewed at follow up 22 met selection criteria and were analysed.	32.8 (8.6)	37.5	NR	NR	105 patients who were interviewed at baseline were not followed up. Reasons unclear.
Xu 2006(8)	201	44.2 (12.5)	44	White: 86 Black: 5.2 Hispanic: 6.7 Other: 2.1	Simple partial seizures: 6 Complex partial seizures: 29 Partial seizures (simple or complex) with or without secondary generalization: 65 Seizures >1 month: 60 Depression: 41 Sleep disturbance: 34 Headaches: 31 Anxiety disorder: 29	NR
Trueman & Duthie 1998(13)	289 with epilepsy 389 without epilepsy	Epilepsy: 46 Non-epilepsy: 47	NR	NR	R	NR
Selai 2005(7)	125	37.5	54	NR	NR	NR
N, number; sd, standard deviation; NR, not reported						

Table A4: Measures used in psychometric analyses in studies included in the systematic review for epilepsy

	GENERIC MEASURES			OTHER MEASURES USED		
Study ref Author, Year	**Descriptive system**	**Tariff used**	**Mean (SD); 95% CI**	**Condition-specific HRQL measures**	**Clinical measures**	**Other generic**
Langfitt 2006(9)	EQ-5D	UK	0.762 (0.262)	QOLIE-89 NHSSS	Consciousness-impairing seizures in previous 2 years (measured at 2 year follow-up)	HUI2, HUI3, SF-6D
Selai 2000(12)	EQ-5D	NR	NR for EQ-5D index	ESI-55	Seizure reduction	QOLAS
Xu 2006(8)	EQ-5D	UK	0.64 (0.35)	QOLIE-89 MOS sleep scale	Diagnosed sleep disturbance	
Trueman & Duthie 1998(13)	EQ-5D	NR	NR	HADS		
Selai 2005(7)	EQ-5D	UK	0.8499 (0.1772)		Seizure frequency	

NHSSS, National Hospital Seizure Severity Scale; QOLIE-89, quality of life in epilepsy-89; Quality of life assessment schedule; ESI-55, epilepsy surgery inventory; MOS, medical outcomes study; HADS, hospital anxiety and depression scale; HUI, health utility index; SF-6D, short form 6 dimensions

Table A5: Psychometric analyses reported in studies included in the systematic review for epilepsy

Author, Year	Comparison and statistical test used	Validity results, Group A(n) vs. Group B(n)' Mean EQ-5D; mean difference in EQ-5D	Authors' conclusions/notes	Our additional conclusions/notes
Reliability				
Langfitt 2006(9)	Reliability, t-test	EQ-5D (HUI2, HUI3, SF-6D, QOLIE-89) were not sensitive to IQ and education, as expected.		EQ-5D did not differ in groups where no difference was expected.
Construct (Known group)				
Xu 2006(8)	Sleep disturbance vs no sleep disturbance ANOVA	Measure: mean (SD) with diagnosed sleep disturbance; mean without diagnosed sleep disturbance MOS sleep scale sleep problems index: 46.8 (19.7); 31.1 (19.2) p<0.001 QOLIE: 55.2 (20.6); 63.7 (20.1), p=0.006 EQ-5D: 0.49 (0.38); 0.71 (0.31), p<0.001		EQ-5D was able to distinguish between patients with and without sleep disturbance as were the QOLIE and MOS measures.
Langfitt 2006(9)	Seizure severity Seizure control F-ratio (>4 considered significant)	**Seizure severity** Measure: F-ratio EQ-5D: 12.18 HUI2: 10.76 HUI3: 6.71 SF-6D: 14.67 QOLIE-89: 8.94 **Seizure control (at 2-years)** Measure: F-ratio EQ-5D: 0.06 HUI2: 2.66 HUI3: 5.71 SF-6D: 4.97 QOLIE-89: 11.29	All measures were sensitive to seizure severity. EQ-5D was relatively insensitive to seizure control (F=0.06). QOLIE-89 was the most sensitive to seizure control; the SF-6D and HUI3 were also related to seizure control, to a lesser extent	

