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Article type : Full length original research paper

Comparisons of direct and indirect utilities in adult epilepsy populations: a systematic review

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/EPL.16396](https://doi.org/10.1111/EPL.16396)

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Key words:

Health economics, Health policy and practice, Cost-utility analysis, Quality of life.

Number of text pages: 18

Number of words: 3,941

Number of figures: 1

Number of tables: 3

Summary and Key Words

Objective: Epilepsy is common and carries substantial morbidity, and therefore identifying cost-effective health interventions is essential. Cost-utility analysis is a widely used method for such analyses. For this, health conditions are rated in terms of utilities, which provide a standardised score to reflect quality of life. Utilities are obtained either indirectly using quality of life questionnaires, or directly from patients or the general population. We sought to describe instruments used to estimate utilities in epilepsy populations, and how results differ according to methods used.

Methods: We undertook a systematic review of studies comparing at least two instruments for obtaining utilities in epilepsy populations. MEDLINE, Embase, ScienceDirect, Cochrane

Library, Google Scholar and grey literature were searched from inception to June 2019. Mean utilities were recorded and compared for each method.

Results: Of the 38 unique records initially identified, eight studies met inclusion criteria. Utilities were highest for direct ‘trade off’ methods, obtained via instruments including standard gamble (0.93) and time trade off (0.92), compared to indirect methods, obtained via instruments including EuroQoL five-dimensions form (range: 0.72-0.86) and health utilities index mark 3 (range: 0.52-0.71). Visual analogue scale (VAS), a direct ‘non-trade off’ instrument, provided equal or lower utilities (range: 68.0 – 79.8) than indirect instruments.

Significance: Direct methods, with the important exception of VAS, may provide higher utilities than indirect methods. More studies are needed to identify the most appropriate utility instruments for epilepsy populations, and to investigate whether there is variation between utilities for different types of epilepsy and other patient- and disease-specific factors.

Key Words: Health economics, Health policy and practice, Cost-utility analysis, Quality of life.

Introduction

Epilepsy is the fourth most common chronic neurological illness, affecting over 70 million people worldwide.^{1,2} Epilepsy commonly affects people’s ability to work, and epilepsy-associated lost wage-based productivity is nearly equal to the combined wage losses associated with diabetes, depression, anxiety and asthma.³ In addition, epilepsy is associated with substantial indirect costs that impose a significant burden on patients, families and communities.⁴ Further, the impact of epilepsy on a patient’s quality of life is considerable, and may have far-reaching consequences. Effective health interventions are needed for this

common and debilitating illness, but the best method to provide evidence of an intervention's effect on health state, and to perform comparisons between interventions, remains unclear.

Comparing different health interventions is a complex process and typically involves estimating the cost per unit of benefit gained.⁵ Standardised measures of health benefit are needed, and economists have developed utilities for this purpose. Utilities reflect the quality of life ascribed to different health conditions and are anchored at 0, representing being dead, and 1, representing perfect health. Negative values are also possible and represent health states considered to be worse than being dead.

Several methods can be used to estimate utilities, and these are broadly grouped into direct and indirect methods which are obtained via various instruments. Direct methods involve trained interviewers asking respondents to trade something; for example, risk of poor outcomes (standard gamble, SG), or time (time trade off, TTO), for better quality of life.⁶ This process is labour intensive and needs to be repeated for every study. Visual analogue scales (VAS) are also considered direct instruments, and involve participants marking their health state on a 'thermometer' from 0, worst health state to 100, best health state. Unlike SG and TTO, this instrument can be self-administered, but there is no 'trade off' as in the former instruments, and so the scores do not reflect the trade-off that is implicit in cost-effectiveness analysis.^{7,8} Indirect methods involve respondents completing questionnaires which measure dimensions such as mobility and pain that are not explicitly considered by direct methods. Questionnaire responses are converted into utilities by pre-determined tariffs attached to various possible health states that have been established previously in unrelated studies obtained from the general population, hence providing 'indirect' utilities.⁵ An example of a widely used generic, indirect instrument is the EuroQoL five-dimensions form (EQ-5D).⁹ This assesses five domains: mobility, pain/discomfort, usual activities, self-care and anxiety/depression, and respondents rate each domain at one of three (original EQ-5D-3L) or five (updated EQ-5D-5L) levels, ranging from 'no problems', through to 'extreme problems'. Other examples of generic questionnaires that provide utilities indirectly include the 15-dimensional instrument of health-related quality of life instrument (15D), quality of well-being self-administered scale (QWB), health utilities index mark 2 and 3 (HUI-2, -3) and short-form 6D (SF-6D).¹⁰⁻¹⁵ Disease-specific quality of life questionnaires have also been developed specifically for use in epilepsy populations, for example NEWQOL-6D and the quality of life in epilepsy inventory available in long- and short-versions (QOLIE-89 and -

