# National Institute for Health and Care Excellence

Final

# Epilepsies in children, young people and adults

## [N] Criteria for referral to specialist services

*NICE guideline NG217*

*Evidence reviews underpinning recommendations 3.1.1-3.1.4 in the NICE guideline*

*April 2022*

*Final*

*These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists*

**Disclaimer**

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.



ISBN: 978-1-4731-4513-9

# Contents

# Evidence review for the criteria for referral to specialist services

## Review question

What are the criteria for referral to specialist services?

### Introduction

Specialist services are defined as tertiary or quaternary epilepsy services, led by a neurologist or paediatric neurologist with expertise in epilepsy. Although the majority of individuals may be reviewed by their local epilepsy service, there may be key situations that warrant referral to specialist services for further advice, investigations and management. The aim of this review is to identify which factors or criteria should be used to help determine who is referred for specialist care.

### Summary of the protocol

See Table 1 for a summary of the Population, Exposure, Presence or absence of a prognostic, risk or predictive factor and Outcome (PPO) characteristics of this review.

**Table 1: Summary of the protocol (PPO table)**

| | |
|---|---|
| **Population** | **Inclusion:**<br>• children, young people and adults with epilepsy<br>**Exclusion:**<br>• newborn babies (under 28 days) with acute symptomatic seizures |
| **Presence or absence of a prognostic, risk or predictive factor** | Suggestive (but not exhaustive) criteria may include:<br>• Age<br>• Behavioural problems<br>• Behavioural regression (neuro- development)<br>• Changes in cognitive performance, neuropsychology,<br>• Continuing seizures<br>• Developmental regression<br>• Diagnostic uncertainty (unclear diagnosis)<br>• Medication failure<br>• Number of medications tried/failed<br>• Pregnancy<br>• Psychiatric co-morbidity<br>• Psychological co-morbidity<br>• Refractory epilepsy, refractory dissociative seizures, seizures, non-epilepsy seizures<br>• Side effects of medication/intolerance<br>• Type of epilepsy<br><br>*Note: studies must make adjustment for confounding factors in their analysis, and this will be accounted for in the GRADE analysis* |
| **Outcome** | **Critical**<br>• Diagnosis (for example improved diagnosis/miss-diagnosis/change in diagnosis)<br>• Improved management (for example unscheduled hospital appointments, admissions/readmissions)<br>• Mortality<br>• Health related quality of life<br>*As measured using odds ratio (OR), or hazard ratio (HR) adjusted from regression analysis.* |

*OR: odds ratio; HR: hazard ratio*

For further details see the review protocol in appendix A.

## Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

## Clinical evidence

### Included studies

A systematic review of the literature was conducted but no studies were identified which were applicable to this review question.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

### Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

## Summary of studies included in the evidence review

No studies were identified which were applicable to this review question (and so there are no evidence tables in appendix D). No meta-analysis was undertaken for this review (and so there are no forest plots in appendix E).

## Quality assessment of studies included in the evidence review

No studies were identified which were applicable to this review question and so there are no evidence profiles in appendix F.

## Economic evidence

### Included studies

A single economic search was undertaken for all topics included in the scope of this guideline but no economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

### Excluded studies

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

## Summary of studies included in the economic evidence review

No studies were identified which were applicable to this review question.

## Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

## Summary of the economic evidence

No evidence was identified which was applicable to this review question.

## The committee's discussion of the evidence

### Interpreting the evidence

#### *The outcomes that matter most*

The aim of this review was to identify the factors and criteria that should be used to determine who is referred for epilepsy specialist care. The committee designated 4 critical outcomes: diagnosis (for example, improved diagnosis or change in diagnosis), improved management (for example, unscheduled hospital appointments, admissions/readmissions),

mortality, and health related quality of life. These outcomes were selected as the most direct indicators of an appropriate referral to epilepsy specialist services.

The committee did not identify any important outcomes.