Trueman & Duthie 1998(13)	EQ-5D response on anxiety/depression scale vs HADS score no formal statistical analysis	EQ-5D anxiety/depression dimension score: Mean HADS score, epilepsy; mean HADS score non-epilepsy No problems: 12.23; 9.55 Some problems: 16.69; 16.26 Extreme problems: 24.41; 23.89		The trend in mean HADS scores is as expected, according to EQ-5D anxiety/depression dimension score
Selai 2005(7) Selai 2002(11) Remak 2004(10)	Seizures per month, only one statistical comparison provided	At baseline Number of seizure per month:mean EQ-5D >10: 0.798 2–9: 0.902 ≤1: 0.934 The end of treatment scores for patients who achieved seizure-freedom were significantly higher than for patients who failed to have a 50% reduction, and those who were no longer on original treatment.		EQ-5D had expected trend in means for frequency of seizures.
Construct validity (convergent)				
Langfitt 2006(9)	correlation with subject characteristics (seizure severity by NHSSS)	Pearson's for continuous variable Spearman's for dichotomous variables (comorbidity present; seizure control) Subscale: comorbidity present; seizure severity; seizure control Mobility: 0.00; -0.16; 0.31* Self-care: -004; -0.10; 0.19 Usual activities: -0.00; -0.25**; 0.17 Pain/discomfort: -0.11; -0.22**; 0.04 Anxiety/depression: -0.13; -0.13; 0.13		EQ-5D dimensions were not well correlated with the presence of a comorbidity on any scale. EQ-5D was significantly correlated with seizure severity for the usual activity and pain/discomfort health dimensions, and with seizure control for the mobility health dimension.
Responsiveness				

Selai 2005(7) Selai 2002(11) Remak 2004(10)	Change over time in EQ-5D from baseline, in several categories No formal statistical analysis	Category (n): difference in mean EQ-5D from baseline Seizure-free on treatment (11): 0.0919 ≥50% reduction in seizures and ≤1 seizure per month (16): 0.0345 ≥50% reduction in seizures and >1 seizure per month (9): 0.079 <50% reduction in seizures on treatment (42): -0.0211 No longer on study drug at end study (47): -0.0122		Change in mean EQ-5D from baseline was positive for those with ≥50% reduction in seizures. The change was higher in patients experiencing >1 seizure per month compared to those experiencing ≤1 seizure per month, and highest in those experiencing no seizures. Discrepancies in trends may be due to small sample numbers.
Langfitt 2006(9)	Effect size and SRM	Measure: t-test; effect size; SRM EQ-5D: -0.20; 0.35; 0.30 HUI2: 0.60; 0.07; 0.09 HUI3: 1.15; 0.36; 0.33 SF-6D: 1.18; 0.71; 0.43 QOLIE-89: 2.22; 0.85; 0.87 Measure: RS-RID; RS-SF; EQ-5D: 0.69; 0.43 HUI2: 1.23; 0.15 HUI3: 0.66; 0.39 SF-6D: 0.88; 0.58 QOLIE-89: 1.53; 1.20	Effect sizes were medium (0.35 to 0.85) for all but the HUI2, which was small. SRMs paralleled effect sizes. By t-test, none of the instruments detected a significant change in HRQoL at 2 years in contrast to the QOLIE-89	The EQ-5D was also able to detect a change (as observed in the change in QOLIE) in subgroups who reported being either much better or much worse on the GRC as observed in the change in QOLIE. However, although the EQ-5D was able to detect a change in patients who were seizure-free at two year follow up, the difference was substantially underestimated when compared to that observed on the QOLIE.

Selai 2000(12)	change over time, statistical test type NR or not performed	Measure: baseline mean (SD); 1-year follow-up mean (SD) EQ-5D: 0.81; 0.91, NS (p NR) QOLAS: 32.3 (8.0); 17.1 (8.8) p,<0.0001 ESI-CMH: 62.2 (14.3); 74.8 (12.1), p<0.0001 ESI-CPH: 73.2 (14); 82.9 (11.6) , p<0.0001 ESI-CRF: 69.6 (22.9); 78.5 (20.8), NS (p NR) EQ-5D health dimensions- % no problems; some problems; extreme problems Mobility: Baseline: 86;9;5, Follow-up: 90;10;0 Self care: Baseline: 86;14;0, Follow-up: 100;0;0 Usual activities: Baseline: 72; 18;9, Follow-up: 89; 1;0 Pain/discomfort: Baseline: 82; 18; 0, Follow-up: 85; 5;0 Anxiety/depression: Baseline: 59;2;9, Follow-up: 80;20;0 Formal statistical comparison NR. At follow-up, no patients were scoring extreme problems in any subscale (statistical comparisons NR), where they had reported extreme problems at baseline.	The EQ-5D utility scores showed improvement but the changes were not significantly different. The QOLAS and two of the three ESI-55 composite scores were sensitive to change as shown by statistically significant differences in scores.	