31).^{16,17} The widely used QOLIE includes measures of overall quality of life, emotional well-being, work/driving/social function, cognitive abilities and worry about seizures and health perceptions. It should be noted that unlike the other instruments included in this systematic review, QOLIE does not directly provide utilities or health state preferences, but rather, a value representing quality of life. Although quality of life values are not interchangeable with utilities, they are closely related, and both are important considerations in cost-utility analyses. Researchers recognise that disease-specific instruments such as QOLIE may provide more relevant information to clinicians than generic instruments, and mapping functions have been developed to predict values of generic utility instruments based on QOLIE scores for use in economic evaluations.¹⁸ Given the central importance of QOLIE in epilepsy research, these values have also been included in this review.

Table 1 summarises differences between direct versus indirect methods for determining utilities.

Given the substantial health and economic burden imposed by epilepsy, it is imperative that researchers and health policy makers are able to accurately understand the differences in utilities obtained from various direct and indirect instruments specifically in epilepsy populations. Understanding these differences will help to explain the impact of choosing one instrument over another in cost-utility analyses, which flows into public decisions around funding of interventions. We undertook a systematic review comparing different direct and indirect utility instruments administered specifically in adult epilepsy populations with worked examples to demonstrate how differences in utilities obtained through different instruments could have substantial implications, particularly with regards to selection and implementation of different health interventions.

Methods

This systematic review followed the methods outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁹

Protocol and registration. The review protocol is registered online on PROSPERO International prospective register of systematic reviews: CRD42018115622.

Eligibility criteria. All study designs were eligible for inclusion if they reported comparisons between two or more instruments for calculating utilities in adults with epilepsy. There were no restrictions on specific epilepsy syndromes or aetiologies, and the study population could include adults with epilepsy as well as non-patient respondents, for example carers, family members or physicians. There was no restriction on language or year of publication.

Information sources. Searches were conducted in MEDLINE, Embase, ScienceDirect and the Cochrane Library including the Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar from inception to 4 June 2019. We additionally hand searched the reference lists of all identified articles for any further studies for inclusion. A grey literature search was performed that included Web of Science, World Health Organisation, Grey Literature database and Opengrey repository. Supplementary table S1 presents the search strategy for MEDLINE which was subsequently adapted for other databases.

Study selection. Abstract screening and full-text assessment were performed independently by two researchers, EF and ZC, and disagreements were resolved via consensus-based discussions.

Data collection process. Data were extracted by two independent reviewers, EF and ZC, and entered into a standardised proforma in duplicate. Any disagreements were resolved via consensus with a third reviewer, RO.

Data items. An exhaustive list of variables for which data were sought are listed in supplementary table S2. In summary, these included general study characteristics, study background, study population, direct or indirect instruments studied, utilities obtained for each instrument, description of results of study and key conclusions. Variables for each included study are displayed in supplementary table S3.

Risk of bias in individual studies. Risk of bias of individual studies was assessed independently by reviewers, EF and ZC, using the Downs and Black checklist for non-

randomised studies, with good inter-rater agreement (percent agreement=83%, Gwet's AC1 = 0.81, 95% confidence interval: 0.71-0.90).²⁰ Where disagreement arose, a third independent reviewer, RO, adjudicated and consensus was reached. This checklist was selected as it meets validity and reliability standards, has a strong methodological rating and is easy to use.²¹ It provided quality appraisal of the included studies but did not influence the decision to include or exclude them from final data analysis. The Downs and Black checklist, independent reviewers' scores and adjudicator's scores are presented in supplementary table S4.

Summary measures. The principal summary measure recorded was the mean and standard deviation of the utilities obtained from each instrument. Pooled means and standard deviations for instruments were not calculated as the heterogeneous nature of the studies meant that factors such as type of respondent (patient, caregiver, public), cultural background, level of education, and type and severity of epilepsy might influence differences in utilities more than the type of instrument used, and so pooled means would be inappropriate and difficult to interpret.