### *The quality of the evidence*

Prospective observational cohort studies were prioritised for inclusion in this review, and it was pre-specified that retrospective and case-control studies of over 50 participants would be considered for inclusion if there was insufficient evidence from prospective observational cohort studies.

The clinical evidence search identified no studies that met the inclusion criteria for this review. Although the search identified prospective cohort studies, most of these studies were excluded either because the criteria for referral to specialist services were not indicated, or they had not reported the outcomes relevant to this review.

### *Benefits and harms*

No evidence was identified for this review question, therefore recommendations are based entirely on committee experience and informal consensus agreement.

The committee discussed the criteria for referral to specialist services and agreed that people with suspected or confirmed epilepsy should have access to tertiary epilepsy services via their specialist if needed. The need for referral would depend on different aspects, such as the person's clinical presentation, need for further treatment or access to clinical trials, therefore the committee agreed on a clear referral process based on their experience and expertise.

The committee discussed some health inequalities that may arise, especially in situations of comorbid presentations. Often, people with comorbidities are being seen by other services which may mask their need for additional expertise to diagnose and manage their epilepsy. Some comorbidities such as a learning, physical or mental health conditions may overshadow, or be overshadowed by, the presence of epilepsy. The committee therefore agreed that people with comorbidities should be supported to access tertiary services if they need additional support to manage their epilepsy.

The committee established that referrals to be seen within 4 weeks should be made when there is uncertainty about the person's diagnosis; in cases of drug resistant epilepsy, or a treatment associated with intolerable side effects; when further assessment or treatment approaches are needed, and if the person is eligible and wishes to participate in a research study or clinical trial. The committee considered the definition of drug resistant epilepsy from the International League Against Epilepsy (ILAE) ("failure of adequate trials of two tolerated and appropriately chosen and used AED schedules [whether as monotherapies or in combination] to achieve sustained seizure freedom" [ILAE 2010]).

The committee agreed on specific criteria that should prompt a referral to a tertiary paediatric epilepsy services to be seen within 2 weeks. This included specific groups of children, such as those under the age of 3 who require early involvement of a paediatric neurologist to minimise the negative effects of the epilepsy on development. As myoclonic seizures may present after the age of 3, the committee agreed that those with myoclonic seizures and under 4 should be referred. In cases of children presenting with a unilateral structural lesion, or seizures associated with behavioural or developmental regression, referral should be made urgently due to the risk of severe neurodevelopmental outcomes if formal assessment and diagnosis is delayed.

### Cost effectiveness and resource use

The committee noted that no relevant published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The committee agreed that there was unlikely to be a significant resource impact from the recommendations made as they will not change current practice on which factors should be used to determine who is referred for epilepsy specialist care. On the contrary, the recommendations made by the committee are likely to reinforce current best practice.

### Other factors the committee took into account

The committee noted that the 2014 guideline on transient loss of consciousness ('blackouts') in over 16s (CG109) and the 2019 guideline on suspected neurological conditions: recognition and referral (NG127) may be relevant when considering referrals.

## Recommendations supported by this evidence review

This evidence review supports recommendations 3.1.1-3.1.4.

# References

**ILAE 2010**

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: Epilepsia. 2010 Sep;51(9):1922. PMID: 19889013.

# Appendices

## Appendix A – Review protocol

### Review protocol for review question: What are the criteria for referral to specialist services?

**Table 2: Review protocol for referral to specialist services**

| Field | Content |
|---|---|
| PROSPERO registration number | CRD42020180469 |
| Review title | Referral to specialist services |
| Review question | What are the criteria for referral to specialist services? |
| Objective | Determining who should receive specialist care is important to ensure those who need this care are referred appropriately and those people who can be managed in non-specialist care are not sent inappropriately.<br>The aim of this review is to identify which factors or criteria should be used to help determine who is referred for specialist care. |
| Searches | The following databases will be searched:<br>• CDSR<br>• CENTRAL<br>• DARE<br>• HTA<br>• MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations<br>• Embase<br>• EMCare<br><br>Searches will be restricted by:<br>• Date: no date limit<br>• English language studies<br>• Human studies |

