Online Resource 2: Health State Utilities and Literature Reviews

A Cost-utility Analysis of Add-on Cannabidiol Versus Usual Care Alone for the Treatment of Seizures Associated With Tuberous Sclerosis Complex in England and Wales

Colin Burke[1], Catriona Crossan[1], Emma Tyas[1], Matthew Hemstock[1], Dawn Lee[1], Sally Bowditch[2]

Journal: PharmacoEconomics - Open

Corresponding author: Colin Burke. **Affiliation:** Lumanity, Inc., Great Suffolk Yard, 121–131 Great Suffolk Street, London, SE1 1PP, UK. **Email:** Colin.Burke@lumanity.com

Declarations

Funding

This study and open access fee were funded by GW Pharmaceuticals, now a part of Jazz Pharmaceuticals, Inc. Authors Colin Burke, Catriona Crossan, Emma Tyas, Matthew Hemstock, and Dawn Lee were employed by Lumanity during the study, and their time for development and completion of the study was supported by Jazz Pharmaceuticals, Inc. Author Sally Bowditch, employed by Jazz Pharmaceuticals, Inc., had the following involvement with the study: study design, interpretation of data, writing of the article, and decision to submit for publication.

Conflicts of interest

All authors met the ICMJE authorship criteria and had full access to the relevant data. Neither honoraria nor payments were made for authorship. Colin Burke and Emma Tyas are employees of Lumanity, Inc.; Catriona Crossan, Matthew Hemstock, and Dawn Lee were employees of Lumanity, Inc., when the study was conducted and are currently employed by Putnam, Source Health Economics, and the University of Exeter, respectively. Sally Bowditch is an employee of Jazz Pharmaceuticals, Inc., and holds stock / stock options in Jazz Pharmaceuticals, Inc.

Contents

Health State Utilities and Literature Reviews

The utility data collected in GWPCARE6 using the Quality of Life in Childhood Epilepsy (QOLCE) and Quality of Life in Epilepsy-31 (QOLIE-31-P) questionnaires were considered unsuitable for use in the analysis. This was because of the low response rates to the QOLIE-31-P (n = 11 in the cannabidiol arm and n = 10 in the placebo arm), the lack of a published mapping algorithm for the QOLCE for the pediatric population, and the fact that the authors of the only mapping algorithm for QOLIE-31-P considered it to have only a weak-to-moderate correlation with the EuroQol 5 Dimensions™ (EQ-5D) [1,2].

A systematic literature review (SLR) and subsequent targeted literature review (TLR) were conducted to source utility evidence for use in the model. From these, two studies were identified: Tritton et al. [3] and Vergeer et al. [4] These were not considered suitable for inclusion in the base-case analysis, as although the study by Tritton et al. collected EuroQol-5 Dimensions-3 Level (EQ-5D-3L) data in Europe and Canada, the results were internally inconsistent: utility was based on seizure frequency recall (from the previous week) [3]. The results of the study differed by patient and caregiver (by proxy) response, with higher caregiver-reported mean values, and the overall utility values were inconsistent with higher utility values for lower seizure frequency health states compared with states with high seizure frequency [3]. Similarly, the study by Vergeer et al. was considered unsuitable as although they used a generic preference-based measure, the health state definitions were not directly matchable to the seizure frequency health state categories used in the cost-effectiveness analysis [4]. Data collected for health states, stratified by the proportion of time patients were refractory to treatment and the elicited utilities,

were based on response to treatment using response cut-offs. As published utility data are lacking in this area, both studies were included as scenario analyses.

A feasibility assessment identified the EQ-5D as unsuitable owing to weak correlations between the EQ-5D and condition-specific measures for epilepsy [1,2]. Therefore, utility data for patients and caregivers were obtained from vignettes, valued by a representative sample (n = 200) of the general public using time trade-off (TTO) methods [5,6]. The vignette descriptions varied in terms of seizure frequency and type on seizure days and were validated with clinicians and caregivers. The health states for the caregiver vignette study considered the perspective of one of two caregivers. In the model analysis, caregiver utilities were applied as decrements [6]. In the economic analysis, each patient was assumed to have two caregivers [6], to reflect the anticipated burden of two parents or family members caring for an individual with a developmental epileptic encephalopathy like tuberous sclerosis complex (TSC)-associated epilepsy [7].

Systematic Literature Review Process

We conducted an SLR to identify relevant papers on the clinical efficacy and safety, or real-world effectiveness of drug treatments used to treat seizures in TSC. This literature review also identified papers on the epidemiology of TSC-associated seizures; model parameters relating to the quality of life (QoL) and utility values of patients with TSC and seizures and their caregivers; costs and resource use associated with TSC; and existing economic models in TSC.