Synthesis of results. A systematic review is presented, and data regarding the study populations, the instruments used to obtain utilities and key conclusions arising from all studies are synthesised to inform the conclusions of this review.

Risk of bias across studies. Risk of bias that may affect the cumulative evidence includes a publication bias, for in spite of a broad grey literature search, no unpublished data were identified.

Additional analyses. Due to lack of data, subgroup analyses by different patient demographics as well as by epilepsy type and duration were unable to be explored.

Patient and Public involvement: Patients were not involved in setting the research question or outcome measures, or in the design or conduct of this systematic review. However, we plan to provide lay summaries associated with this publication and to explore any media opportunities to disseminate the study findings more broadly.

Results

Study selection. Of the 52 records initially identified through our systematic search, 14 duplicates were identified and excluded, and a further 30 were excluded as these studies focused on a non-epilepsy condition, reported utilities from only one instrument or did not provide utilities. Eight studies met inclusion criteria.^{18,22-28} Figure 1 displays a flowchart of the study selection process.

Risk of bias within studies. Downs and Black checklist revealed that risk of bias ranged from low to moderate across the eight included studies.

Results of individual studies. Stavem's cross-sectional cohort study compared utilities for three direct and one indirect instrument obtained through face-to-face interviews and questionnaires from 57 randomly selected people with epilepsy (PWE) recruited from in- and outpatient departments of a Norwegian hospital.²² The mean age of the cohort was 43.7 years (standard deviation [SD] = 11.7), 57.9% were female, the mean duration of epilepsy was 16.8 years and 26.3% had seizures within the previous year. Stavem reported the direct 'trade off' instruments, SG and TTO, obtained almost equally high utilities, followed by the indirect instrument 15D, and lowest utilities were obtained by the direct 'non-trade off' instrument VAS.

Gao et al. published results of a cross-sectional study comparing utilities for one direct and two indirect instruments collected through face-to-face interviews from 144 PWE recruited from two hospitals in China and compared these to a healthy control cohort that rated their own health through the same methods, and included relatives of PWE, medical staff and students.²³ The mean age of the study population was 33.1 years (SD = 13.0), 52.1% were male, the mean duration of epilepsy was 9.6 years and 25.7% had refractory epilepsy. The indirect EQ-5D instrument provided the highest utilities, followed by direct instrument VAS, then the indirect instrument QWB. Compared to the healthy controls, PWE had substantially lower health-related quality of life.

Mulhern et al. developed an indirect epilepsy-specific instrument, the NEWQOL-6D, and compared utilities to those generated using the indirect generic EQ-5D instrument.²⁴ The study population consisted of 1,611 patients with newly diagnosed focal epilepsy recruited from the Standard And New Antiepileptic Drugs (SANAD) study in the United Kingdom (UK). The mean age of the cohort was 39.7 years (SD = 16.5), 55.2% were male and approximately 40% reported at least 10 seizures within the previous year. NEWQOL-6D provided slightly higher utilities compared to EQ-5D and was a better discriminator across different health states, and both instruments had some ability to provide utilities for economic evaluation of newly diagnosed focal epilepsy. In comparison, direct instrument VAS provided lower utilities than both these indirect instruments.

Wiebe et al. reported utilities for three indirect instruments as part of a longitudinal study of 40 patients with medically refractory temporal lobe epilepsy.²⁵ The mean age of the cohort was 36 years, 58% were female and participants experienced on average nine focal seizures per month. The indirect generic instrument HUI-3 provided the highest utilities. Indirect epilepsy-specific instruments QOLIE-89 and QOLIE-31 provided the lowest quality of life values.

Langfitt et al. reported utilities for a direct instrument, five indirect generic instruments and one indirect epilepsy-specific instrument, obtained from 140 patients enrolled in the longitudinal United States (US)-based Multicenter Study of Epilepsy Surgery (MSES).²⁶ The mean age of the cohort was 37.4 years (SD = 11.4), and 53.0% were female. At baseline, subjects had medically refractory epilepsy and experienced seizures on at least a monthly basis for the two or more years leading up to study enrolment. Indirect generic instrument, EQ-5D, interpreted with both US- and UK-based tariffs, produced the highest utilities, as did indirect generic instrument HUI-2. In contrast, HUI-3 produced the lowest utilities. Indirect generic instrument SF-6D and direct instrument VAS obtained utilities that fell between these extremes. The indirect epilepsy-specific instrument QOLIE-89 provided the lowest quality of life scores.