| Field | Content |
|---|---|
| Condition or domain being studied | All epilepsy types |
| Population | Inclusion:<br>• children, young people and adults with epilepsy<br><br>Exclusion:<br>• newborn babies (under 28 days) with acute symptomatic seizures |
| Exposure (criteria for referral) | Suggestive (but not exhaustive) criteria may include:<br>• Age<br>• Behavioural problems<br>• Behavioural regression (neuro- development)<br>• Changes in cognitive performance, neuropsychology,<br>• Continuing seizures<br>• Developmental regression<br>• Diagnostic uncertainty (unclear diagnosis)<br>• Medication failure<br>• Number of medications tried/failed<br>• Pregnancy<br>• Psychiatric co-morbidity<br>• Psychological co-morbidity<br>• Refractory epilepsy, refractory dissociative seizures, seizures, non-epilepsy seizures<br>• Side effects of medication/intolerance<br>• Type of epilepsy |
| Confounding factors | • Any of those listed above<br><br>*Note: studies must make adjustment for confounding factors in their analysis, and this will be accounted for in the GRADE analysis* |
| Types of study to be included | • Systematic review of observational cohort studies<br>• Prospective or retrospective cohort studies<br>• If cohort studies are unavailable to inform decision making, then case-control studies of at least 50 people in each arm will be considered for inclusion |

| Field | Content |
|---|---|
| | • Prospective study designs will be prioritised over retrospective study designs<br>• Population-based studies and multicentre studies will be prioritised<br>Univariate studies will only be included if no studies with multivariate analysis are identified<br><br>Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual. |
| Other exclusion criteria | • Studies with a mixed population (this is, including children, young people and adults with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported.<br>• Conference abstracts will not be included because these do not typically provide sufficient information to fully assess the risk of bias |
| Context | Recommendations will apply to those receiving care in healthcare settings (for example, community, primary, secondary care). |
| Critical outcomes | • Diagnosis (for example improved diagnosis/miss-diagnosis/change in diagnosis)<br>• Improved management (for example unscheduled hospital appointments, admissions/readmissions)<br>• Mortality<br>• Health related quality of life<br><br>As measured using odds ratio (OR), or hazard ratio (HR) adjusted from regression analysis. |
| Important outcomes | Not applicable<br><br>NB: Outcomes are in line with those described in the core outcome set for epilepsy (http://www.comet-initiative.org/studies/searchresults) |
| Data extraction (selection and coding) | All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated.<br><br>Titles and abstracts of the retrieved citations will be screened. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria outlined in the review protocol. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. Draft included and excluded study lists will be circulated to the committee for their comments, resolution of any disputes will be by discussion between the senior reviewer, topic advisor and chair.<br><br>Duplicate screening will not be undertaken for this question.<br><br>A standardised form will be used to extract data from studies and will include: study setting; study design; study aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of criteria included in the study, details of confounding factors measured and adjusted for, study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. |

| Field | Content |
|---|---|
| | All data extraction will be quality assured by a senior reviewer.<br><br>For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual. |
| Risk of bias (quality) assessment | Quality assessment of individual studies will be performed using the following checklists:<br>• ROBIS tool for systematic reviews<br>• ROBINS-I for non-randomised studies<br>• QUIPS checklist for prognostic factor studies<br>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer. |
| Strategy for data synthesis | Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.<br><br><u>Data synthesis</u><br>Where possible, meta-analysis to combine the effect estimates across studies for an independent prognostic factor will be conducted only if there is sufficient number of studies, a consistent measure to assess this factor is used, and each study has adjusted for similar sets of confounders. We will assess the confounders which have been included in the multiple regression of included studies, and make a decision regarding levels of similarity in adjustment, unless sufficiently similar, data will not be pooled.<br><br>We will extract either OR or HR, however, we will conduct analysis for those studies reporting OR and those reporting HR, as it is inappropriate to pool OR and HR.<br>If no meta-analysis is conducted a narrative summary of the available results for each factor will be provided.<br>If studies do not report HR or OR, but provide the number of participants, for example who have improved management following specialist care, these data will be extracted and described narratively or pooled across studies using fixed effect meta-analysis.<br><br><u>Heterogeneity</u><br>Heterogeneity in the effect estimates of the individual studies will be assessed using the $I^2$ statistic. $I^2$ values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively.<br><br>In the presence of heterogeneity, sub-group analysis will be conducted:<br>• according to the risk of bias of individual studies<br>• study location<br><br>Exact sub-group analysis may vary depending on differences identified within included studies. If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. |