We searched the following databases and sources for relevant publications:

- MEDLINE® via Embase® (for studies on efficacy and safety, effectiveness, QoL, economic evaluations, costs, and resource use)

- Embase via ProQuest (for studies on efficacy and safety, effectiveness, QoL, economic evaluations, costs, and resource use)
- Heoro.com (for studies on costs, resource use, QoL, economic evaluations, and mortality)
- Cochrane Library (for reviews, technology assessments, studies on efficacy and safety, effectiveness, and economic evaluations)
- American Epilepsy Society (AES)
- International Epilepsy Congress (ILAE)
- European Congress on Epileptology (EEC)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference abstracts 2015–2018
- The All Wales Medicines Strategy Group (AWMSG)
- The Scottish Medicines Consortium (SMC)
- The National Institute for Health and Care Excellence (NICE)
- ClinicalTrials.gov
- National Health Service (NHS) Economic Evaluation Database 1968 to April 2015 and Health Technology Assessment (HTA) search via University of York Centre for Reviews and Dissemination site
- The University of Sheffield Health Utilities Database (ScHARRHUD)
- EuroQol Database (for QoL studies)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- The Pharmaceutical Benefits Advisory Committee, Australia (PBAC)
- Ireland National Centre for Pharmacoeconomics (NCPE)
- American Academy of Neurology (AAN)
- World Congress of Neurology (WCN) 2019 and 2017
- International TSC Research Conference 2019, 2018, and 2017
- Agence nationale de sécurité du médicament et des produits de santé (ANSM)

The databases and gray literature sites were searched on November 1, 2021, using the search strategies in Online Resource Table 2.

Online Resource Table 2 Search strategies

Database	#	Search	November 1, 2021
EMBASE	#1	('tuberous sclerosis'/exp OR 'tuberous sclerosis' OR 'tuberous sclerosis':ab,ti OR tsc:ab,ti) AND [embase]/lim AND [humans]/lim AND [abstracts]/lim	10,152
	#2	('epilepsy'/exp OR 'epilepsy' OR 'seizure'/exp OR 'seizure' OR 'generalized epilepsy' OR 'focal epilepsy' OR epilepsy:ab,ti OR epilept*:ab,ti OR seizure*:ab,ti OR convuls*:ab,ti OR fit*:ab,ti OR spasm*:ab,ti OR attack*:ab,ti OR atonic:ab,ti OR myoclonic:ab,ti OR drop:ab,ti OR tonic:ab,ti OR clonic:ab,ti OR partial:ab,ti OR focal:ab,ti OR absence:ab,ti) AND [embase]/lim AND [abstracts]/lim AND [humans]/lim	1,391,535
	#3	#1 AND #2	**4096**
	#4	'quality of life'/exp OR 'quality of life' OR 'quality of life':ab,ti OR qol:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR hql:ab,ti OR hrql:ab,ti OR utilit*:ab,ti OR 'patient reported':ab,ti OR 'patient-reported':ab,ti OR euroqol:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq vas':ab,ti OR 'health utilit* index':ab,ti OR hui:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 'hui 2':ab,ti OR 'hui 3':ab,ti OR (('short form':ab,ti OR 'short-form':ab,ti OR shortform:ab,ti OR sf:ab,ti) AND (6:ab,ti OR 12:ab,ti OR 36:ab,ti)) OR 'time trade off':ab,ti OR 'time trade-off':ab,ti OR tto:ab,ti OR 'standard gamble':ab,ti OR 'patient preference':ab,ti OR 'self-reported':ab,ti OR 'outcome assessment':ab,ti	837,937
	#5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR financ*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali?ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti))	1,403,721
	#6	#4 OR #5	2,084,770
	#7	#1 AND #6	876
	#8	#3 OR #7	**4537**
Medline and PubMed-not-Medline	#1	('tuberous sclerosis'/exp OR 'tuberous sclerosis' OR 'tuberous sclerosis':ab,ti OR tsc:ab,ti) AND [medline]/lim AND [abstracts]/lim	7253
	#2	('epilepsy'/exp OR 'epilepsy' OR 'seizure'/exp OR 'seizure' OR 'generalized epilepsy' OR 'focal epilepsy' OR epilepsy:ab,ti OR epilept*:ab,ti OR seizure*:ab,ti OR convuls*:ab,ti OR fit*:ab,ti OR spasm*:ab,ti OR attack*:ab,ti OR atonic:ab,ti OR myoclonic:ab,ti OR drop:ab,ti OR tonic:ab,ti OR clonic:ab,ti OR partial:ab,ti OR focal:ab,ti OR absence:ab,ti) AND [medline]/lim AND [abstracts]/lim AND [humans]/lim	1,026,317