Wijnen et al. provided utilities for one direct, one indirect generic and one indirect epilepsy-specific instrument, as obtained from 509 patients enrolled in the prospective SMILE and ZMILE cohort studies based in the UK and Netherlands, respectively.¹⁸ The majority of patients were aged between 25-44 years, 53.0% were female, and they had at least two

seizures in the 12 months prior to study enrolment. EQ-5D produced the highest utilities, followed by direct instrument VAS. Indirect epilepsy-specific instrument QOLIE-31 provided the lowest quality of life scores.

Fiest et al. reported changes in quality of life as measured through indirect instruments HUI-3, QOLIE-31 and QOLIE-89 in a cohort of 80 patients with refractory temporal lobe epilepsy randomised to medication-only versus surgical intervention arms.²⁷ The median age of the arms were 34.4 years (SD = 9.9) and 35.5 years (SD = 9.4), respectively; and 47.5% and 57.5% were female, respectively. Patients had experienced on average one seizure a month for the 12 months prior to study enrolment. QOLIE-31 obtained highest quality of life values in both medication-only and surgical intervention arms; QOLIE-89 produced the next highest in the medication-only arm, and HUI-3 for the surgical intervention arm.

Phumart et al. compared differences in utilities for PWE of varying severity.²⁸ 224 patients were recruited from two tertiary Thai hospitals; mean age was 38.7 years (SD = 11.5), 54.0% were female, mean duration of epilepsy was 15.7 years (SD = 11.5) and 30% of the cohort were seizure-free. Indirect generic instrument EQ-5D produced higher utilities than direct instrument VAS for patients who were seizure-free or had experienced a reduction in their seizures; VAS however provided higher utilities than EQ-5D for patients who reported no improvement in their seizures.

Synthesis of results. Generally, direct methods obtained higher utilities than indirect methods in epilepsy populations. The direct ‘trade off’ instruments SG and TTO resulted in utilities of 0.93 and 0.92, respectively. An exception was VAS, a direct instrument without a ‘trade off’ component, which produced utilities comparable to those obtained through indirect instruments. Stavem and Langfitt et al. divided the VAS score by 100 to allow comparability to utilities obtained from other instruments; they reported VAS utilities of 0.74 and 0.68, respectively.^{22,26} The other studies reported VAS as the original 0-100 score that participants marked on the VAS ‘thermometer’, and these ranged from 68.14-79.57. Indirect generic instruments and their respective utilities included 15D (0.89), EQ-5D (range: 0.72-0.86), HUI-2 (0.78), HUI-3 (range: 0.52-0.71), SF-6D (0.70) and QWB (0.66). Indirect epilepsy-specific instrument NEWQOL-6D utility was 0.77, and quality of life scores from epilepsy-specific QOLIE instruments were QOLIE-31 (range: 64.4-86.6) and QOLIE-89 (range: 52.9-

69.9). Table 2 presents the range of utilities obtained from these various instruments for each study.

Risk of bias across studies. Most studies performed moderately well on the Downs and Black checklist.

Most models used in economic evaluations use published sources to derive utilities rather than primary patient data underpinning interventions. Table 3 provides a hypothetical case scenario that demonstrates the process of economic evaluations, and how different instruments with different utilities alters the estimated cost-effectiveness of an intervention. The utilities and costs ascribed to analysis are presented to illustrate concepts and may not be specifically applicable to individual cases.

Discussion

This systematic review demonstrates that in PWE, direct ‘trade off’ instruments provide higher utilities compared to indirect instruments and direct instruments without a ‘trade off’ component generally produce equal or lower utilities compared to indirect instruments. Based on our stylised examples, these variations in utilities may lead to large differences in estimated cost-effectiveness of an intervention and this may have consequences for health policy decision-making. However, utilities are only one part of the complex decision-making process regarding choice of methods and instruments; some may be more clinically appropriate than others depending on the patients and diseases in question. Further, utilities taken from an otherwise well, general population regarding a certain disease may not be readily applicable to a population with the actual disease of interest. Clearly, many factors need to be considered by researchers and health policy makers with regards to interpretation of cost-effectiveness of various epilepsy interventions, and more research in this area is needed for this common and important condition.