Langfitt 2006(9)	Ceiling effect, % scoring full health	34% of patients with epilepsy scored full health on the EQ-5D. <10% scored full health by HUI2, HUI3, SF-6D and QOLIE-89.	The EQ-5D had a substantial ceiling effect.	

* p<0.05; **p<0.01

RS=responsiveness statistic where denominator was sd of change between baseline and follow-up in 'clinically stable' patients

RS-RID: mean absolute change from baseline to follow-up in subjects who reported to be much better or much worse on the global rating of change item.

RS-SF: mean absolute change from baseline to 2 year follow-up in subjects who were free from consciousness-impairing seizures during 2 year follow-up

NHSSS, National Hospital Seizure Severity Scale; QOLIE-89, quality of life in epilepsy-89; Quality of life assessment schedule; ESI-55, epilepsy surgery inventory; MOS, medical outcomes study; HADS, hospital anxiety and depression scale; HUI, health utility index; SF-6D, short form 6 dimensions, GRC, global rating of change; SRM, standardised response mean.

Table A6: Papers excluded on 2nd sieve (full paper) for epilepsy in paediatrics

EXCLUDE: Not available yet	Bansal, D.(52)
EXCLUDE: Library cannot locate this	Chen, Q. (53)
EXCLUDE: Library cannot locate this	Lai, J.S. (54)
EXCLUDE: adults	Wiebe, S. 2002.(55)
EXCLUDE: adults	Fiest, K.M. 2014.(56)
EXCLUDE: adults	Hamid. 2014(57)
EXCLUDE: this is conference abstract for MODI which is included	Koumoutsos, J. (58)
EXCLUDE: this is a conference abstract for Branklaus which is included	Brunklaus, 2011.(46)
EXCLUDE: conference abstract with no detailed results (hard copy)	Muthugovindan, (59)
EXCLUDE: conference abstract with no detailed results (hard copy)	Matic, P. (60)
EXCLUDE: conference abstract with no detailed results (hard copy)	Partikian, A.(61)
EXCLUDE: conference abstract with no detailed results	Beyoglu, E S. (62)
EXCLUDE: written in Japanese	Matsuda, 2006(63)
EXCLUDE: not psychometric analysis of instruments (presents mean values on patient and parent scores on PedsQoL, insufficient detailed analyses and no comparator or other analyses)	Mcrandal,(64)
EXCLUDE: not psychometric analysis of instruments (presents mean QoL after surgery (n=11 for children), QoL instrument used: Child epilepsy Parental form III (ie Quality of life in Childhood epilepsy questionnaire QOLCE ref Sabaz 2000)	Mikati, 2009.(65)
EXCLUDE: not psychometric analysis of instruments (compares means scores on PedsQL dimensions for patients with epilepsy (n=11) and those with HH (hypothalmic hamartoma n=21))	Park, C., 2013.(66)
EXCLUDE: not psychometric analysis of instruments (n=16, so too small sample to draw conclusions)	Kulpeng, 2013(67)
EXCLUDE: not psychometric analysis of instruments (reports mean scores on the QOLIE AD for an Iranian subgroup, comparing with mean scores on the QOLIE AD from other settings – not useful for English setting	Zamani, G. 2014.(68)
EXCLUDE: not psychometric analysis of any of instruments (although includes PEDsQl, only states there was a sig association ($p<0.001$) between siezure severity and HRQoL - no values	Lagunju(69)
EXCLUDE: not psychometric analysis of instruments (does not present sufficient QoL data to be informative on psychometric properties and sample size n<10 in total	Whitney, 2013.(70)
EXCLUDE: study looking at the 'How are you questionnaire' to assess HrQoL (125 questions)	van, ER, 2005.(71)
EXCLUDE: assessing psychometric properties of a translated version of the QOLIE-AD-48 using the Chinese version of the PedsQL as comparator- not useful for English setting	Wang, M, 2009.(72)