Database	#	Search	November 1, 2021
	#3	#1 AND #2	2656
	#4	'quality of life'/exp OR 'quality of life' OR 'quality of life':ab,ti OR qol:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR hql:ab,ti OR hrql:ab,ti OR utilit*:ab,ti OR 'patient reported':ab,ti OR 'patient-reported':ab,ti OR euroqol:ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR 'eq vas':ab,ti OR 'health utilit* index':ab,ti OR hui:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR 'hui 2':ab,ti OR 'hui 3':ab,ti OR (('short form':ab,ti OR 'short-form':ab,ti OR shortform:ab,ti OR sf:ab,ti) AND (6:ab,ti OR 12:ab,ti OR 36:ab,ti)) OR 'time trade off':ab,ti OR 'time trade-off':ab,ti OR tto:ab,ti OR 'standard gamble':ab,ti OR 'patient preference':ab,ti OR 'self-reported':ab,ti OR 'outcome assessment':ab,ti	593,030
	#5	('economic evaluation'/exp OR 'economic evaluation' OR 'cost of illness'/exp OR 'cost of illness' OR cost*:ab,ti OR budget*:ab,ti OR financ*:ab,ti OR resource*:ab,ti OR 'resource use':ab,ti OR 'length of stay':ab,ti OR admission*:ab,ti OR economic*:ab,ti OR hospitali?ation:ab,ti OR absenteeism:ab,ti OR productivity:ab,ti OR ((value NEAR/1 (money OR monetary)):ab,ti))	1,034,817
	#6	#4 OR #5	1,524,965
	#7	#1 AND #6	447
	#8	#3 OR #7	**2887**
Cochrane library	#1	MeSH descriptor: [tuberous sclerosis] explode all trees	65
	#2	tuberous sclerosis OR TSC	723
	#3	#1 OR #2	**723**
Heoro.com	#1	Disease: tuberous sclerosis	**21**
NICE	#1	Tuberous sclerosis	3
SMC	#1	Tuberous sclerosis	3
PBAC	#1	Tuberous sclerosis	0
CADTH	#1	Tuberous sclerosis	2
NCPE	#1	Tuberous sclerosis	0
ISPOR	#1	Search site: Disease/disorder: neurological disorders Keywords: "tuberous sclerosis" Topic: all Conference: 2017, 2018, 2019, 2020	18

Database	#	Search	November 1, 2021
AAN	#1	Tuberous sclerosis	0
AES	#1	Tuberous sclerosis	109
WCN	#1	2017: tuberous sclerosis	25
	#1	2019: downloaded abstract book, hand searched	1
AWMSG	#1	Tuberous sclerosis	2
Clinicaltrials.gov	#1	Tuberous sclerosis	74
York CRD	#1	Tuberous sclerosis OR TSC	7
ILAE	#1	2017: booklet downloaded for hand searching 2019: booklet downloaded for hand searching	23
EEC	#1	2016: booklet downloaded for hand searching 2018: booklet downloaded for hand searching	27
ScHARRHUD	#1	Unavailable	0
EuroQol	#1	Tuberous sclerosis	0
ANSM	#1	Tuberous sclerosis	0
International TSC Research Conference	#1	2017: booklet downloaded for hand searching 2018: booklet downloaded for hand searching 2019: booklet downloaded for hand searching	32
		Combined, after deduplication	**5692**

AAN, American Academy of Neurology; AES, American Epilepsy Society; ANSM, Agence nationale de sécurité du médicament et des produits de santé; AWMSG, All Wales Medicines Strategy Group; CADTH, Canadian Agency for Drugs and Technologies in Health; CRD, Centre for Research and Dissemination; EEC, European Congress on Epileptology; ILAE, International Epilepsy Congress; ISPOR, International Society for Pharmacoeconomics and Outcomes Research congress; NCPE, Ireland National Centre for Pharmacoeconomics; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee, Australia; ScHARRHUD, University of Sheffield Health Utilities Database; SMC, Scottish Medicines Consortium; TSC, Tuberous sclerosis complex; WCN, World Congress of Neurology.

The de-duplicated list of abstracts was screened independently according to agreed inclusion criteria by two researchers, and any discrepancies were resolved by discussion with the project leader.

Study Selection

The inclusion criteria used to screen studies were the same for abstract and full-text screening and are reported below. Any study of unclear relevance from the abstract was retrieved and screened as the full text.

Inclusion Criteria

Disease:

- Seizures associated with TSC
- Costs and QoL only: general TSC with or without seizures (excluding studies specifically in other, non-neurological manifestations of TSC)

Population:

- Adults or children

Topics:

- Effectiveness of interventions for seizures
  - QoL studies with utility values
  - Economic evaluations
  - Cost and resource use in the UK

Study Type:

- Primary research reports of any relevant methodology
- Systematic reviews of relevant studies

- Narrative reviews on the burden of illness in seizures related to TSC (costs, QoL, economics)
- Study protocols for efficacy/safety studies

Intervention:

- Any or none

Comparators:

- Any or none

Study Size:

- >5 participants

Publication Date:

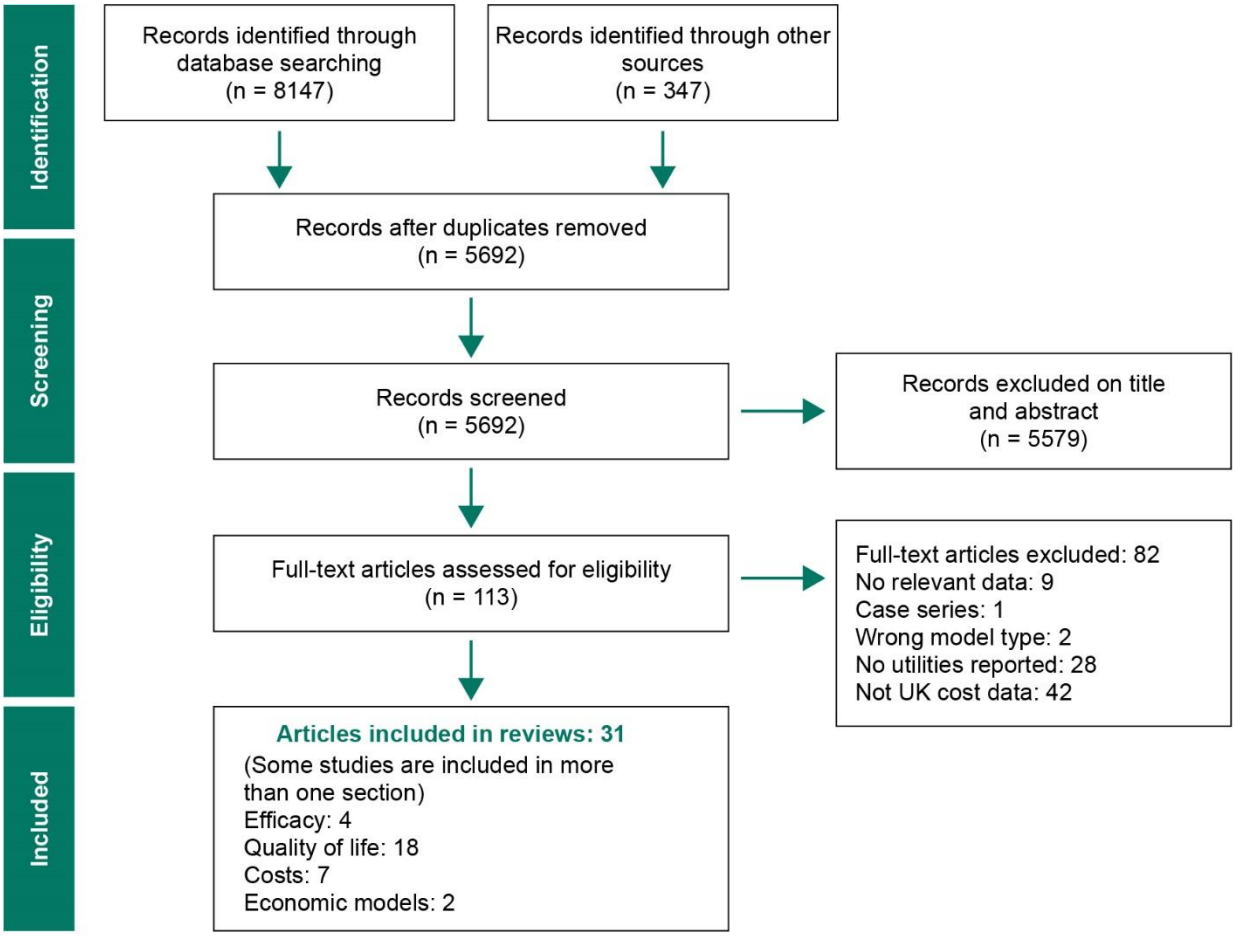
- Any

Publication Language:

- Any

The flow of literature for this review is presented in Online Resource Fig. 1.

Online Resource Fig. 1 PRISMA diagram (based on SLR conducted on Nov 1, 2021)



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

A full list of included and excluded studies is available on request.

Targeted Literature Review Process

As the SLR did not identify any suitable health-related quality of life (HRQL) data sources, a TLR with systematic searches was conducted to expand on the SLR and identify HRQL data for patients in the broader fields of epilepsy and refractory epilepsy.

The systematic searches were performed in three parts: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; a review of the potentially relevant studies to identify suitability to inform HRQL data for the cost-effectiveness model; and extraction of relevant data from the relevant studies into summary tables.

MEDLINE In-Process® (using Pubmed.ncbi.nlm.nih.gov) was searched on May 12, 2020, with a time limit of the past 5 years (this time limit was imposed owing to the extremely large number of hits found in an unrestricted search to identify the most relevant recent evidence). An update of the TLR (with a time limit from the original search date) was conducted on February 14, 2022. In addition, manual searches were conducted, such as bibliography searches of included studies. The search strategy used is presented in Online Resource Table 3.

Online Resource Table 3 Search strategy for HRQL utility evidence in TSC-associated epilepsy May 12, 2020, and Feb 14, 2022 (pubmed.ncbi.nlm.nih.gov)