Our findings are consistent with previous studies in non-epilepsy populations that have also noted that direct methods, with the important exception of VAS that does not include a ‘trade off’ component, tend to generate higher utilities than indirect methods. A large review that

compared direct and indirect methods for a large range of health conditions, including rheumatic, neuropsychiatric, vascular, respiratory, gastrointestinal, renal and infectious diseases, reported that overall mean utilities for direct methods were 0.81 for SG and 0.77 for TTO, as compared to indirect methods including EQ-5D (0.59), SF-6D (0.63), HUI-2 (0.75) and HUI-3 (0.68).⁵ Direct instrument VAS was an exception in our study, and several studies in non-epilepsy populations have also noted VAS' tendency to produce low utilities.^{7,8,29} As an example, Turner et al. compared various instruments for estimating utilities in patients with depression.²⁹ VAS obtained utilities of 0.51, compared to indirect methods SF-6D (0.56) and SF-12 new algorithm (0.57). These findings are noteworthy, as the substantial lack of agreement between different instruments and methods may subsequently lead to marked differences in cost-effective estimates for interventions. This in turn will result in vastly different assessments as to the benefit of different interventions and uncertainty as to whether or not an intervention should be recommended and/or funded.^{29,30}

Strategic study design and interpretation may involve the deliberate choice of certain instruments to purposefully obtain favourable (or otherwise) utilities; however, the selection of instruments needs to also take into account the specific disease and patient population under consideration. Some instruments are less suited than others for populations with particular diseases, for instance, establishing utilities via direct methods may be more difficult in those with relatively lower cognitive ability. Instruments may not be appropriate if relevant domains are not covered, for example, EQ-5D does not assess vision and so is not an adequate instrument for assessing vision-specific interventions. Even in situations where several instruments seem equally appropriate, careful exploration may reveal that one is more suited than the others to a particular patient or disease population. Turner et al. explored the most appropriate instrument to assess utilities in depressed patients, and these were evaluated with regards to sensitivity; that is, the presence of ceiling or floor effects and ability to discriminate between different health states, responsiveness of different methods to changes in depressed state, and ease of use as determined by completion rates.²⁹ Based on these criteria, the indirect generic instruments SF-6D and SF-12 were found to be more suitable instruments for determining utilities in depressed patients than EQ-5D. Extant instruments may not sufficiently evaluate certain diseases, and the development of robust disease-specific instruments may be warranted. Mulhern et al. developed NEWQOL-6D, an indirect epilepsy-specific instrument, and demonstrated that this provided higher utilities and was a better discriminator across different health states than EQ-5D.²⁴ The context of Turner's and

Mulhern's research is important; both studies were set in the UK, where the National Institute for Health and Care Excellence recommends the EQ-5D instrument for establishing utilities. Certainly, the consistent use of a standard instrument may facilitate comparisons of interventions between different studies and different diseases, however, as demonstrated by these researchers, other instruments may be more optimal for generating utilities for certain diseases. These findings have implications for researchers and health policy makers and highlight the need for careful selection of clinically appropriate instruments based on the disease and patient population under study.

Governments and other funding agencies often obtain utilities regarding certain diseases from otherwise well general populations. This ensures tax dollars are spent according to the views of society, however, these utilities may not be representative of those taken from a population with the actual disease of interest. Kang et al.'s study enrolled 300 people without epilepsy from the South Korean general population and obtained utilities for epilepsy of varying degrees of severity.³¹ As may be predicted, a seizure-free state obtained highest utilities, followed by a state with seizure frequency reduction of greater than 50% compared to baseline, followed by seizure frequency reduction of less than 50% compared to baseline. Utilities varied greatly with epilepsy severity; as an example, EQ-5D utilities were 0.96 for seizure-free state and 0.26 for most severe epilepsy state. This wide variation is not seen in the recent study from Phumart et al., which evaluated utilities in people with varying degrees of epilepsy severity.²⁸ This study also used the EQ-5D instrument, and recorded lower utilities of 0.82 for seizure-free (best) state and far more moderate utilities of 0.72 for an unimproved (worst) seizure state. Clearly, clinicians and health policy makers need to be cognisant of the population from which utilities are obtained. As evident from the above comparison between Kang et al.'s and Phumart et al.'s studies, data obtained from well populations may not accurately represent certain health states, providing far higher or far lower utilities than when measured in a population with the actual disease.