Table A7: Measures reviewed or used in the seven studies in the epilepsy paediatric systematic review

	Cowan 2004(22)	Waters 2009(21)	Davies 2009(5)	Eiser 2001(19)	Brunklaus 2011(46)	Modi 2009(23)	Stevanovic 2011(24)
Study population	Review of literature	Review of literature	Review of literature	Review of literature	Dravet syndrome	Children with single seizure or newly diagnosed untreated	Children and adolescents with epilepsy
ELDQOL(25-28)	yes	-			yes[@]		
HRQoLCE(18)	yes	yes	yes				
ICND(73)	yes	-					
IPEF (29)		yes			yes		
QOLCE(31;32)	yes	yes					
QOLIE-AD-48(33)	yes	yes	yes				
QVCE-50(34)	-	yes					
SDQ(35;36)					yes		
CHQ(20)	-	yes[~]		yes			
HUI2(3)				yes			
KIDSCREEN(43)	-	yes[~]					
PedsQL(4)	-	Yes(74)		yes	yes	yes	yes[#]

CHQ Child Health Questionnaire, ELDQOL Epilepsy and Learning Disabilities Quality of life Scale, SDQ=Strength and difficulties questionnaire, HRQoLCE the HRQoL in Children with Epilepsy measure, HUI2, ICND the Impact of Childhood Neurologic Disability Scale, IPEF=impact of paediatric epilepsy, KIDSCREEN, PedsQL
QOLCE the Quality of Life with Children in Epilepsy , QOLIE-AD-48 the Quality of Life in Epilepsy Inventory for Adolescents, [#]used Serbian version of PedsQL [TM] [Stevanovic 2010], [~] the psychometric evidence presented is from children with cerebral palsy (Vargus-Adams 2006], [@]used just five items from the ELDQOL relating to seizures over the previous 4 weeks to rate epilepsy severity as: very severe, somewhat severe, moderate or mild

Table A8: Epilepsy specific measures used in the studies included in the paediatric epilepsy review

	ELDQOL	HRQoLCE	ICND	QOLCE	QOLIE-AD-48	IPEF	SDQ	CHQ	HUI2	KIDSCREEN	PedsQL
Age(years)	2-18	8-15	2-18	4-18	11-17	?	2-18	0-19	6-18	8-18	2-18
Respondent	Parent	Child and parent	Parent	Parent	Child	Parent	Parent/ caregiver	Parent /proxy, adolescent	Parent	Child and parent/proxy	Child and parent/proxy
Items	-	25	11	31	48	11	-	50	6	-	30
Domains	yes	yes	no	yes	yes	yes	yes	yes	yes	-	5
Summary scores	-	-	yes	yes	yes	yes	-	2x	yes	-	yes

NB: Data presented here are as reported verbatim from the studies included in the review and have not been checked at source.

Table A9: Mandatory fields collected in the epilepsy NCA

PATIENT INCLUSION CRITERIA[a]

NHS (CHI or H&C) number, Date Of birth, Date on which the first paediatric assessment for the episode or episodes occurred, How old was the patient at first paediatric assessment, Is the patient male or female, Date the patient received their first EEG, Does the child have any of the following exclusion criteria (All episodes the patient had were 'febrile seizures', all episodes the patient had were acute symptomatic seizures or occurred within a week of a traumatic head injury, patient has had a paediatric assessment previously for similar episode or episodes or epilepsy prior to first paediatric assessment, patient's care was permanently transferred to a secondary paediatric service outside the 'audit unit' boundaries or an adult service during the year after first paediatric assessment)

CLINICAL QUESTIONNAIRE[a]

Has the Unique Identifier Number been noted on the ascertainment sheet, GP practice code, The main trust involved in managing patient's seizure(s),[¥] the main hospital, if any, that has been involved in managing this patient's seizure(s),[¥] The main community paediatric service, if any, that has been involved in managing this patient's seizure(s)[¥]