Search no.	Potential TLR systematic searches	Results (May 12, 2020)	Results (February 14, 2022)
1.	(((((((('epilepsy'[Title/Abstract] OR seizure[Title/Abstract] OR 'generalized type epilepsy'[Title/Abstract] OR 'focal epilepsy'[Title/Abstract] OR epileptic[Title/Abstract] OR seizure[Title/Abstract] OR convuls[Title/Abstract] OR fit[Title/Abstract] OR spasm[Title/Abstract] OR attack[Title/Abstract] OR atonic[Title/Abstract] OR myoclonic[Title/Abstract] OR drop[Title/Abstract] OR tonic[Title/Abstract] OR clonic[Title/Abstract] OR partial[Title/Abstract] OR focal[Title/Abstract] OR absence[Title/Abstract])))))) OR ('refractory epilepsy'[Title/Abstract] OR 'refractory seizure'[Title/Abstract] OR 'refractory seizures'[Title/Abstract])) Sort by: Best Match Filters: Full text; published in the past 5 years; Humans	154,723	68,603
2.	(('seizure severity'[Title/Abstract] OR severity[Title/Abstract] OR frequency[Title/Abstract] OR 'seizure free days'[Title/Abstract] OR 'seizure frequency')[Title/Abstract]) Sort by: Best Match Filters: Full text; published in the past 5 years; Humans	166,569	79,487
3.	(((utility[Title/Abstract] OR utilities[Title/Abstract] OR disutility[Title/Abstract] OR disutilities[Title/Abstract] OR 'sf 6'[Title/Abstract] OR short form 6'[Title/Abstract] OR short form 6'[Title/Abstract] OR sf six[Title/Abstract] OR euroqol[Title/Abstract] OR euro qol[Title/Abstract] OR euroqol 5d'[Title/Abstract] OR 'euroqol-5d'[Title/Abstract] OR euroqol 5-d'[Title/Abstract] OR eq5d[Title/Abstract] OR 'eq 5d'[Title/Abstract] OR health utility[Title/Abstract] OR hui[Title/Abstract] OR hui1[Title/Abstract] OR hui2[Title/Abstract] OR 'hui-2'[Title/Abstract] OR hui3[Title/Abstract] OR 'hui-3'[Title/Abstract] OR standard gamble'[Title/Abstract] OR time trade off[Title/Abstract] OR time tradeoff[Title/Abstract] OR tto[Title/Abstract] OR patient preference/exp[Title/Abstract] OR european quality of life 5 dimension[Title/Abstract] OR hye[Title/Abstract] OR hyes[Title/Abstract] OR visual analog scale[Title/Abstract] OR hsuv[Title/Abstract] OR quality of life[Title/Abstract] OR hrql[Title/Abstract] OR hrqol[Title/Abstract] OR qual[Title/Abstract] OR '5 dimension*'[Title/Abstract] OR '5-dimension'[Title/Abstract] OR five dimension) title/abstract OR '5 d'[Title/Abstract] OR '6 d'[Title/Abstract] OR '6-d'[Title/Abstract] OR '6 dimension'[Title/Abstract] OR '6-dimension'[Title/Abstract] OR six dimension title/abstract OR (quality near/3 (wellbeing[Title/Abstract] OR well being[Title/Abstract] OR well being)) title/abstract OR '15 d'[Title/Abstract] OR 15d[Title/Abstract] OR '15-d'[Title/Abstract] OR '15 dimension[Title/Abstract] OR fifteen dimension'[Title/Abstract] OR multi attribute'[Title/Abstract] OR multiattribute[Title/Abstract] OR multi attribute[Title/Abstract] OR 'aqol-8d'[Title/Abstract] OR aqol 8d'[Title/Abstract] OR ((quality of life[Title/Abstract] OR qol[Title/Abstract] OR eortc[Title/Abstract] OR '8 d'[Title/Abstract] OR '8-d'[Title/Abstract] OR '8 dimension'[Title/Abstract] OR '8-dimension[Title/Abstract] OR eight dimension[Title/Abstract]))	3,293,879	486,162

Search no.	Potential TLR systematic searches	Results (May 12, 2020)	Results (February 14, 2022)
	title/abstract OR c10d[Title/Abstract] OR crosswalk[Title/Abstract] OR cross walk[Title/Abstract] OR valuation[Title/Abstract] OR ((health state'[Title/Abstract] OR illness state) near/2 (utility[Title/Abstract] OR disutility[Title/Abstract] OR preference[Title/Abstract] OR value)) title/abstract OR psychometry/exp[Title/Abstract] OR quality adjusted life year/exp[Title/Abstract] OR quality adjusted life[Title/Abstract] OR qaly[Title/Abstract] OR qald[Title/Abstract] OR qale[Title/Abstract] OR time[Title/Abstract] OR disability adjusted life year[Title/Abstract] OR disability adjusted life years[Title/Abstract] OR daly[Title/Abstract] OR quality of life[Title/Abstract]))		
4.	#1 AND #2 AND #3 Sort by: Best Match Filters: Full text; published in the past 5 years; Humans	3906	1687

HRQL, health-related quality of life; TLR, targeted literature review; TSC, tuberous sclerosis complex.

Study Selection

Potentially relevant publications were reviewed and assessed to collate studies that might inform patient HRQL data for the model. To determine the final set of studies eligible for review, explicit inclusion and/or exclusion criteria were applied to the literature search results. A detailed list of the inclusion and exclusion criteria for the HRQL evidence TLR is outlined in Online Resource Table 4. These criteria were designed to only include studies that would be of added benefit to those already identified in the TSC-associated seizures HRQL SLR and previous Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) HRQL SLRs. On this basis, the search was limited to the past 5 years to avoid inclusion of outdated information. It was also limited to English language papers and European and North American countries only – non-English language papers and countries outside of Europe and North America are unlikely to contain information relevant to a UK setting.