This systematic review identifies several important areas for future research. Firstly, the large range of utility estimates by different instruments may lead to contradictory findings in cost-utility analyses. There is urgent need for consensus on the optimal instrument to use for measuring utility in epilepsy, to reduce the current large range to that which is both accurate and practical to apply to future research projects. Secondly, while 'generic' instruments such as EQ-5D are useful for health economic decision-making, disease specific instruments are

more clinically relevant for clinicians. Further research may focus on mapping general instruments to disease-specific instruments. Thirdly, utilities may complement and build upon data provided by existing, well-designed studies. A recent paper reports the substantial burden of epilepsy on global, regional, and national levels.³² Deaths, prevalence, and disability-adjusted life-years were used to measure disease burden and found epilepsy to be an important cause of disability and mortality. This paper provides an excellent foundation for cost-utility analyses. Calculating utilities for various interventions, such as improved access to existing treatments in low-income countries and development of new, effective drugs, may guide international aid programs and research efforts.

Limitations. Studies included in this analysis were published between 1998 and 2018. In this 20-year time frame, much progress has been made regarding medications and interventions for PWE, and thus the findings may not be directly comparable across time. With the exception of Mulhern's study, which specified a newly diagnosed focal epilepsy cohort, the included studies involved heterogeneous epilepsy populations and so results may not be generalisable to specific subsets of PWE. Although a comprehensive search strategy was undertaken to maximise search yield, studies without the prespecified search terms in the title, abstract or keywords may not have been captured. There were insufficient data to determine if and to what extent patient demographics, epilepsy types, severity or duration influenced utilities. These are crucial factors to consider, as they may explain differences in the utilities obtained across studies rather than the instrument used.

Conclusion

When measuring utilities of PWE, direct methods, with the important exception of VAS, generate higher utilities than indirect methods. This systematic review highlights the need for more detailed evaluation of the methods for estimating utilities in epilepsy populations. Further research should seek to identify whether there is variation between utilities for different types of epilepsy, such as between focal and generalised epilepsy, and patient factors and disease-specific factors, such as between drug-responsive and drug-resistant epilepsy.

Key Point Box

- Epilepsy is common and carries substantial morbidity and economic burden, and identifying cost-effective health interventions is essential
- Utilities describe different health states and are widely used for cost-utility analyses
- Few studies explore the best instruments for obtaining utilities in epilepsy populations
- This systematic review revealed great variation in utilities, and thus perceived health states, between different instruments
- These data may inform researchers and health policy makers when assessing cost-effectiveness of interventions in epilepsy populations

Acknowledgements and Disclosure of Conflicts of Interest

Dr Foster has received research grants and scholarships from the National Health and Medical Research Council (NHMRC) of Australia, The Royal Australian College of Physicians Research Entry Scholarship and AVANT Doctors in Training Scholarship.

Dr Chen has received research grants from NHMRC Early Career Fellowship, and from the University of Melbourne Early Career Researcher Grant Scheme.

Professor O'Brien reports grants and other from Eisai Pharmaceuticals, other from Teva Pharmaceuticals, grants and other from UCB Pharma, grants and other from Zynerba Pharmaceuticals, grants and other from Liva Nova, grants and other from Praxis Pharmaceuticals.

Professor Kwan reports grants and non-financial support from UCB Pharma, during the conduct of the study, grants from Biscayne, grants and personal fees from Eisai, grants from

GW Pharmaceuticals, grants and personal fees from LivaNova, grants and personal fees from UCB Pharma, grants from Zynerva.

Professor Liew reports grants and personal fees from Abbvie, grants and personal fees from Astellas, grants and personal fees from AstraZeneca, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Novartis, grants and personal fees from Pfizer, grants and personal fees from Sanofi; grants from CSL-Behring, grants from Shire, and personal fees from Bayer.

The remaining authors have no conflicts of interest.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Contribution of authors to manuscript

Dr Foster – study conception, registered study, systematic literature review, manuscript preparation, critical revision of manuscript for intellectual content.

Dr Chen – systematic literature review, critical revision of manuscript for intellectual content.

Dr Richard Ofori-Asenso – critical revision of manuscript for intellectual content.

Associate Professor Richard Norman – critical revision of manuscript for intellectual content.

Dr Patrick Carney – critical revision of manuscript for intellectual content.