SECTION 1: FIRST PAEDIATRIC ASSESSMENT[a]

Was the first paediatric assessment in an acute or non-acute setting, During the time period from the patient's first paroxysmal episode to the first paediatric assessment was there documentation of the following: A description of the episode or episodes, Approximately when the first episode was, or how old the child was at that time, The approximate frequency or number of episodes since the first episode, A general examination, A neurological examination, The presence or absence of developmental, learning or schooling problems, The presence or absence of behavioural or emotional problems

SECTION 2: DIAGNOSIS AT FIRST PAEDIATRIC ASSESSMENT[a]

Which statement best describes the number of paroxysmal episodes by the time of the first paediatric assessment, Which statement best describes the diagnosis made by the paediatric team by the end of the first paediatric assessment, Was a diagnosis of probable syncope, faints, breath-holding episodes or reflex anoxic seizures made, Was a diagnosis of probable tics made?

SECTION 3: DIAGNOSIS AT 12 MONTHS AFTER FIRST PAEDIATRIC ASSESSMENT[a]

Which statement best describes: the total number of paroxysmal episodes occurring[¥]; the diagnosis made by the paediatric team[¥], Was there any evidence that a diagnosis of epilepsy (two or more epileptic seizures) was made and then later withdrawn at any time[¥], Were any afebrile episodes documented as convulsive, Which of the listed epileptic seizure type(s) were identified, Which of the listed epilepsy syndromes were diagnosed, Were there any of the listed epilepsy syndrome categories identifiers used, Were there any of the listed epilepsy syndrome categories identifiers used, Was there evidence of a neurodisability diagnosis recorded by professionals involved, If yes, were any of the following diagnoses documented (list)

SECTION 4: PROFESSIONAL INVOLVEMENT[a]

Was there any evidence of input from a Consultant Paediatrician with expertise in[¥] a) epilepsy, b) a Paediatric Neurologist, Was there any evidence the child had a referral to or input from an epilepsy specialist nurse.

SECTION 5: INVESTIGATIONS[a]

Is there: an MRI head result documented,[¥] a CT head result documented,[¥] a 12 lead ECG result documented or contained within notes[¥]

SECTION 6: TREATMENT[a]

What number of different (maintenance) antiepileptic drugs had been used[¥]? Was Carbamazepine prescribed at any time[¥]?

SECTION 7: COMMUNICATION[a]

Was there any evidence of discussion with the parent and/or patient about issues relating to contraception, preconception or pregnancy[¥]?

SECTION 8: OUTCOME[a]

Was there documentation to suggest that seizures occurred between 6 months after first paediatric assessment to 12 months after first paediatric assessment, Was there documentation to suggest that seizures occurred between 9 months after first paediatric assessment to 12 months after first paediatric assessment, Is there any evidence that the child has died?

SERVICE PROFORMA[b] ***(referring to data on the census day only)***

¤*questions refer to whole time equivalent employed within the 'audit unit' (AU)*

How many: general paediatric consultants (community or hospital based),¤ general paediatric consultants with 'expertise in epilepsy',¤ Epilepsy specialist nurses,¤ Names of the consultant paediatricians having 'expertise in epilepsy'

How many consultant (or associate specialist) led secondary level 'epilepsy clinics' for children or young people take place within your audit unit per week? Do any of the paediatric services within the 'audit unit' maintain a database or register of children with epilepsies? Which of the following investigations can be obtained at a location within the 'audit unit'(12 lead ECG, 'awake' MRI, MRI with sedation, MRI with general anaesthetic, Routine EEG, Sleep-deprived EEG, Melatonin induced EEG, Sedated EEG, 24-48h ambulatory EEG, Video telemetry, Portable EEG on paediatric ward within audit unit)

Does the 'audit unit' host paediatric neurology clinics? (e.g. a paediatric neurologist visits a site within the audit unit or is based within that 'audit unit'), Which of the following 'transition services' are available within the 'audit unit'(A specific clinic for 'young people' or 'teenagers' with epilepsies, a 'Handover clinic', Other defined handover or referral process, Local adult specialist epilepsy nurse, Youth worker), From what age do 'outpatient' adult services within your audit unit begin to accept referrals from General Practitioners for young people with a seizure or seizures?