Online Resource Table 4 Eligibility criteria applied to HRQL utility evidence literature search

Category	Inclusion criteria	Exclusion criteria
Population	Pediatric and adult patients experiencing seizures due to epilepsy	Disease other than epilepsy Patients with PNES experiencing non-seizure epilepsy
Interventions	Unrestricted	Unrestricted
Comparators	Unrestricted	Unrestricted
Outcomes	HRQL data based on seizure frequency, seizure-free days, and/or seizure severity outcomes that could be used to inform the cost-effectiveness model HRQL data collected using a preference-based measure or instrument HRQL data collected using a disease-specific measure for which a published mapping algorithm is available	Outcomes other than HRQL utility data specific to the model outcome needs
Study type	Randomized controlled trials Non-randomized controlled trials Single-arm trials Retrospective and prospective cohort studies Real-world evidence studies Systematic reviews Published economic models	Letters, comments, and editorials Case studies or case reports
Language	English	Non-English
Countries	North America, Europe	Not reporting any of the countries included in the list

HRQL, health-related quality of life; PNES, psychogenic non-epileptic seizures.

Primary (Level 1) screening was performed by one researcher who reviewed each reference (title and abstract) identified in the literature search, applied basic study selection criteria (population, outcome, study design [see Online Resource Table 4]), and decided whether to include or exclude the study reference. If there was uncertainty, a second independent researcher assessed the full reference (title and abstract), and the applicability of the selection criteria was decided following debate.

Full-text articles were obtained for secondary (Level 2) screening of potentially relevant articles. One reviewer independently inspected and assessed each reference against the full eligibility

criteria; any uncertainty regarding the inclusion of a study was independently checked by a second reviewer.

Data Extraction

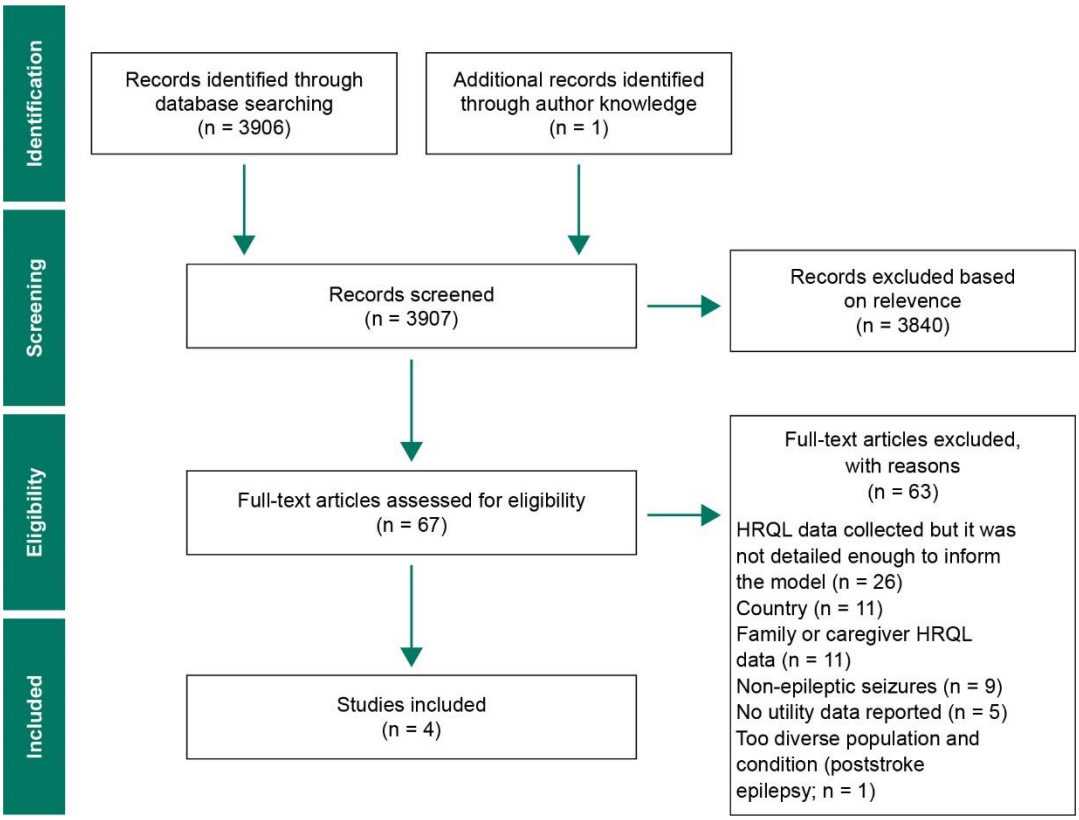
As this was a rapid TLR, a data extraction grid was not used. However, one reviewer assessed the quality of the articles retrieved, and a second reviewer assessed their suitability for inclusion in the model.

Search Results

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies identified for the HRQL data review are presented in Online Resource Fig. 2.