Professor Terence J O'Brien – critical revision of manuscript for intellectual content.

Professor Patrick Kwan – critical revision of manuscript for intellectual content.

Professor Danny Liew – critical revision of manuscript for intellectual content.

Associate Professor Zanfina Ademi – study conception, systematic literature review, critical revision of manuscript for intellectual content.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure 1. Flowchart of systematic review methodology.

Table 1: Description, advantages and disadvantages of direct versus indirect methods of estimating utilities

Methods / instruments	Description	Advantages	Disadvantages
Direct methods Direct ‘trade off’ instruments include: SG, TTO	Trained interviewers ask respondents to trade something, for example, risk of poor outcomes or time trade off, for better quality of life.	Tendency towards higher utilities; interventions may appear more favourable than if measured by indirect instruments.	Labour-intensive; requires trained interviewer to collect data from each participant for each study.
Direct methods Direct instrument without ‘trade off’	Respondents mark their health state on a ‘thermometer’ from 0, worst health state	Ease of administration; usually instrument completed independently by	Tendency towards lower utilities compared to direct ‘trade off’ instruments

component includes: VAS	to 100, best health state.	participants.	and indirect instruments; interventions may appear less favourable than if measured by other instruments.
Indirect methods (generic) Indirect, generic instruments include: 15D, EQ-5D, HUI-2, HUI-3, QWB, SF-6D	Respondents complete questionnaires which measure dimensions that are not explicitly considered by direct methods, for example mobility or	Ease of administration; usually data collected via simple questionnaires completed independently by participants.	Tendency towards lower utilities; interventions may appear less favourable than if measured by direct instruments.
Indirect methods (disease-specific) Indirect epilepsy-specific instruments include: NEW-QOL	pain. Results are converted into utilities by pre-determined tariffs attached to various possible health states that have been established previously in unrelated studies obtained from the general population.	Questionnaires are tailored to the disease of interest, and so can more comprehensively evaluate morbidity that may not otherwise be captured by generic indirect measures.	Researchers need to map these disease-specific tools to generic tools in order to compare utilities between epilepsy and other diseases; this is essential for policy makers to prioritise funding and resources for different diseases.

15D: 15-dimensional instrument of health-related quality of life instrument, EQ-5D: EuroQoL five-dimensions form, HUI-2: health utilities index mark 2; HUI-3: health utilities index mark 3, NEWQOL-6D: NEWQOL six-dimensions form, QWB: quality of well-being self-administered scale, SF-6D: short-form 6D, SG: standard gamble, TTO: time trade off, VAS: visual analogue scale.

Table 2: Utilities for direct and indirect methods for each study (mean and SD presented).

	Direct method			Indirect method								
				Generic						Epilepsy-specific		
Study group: PWE	SG	TTO	VAS	15D	EQ-5D*	HUI-2	HUI-3	QWB	SF-6D	NEW-QOL	QOLIE-31	QOLIE-89
Stavem ²¹ , 1998	0.93 (0.11)	0.92 (0.11)	0.74 [#] (0.17)	0.89 (0.09)								
Gao et al ²² , 2015			79.57 (16.42)		0.83 (0.21)			0.66 (0.14)				
Mulhern et al ²³ , 2017			68.14 (20.7)		0.74 (0.30)					0.77 (0.13)		
Wiebe et al ²⁴ , 2001							0.71 (0.29)				64.4 (17.4)	69.9 (15.2)
Langfitt et al ²⁵ , 2006			0.68 [#] (0.20)		0.76 (0.26)(UK) 0.82 (0.18)(US)	0.78 (0.18)	0.61 (0.30)		0.70 (0.14)			60.7 (16.4)
Wijnen et al ²⁶ , 2018			68.53		0.86						65.82	
Fiest et al ²⁷ , 2014 (Medical group)							0.52 (0.32)				77.4 (31.9)	52.9 (19.2)
Fiest et al ²⁷ , 2014 (Surgical group)							0.62 (0.25)				86.6 (33.7)	60.5 (15.3)
Phumart et al ²⁸ , 2018 (Seizure-free)			78.9 (14.5)		0.82 (0.15)(Thai)							
Phumart et al ²⁸ , 2018			75.5		0.79							

s(Seizure reduction)			(15.2)		(0.16)(Thai)							
Phumart et al ²⁸ , 2018			73.5		0.72							
(No improvement)			(19.5)		(0.21)(Thai)							