[a]collected via Epilepsy12 clinical audit Clinical proforma; [b]collected via Epilepsy12 Service Proforma July 2011; ¥relate to the 12 month period after first paediatric assessment

Table A10: Optional fields collected in the Epilepsy NCA (WP1.3)

PART A: PARENT/CARER QUESTIONNAIRE[c]
Child's year of birth, Child's sex, On average over the past year, how often does your child have seizures (<1/month, ≥1/month but <1/week, ≥1/week but <1/day, ≥1/day, unsure, other), Has your child ever been diagnosed with any of the following conditions (learning difficulties/developmental delay, cerebral palsy, autism or autistic spectrum disorder, attention deficit hyperactivity disorder (ADHD), none of the above, other), What type of clinic does your child attend for their seizures or epilepsy (general paediatric community paediatric, teenage epilepsy, specific epilepsy, paediatric neurology, don't know, other), Have you found it easy to contact the health service looking after your child's seizures or epilepsy, Over the last year, including planned appointments, how many times have you been in contact with this health service (either by visiting the clinic, by telephone or by email? (none, 1-5 times, 6-10 times, more than 10 times), Which areas, if any, would you like more information on (guidance on what my child can or can't do, the cause of my child's epilepsy or seizures, possible side effects of medication, reasons for changing medication, reason for, and results of, tests, support groups, contacting other families living with epilepsy, what to tell other people about my child's seizures or epilepsy, other), What is the level of education that you (not your child) have completed (secondary school, college/apprenticeship, undergraduate university, postgraduate university) Indicate whether strongly agree, agree, unsure, disagree, strongly disagree or not applicable, basing answers on experiences over all the last year: Overall, I received enough information on seizures or epilepsy, Staff listened to what I had to say, The information I was given was hard to understand, Staff did not take time to get to know me and my child, Staff did not explain things in a way I could follow, Staff took my views into account in making decisions, I felt the staff respected our need for privacy during clinic visits, Overall, staff seemed to know what they were doing, At times I felt I was not allowed to ask questions, It is easy to contact someone in the epilepsy team, Staff make sure it is easy to attend the clinic e.g. when making appointments, My child is not seen by the service often enough, When attending the clinic staff tell me if the appointment is going to be delayed, The waiting area does not have activities for my child, Overall, the length of time spent with staff at the clinic is just about right, Staff are not good at working together with others e.g. the G.P., when looking after my child, Staff are good at working together with school or nursery, Overall, staff are friendly and polite? What are the 3 best things about the epilepsy service, What are the 3 worst things about the epilepsy service, Overall are you satisfied with the care your child receives from the epilepsy service (yes, no, unsure)
PART A: CHILD OR YOUNG PERSON[c]
Overall, I received enough information on seizures or epilepsy, Staff listened to what I had to say, The information I was given was hard to understand, Staff did not take time to get to know me, Staff did not explain things in a way I could follow, Staff took my views into account in making, decisions, I felt the staff respected my need for privacy during clinic visits, Overall, staff seemed to know what they were doing, At times I felt I was not allowed to ask questions, It is easy to contact someone in the epilepsy team, Staff make sure it is easy to attend the clinic e.g. when making appointments, I am not seen by the service often enough, When attending the clinic staff tell me if my appointment is delayed, The waiting area does not have activities for my age, Overall, the length of time spent with staff at the clinic is just about right, Staff are not good at working together with others e.g. the GP, when looking after me, Staff are good at working with school or nursery, Overall, staff are friendly and polite? Which areas, if any, would you like more information on? (Guidance on what I can or can't do, Support groups, Contact with other young people with epilepsy, Cause of my epilepsy, What to tell other people about my epilepsy, Reasons for changing medication, Possible side effects of medication, Reasons for, and results of, tests) What are the 3 best things about the epilepsy service, What are the 3 worst things about the epilepsy service, overall, are you satisfied with the care you receive from the epilepsy service?

[a] Epilepsy Patient questionnaire v8 11.01.11 (older version)

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