A total of 3907 potentially relevant titles or abstracts were identified and reviewed. Of these, 3840 were excluded at the primary screening (Level 1) stage as they were not relevant to the research question. The remaining 67 studies were further screened (Level 2) based on information reported in the full-text articles. Fourteen studies were identified as potentially containing relevant information for the economic model. Following a secondary screening of the 14 full-text articles by the second reviewer, four publications were included in the TLR [8–11].

Online Resource Fig. 2 PRISMA flow diagram TLR (based on TLR conducted on May 12, 2020)

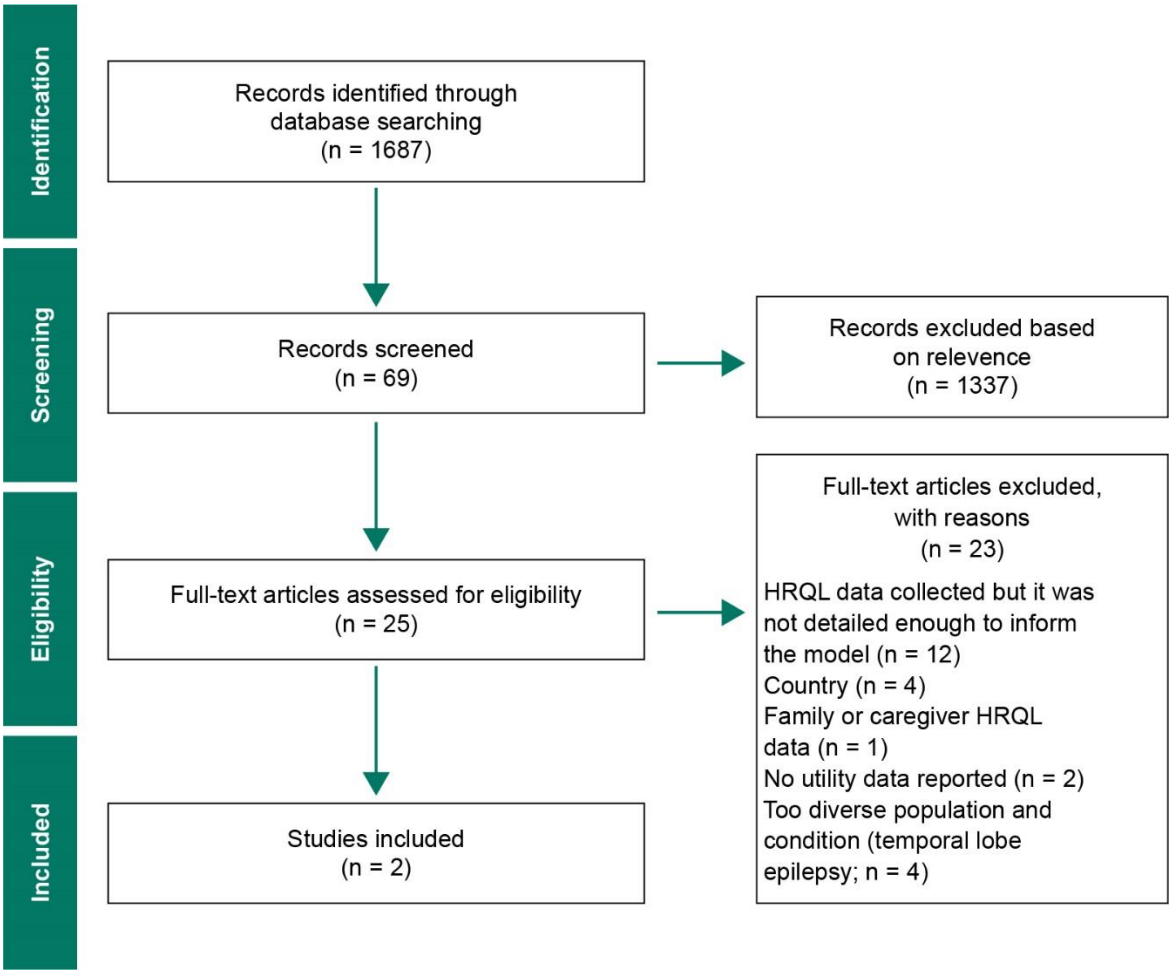


HRQL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TLR, targeted literature review.

TLR Update

An update to the TLR was conducted on February 14, 2022 (from the original search date) using the same search strategy and eligibility criteria listed in Online Resource Tables 3 and 4. The PRISMA flow diagram of studies identified for the updated HRQL data review is presented in Online Resource Fig. 3. A total of 1687 potentially relevant titles or abstracts were identified and reviewed. Of these, 1685 studies were excluded as they were not relevant to the research question. Two studies were identified as potentially containing relevant information for the economic model, and these two studies were also included in the TLR [12,13].

Online Resource Fig. 3 PRISMA flow diagram TLR (based on TLR conducted on Feb 14, 2022)



HRQL, health-related quality of life; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; TLR, targeted literature review.