* UK-tariffs presented for EQ-5D unless otherwise stated

Researchers divided VAS scores by 100 to enhance comparability

15D: 15-dimensional instrument of health-related quality of life, EQ-5D: EuroQoL five-dimensions form, HUI-2: health utilities index mark 2; HUI-3: health utilities index mark 3, NEWQOL-6D: NEWQOL six-dimensions form, QOLIE-89: Quality Of Life In Epilepsy inventory-89, QOLIE-31: Quality Of Life In Epilepsy inventory-31, QWB: quality of well-being self-administered scale, SF-6D: short-form 6D, SG: standard gamble, TTO: time trade off, VAS: EQ-5D visual analogue scale.

Please note: QOLIE-31 and QOLIE-89 are not utility instruments, and are included only for the purpose of comparison.

Table 3. Scenario demonstrating how choice of instrument and related utilities may affect policy decision-making, using incremental cost-effectiveness ratio (ICER) for cost-utility analysis.

Scenario: A 32-year-old male with non-lesional focal epilepsy is commenced on an anti-epileptic drug (AED) as routine standard of care. With this he achieves 50% reduction in seizure frequency; as an assumption this health state corresponds to a utility of 0.60, with yearly costs of AUD 5,000. He is transitioned to a newly-developed AED and achieves 90% seizure freedom at 12-months. We will assume that this new health state corresponds to various utilities as per Stavem et al. and Gao et al., set out in table 2, and yearly costs of the new AED are AUD 6,000.^{21,22} To demonstrate how the choice of instrument and related utilities may affect policy decision-making, we will use incremental cost-effectiveness ratio (ICER) for cost-utility analysis. The ICER represents the average incremental cost associated with one additional unit of effect. We will

assume a hypothetical example where patients with non-lesional focal epilepsy are followed up for 5 years. These utilities are assumed to remain unchanged for the duration of follow up.

Established AED	Analysis 1 for newer AED	Analysis 2	Analysis 3	Analysis 4
Utility 0.60	Utility SG=0.93 (Stavem)²²	Utility VAS=0.74 (Stavem)²²	Utility EQ-5D=0.83 (Gao)²³	Utility QWB=0.66 (Gao)²³
Cost=\$5000*5=\$25,000 Utility=0.6*5=3.00	Cost=\$6000*5=\$30,000 Utility=0.93*5=4.65 Cost difference=\$30,000-\$25,000=\$5,000 Utility difference=4.65-3.00=1.65 ICER=\$5,000/1.65 SG=\$3,030	Cost=\$6000*5=\$30,000 Utility=0.74*5=3.70 Cost difference=\$30,000-\$25,000=\$5,000 Utility difference=3.70-3.00=0.70 ICER=\$5,000/0.70 VAS=\$7,143	Cost=\$6000*5=\$30,000 Utility=0.83*5=4.15 Cost difference=\$30,000-\$25,000=\$5,000 Utility difference=4.15-3.00=1.15 ICER=\$5,000/1.15 EQ-5D=\$4,347	Cost=\$6000*5=\$30,000 Utility=0.66*5=3.30 Cost difference=\$30,000-\$25,000=\$5,000 Utility difference=3.30-3.00=0.30 ICER=\$5,000/0.30 QWB=\$16,666

Conclusion: When the economic model takes utilities from different instruments, the end result is vastly different ICERs. Using utilities based on the SG and EQ-5D instruments, the newer AED was more cost-effective than when interpreted by utilities from the QWB or VAS instruments. The differences in ICER are large, and depending on which is used, may either support or deter health policy makers from recommending and/or funding the newer AED.

AED: antiepileptic drug, AUD: Australian dollar, EQ-5D: EuroQoL five-dimensions form, ICER: incremental cost-effectiveness ratio, QWB: quality of well-being self-administered scale, SG: standard gamble, VAS: EQ-5D visual analogue scale

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Title:

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Date:

2019-12-01

Citation:

Foster, E., Chen, Z., Ofori-Asenso, R., Norman, R., Carney, P., O'Brien, T. J., Kwan, P., Liew, D. & Ademi, Z. (2019). Comparisons of direct and indirect utilities in adult epilepsy populations: A systematic review. *EPILEPSIA*, 60 (12), pp.2466-2476. <https://doi.org/10.1111/epi.16396>.

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