Summary of the Utility Studies Identified by the TLR

All six studies identified by the TLR reported HRQL data associated with seizure frequency. Three of the studies used the EQ-5D [2,14,15] and different ranges of seizure frequency categories. Three studies used health state vignettes: de Kinderen et al. [16] collected HRQL values in a population with epilepsy using vignettes with health state descriptions reflecting six levels of seizure frequency; Auvin et al. [17] collected HRQL values in patients and caregivers of patients with LGS and DS measured using a visual analog scale; Lo et al. [18] elicited HRQL for patients and caregivers of patients with LGS or DS from the general population valued using TTO methods; data were collected using vignettes with heath states based on seizure frequency and seizure-free days per month. The studies were limited in their use to inform the cost-effectiveness model due to inconsistency in the reported values across health states [2], seizure frequency categories not representative of patients with TSC-associated epilepsy [14,16–18], and reporting of mean utility values that were not defined by seizure frequency [15].

Based on these limitations, it was not possible to use any of the studies identified by the TLR to derive utility scores that are reflective of the model health states in the base-case model analysis.

References

1. Wijnen BF, Mosweu I, Majoie MH, Ridsdale L, de Kinderen RJ, Evers SM, et al. A comparison of the responsiveness of EQ-5D-5L and the QOLIE-31P and mapping of QOLIE-31P to EQ-5D-5L in epilepsy. Eur J Health Econ. 2018;19:861–70.

2. Mukuria C, Young T, Keetharuth A, Borghs S, Brazier J. Sensitivity and responsiveness of the EQ-5D-3L in patients with uncontrolled focal seizures: an analysis of Phase III trials of adjunctive brivaracetam. Qual Life Res. 2017;26:749–59.

3. Tritton T, Bennett B, Brohan E, Grant L, Cooper A, Fladrowski C, et al. Health utilities and quality of life in individuals with tuberous sclerosis complex (TSC) who experience epileptic seizures: a web-based survey. Epilepsy Behav. 2019;92:213–20.

4. Vergeer M, Ranitz-Greven WL, Neary MP, Ionescu-Ittu R, Emond B, Sheng Duh M, et al. Epilepsy, impaired functioning, and quality of life in patients with tuberous sclerosis complex. Epilepsia Open. 2019;4:581–92.

5. Brazier J, Rowen D. NICE DSU Technical Support Document 11: alternatives to EQ-5D for generating health state utility values [Internet]. London, UK: National Institute for Health and Care Excellence (NICE); 2011. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425861/

6. Lo SH, Marshall J, Skrobanski H, Lloyd A. Patient and caregiver health state utilities in tuberous sclerosis complex. PharmacoEconomics Open. 2022;6:105–21.

7. Lagae L, Irwin J, Gibson E, Battersby A. Caregiver impact and health service use in high and low severity Dravet syndrome: a multinational cohort study. Seizure. 2019;65:72–9.

8. Patel A, Chin R, Mitchell W, Perry S, Weinstock A, Checketts D, et al. Long-term safety and efficacy of cannabidiol (CBD) treatment in patients with Lennox Gastaut syndrome (LGS): 3-year results of an open-label extension (OLE) trial (GWPCARE5). Neurology. 2020;94(Suppl. 15):668 (Abstract).

9. Halford JJ, Scheffer I, Nabbout R, Sanchez-Carpintero R, Malawky YS, Wong M, et al. Long-term safety and efficacy of cannabidiol (CBD) treatment in patients with Dravet syndrome (DS): 3-year interim results of an open-label extension (OLE) trial (GWPCARE5). Neurology. 2020;94(Suppl. 15):439 (Abstract).

10. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2021;78:285–92.

11. Thiele E, Bebin EM, Filloux F, Kwan P, Loftus R, Sahebkar F, et al. Long-term safety and efficacy of cannabidiol (CBD) for the treatment of seizures in patients with tuberous sclerosis complex (TSC) in an open-label extension (OLE) trial (GWPCARE6). Neurology. 2020;94(Suppl.):677 (Abstract).

12. Tye C, Mcewen FS, Liang H, Underwood L, Woodhouse E, Barker ED, et al. Long-term cognitive outcomes in tuberous sclerosis complex. Dev Med Child Neurol. 2020;62:322–9.

13. Weinstock A, Bebin EM, Checketts D, Clark G, Szaflarski J, Seltzer L, et al. Long-term efficacy and safety of cannabidiol (CBD) in patients with tuberous sclerosis complex (TSC): 4-year results from the expanded access program (EAP). Neurology. 2021;96(Suppl. 15):2405 (Abstract).

14. Kirkham FJ, Vigevano F, Raspall-Chaure M, Wilken B, Lee D, Le Reun C, et al. Health-related quality of life and the burden of prolonged seizures in noninstitutionalized children with epilepsy. Epilepsy Behav. 2020;102:106340.

15. Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol. 2018;60:63–72.

16. de Kinderen RJ, Wijnen BF, van Breukelen G, Postulart D, Majoie MH, Aldenkamp AP, et al. From clinically relevant outcome measures to quality of life in epilepsy: a time trade-off study. Epilepsy Res. 2016;125:24–31.

17. Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy Behav. 2021;123:108239.

18. Lo SH, Lloyd A, Marshall J, Vyas K. Patient and caregiver health state utilities in Lennox-Gastaut syndrome and Dravet syndrome. Clin Ther. 2021;43:1861–76.