| Field | Content | | |
|---|---|---|---|
| | Validity<br>The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ | | |
| Analysis of sub-groups (Stratification) | If data is available, results will be presented separately by:<br>• Children and adults | | |
| Type and method of review | ☐ | Intervention | |
| | ☐ | Diagnostic | |
| | ☒ | Prognostic | |
| | ☐ | Qualitative | |
| | ☐ | Epidemiologic | |
| | ☐ | Service Delivery | |
| | ☐ | Other (please specify) | |
| Language | English | | |
| Country | England | | |
| Anticipated or actual start date | 01 May 2020 | | |
| Anticipated completion date | 02 June 2021 | | |
| Stage of review at time of this submission | **Review stage** | **Started** | **Completed** |
| | Preliminary searches | x | x |
| | Piloting of the study selection process | x | x |
| | Formal screening of search results against eligibility criteria | x | x |
| | Data extraction | x | x |
| | Risk of bias (quality) assessment | x | x |
| | Data analysis | x | x |

| Field | Content |
|---|---|
| Named contact | **5a. Named contact**<br>National Guideline Alliance<br><br>**5b. Named contact e-mail**<br>epilepsies@nice.org.uk<br><br>**5c. Organisational affiliation of the review**<br>National Institute for Health and Care Excellence (NICE) and National Guideline Alliance |
| Review team members | National Guideline alliance (NGA) technical team |
| Funding sources/sponsor | This systematic review is being completed by the National Guideline Alliance which receives funding from NICE. |
| Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/gid-ng10112/documents/committee-member-list |
| Other registration details | Not applicable |
| URL for published protocol | https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180469 |
| Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| Keywords | Epilepsy, specialist epilepsy services |
| Details of existing review | Not applicable |

| Field | Content |
|---|---|
| of same topic by same authors | |
| Additional information | Not applicable |
| Details of final publication | www.nice.org.uk |

*CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: The Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; HTA: Health Technology Assessment; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; OR: odds ratio; QUIPS: Quality in Prognostic Studies; ROBINS-I: Risk Of Bias In Non-randomised Studies - of Interventions; ROBIS: risk of bias in systematic reviews*

# Appendix B – Literature search strategies

## Literature search strategies for review question: What are the criteria for referral to specialist services?

### Clinical

### Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID

EMCare 1995 to May 07, 2020; Embase Classic+Embase 1947 to 2020 May 07; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2020 May 07, 2020
Date of last search: 07 May 2020

*Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily*

| # | Searches |
|---|---|
| 1 | exp epilepsy/ or landau kleffner syndrome/ or exp seizure/ or "seizure, epilepsy and convulsion"/ |
| 2 | 1 use emcr |
| 3 | exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/ |
| 4 | 3 use ppez |
| 5 | (convulsion* or dravet syndrome or epilep* or continous spike wave of slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab. |
| 6 | infantile spasm/ use emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab. |
| 7 | myoclonic astatic epilepsy/ use emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab. |
| 8 | exp benign childhood epilepsy/ use emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab. |
| 9 | landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or smei or lennox gastaut or lgs or (landau adj2 kleffner)).ti,ab. |
| 10 | severe myoclonic epilepsy in infancy/ use emcr or exp epilepsies, myoclonic/ use ppez or (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab. |
| 11 | (((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab. |
| 12 | (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab. |
| 13 | (atonic seizure or tonic seizure).sh. use emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab. |
| 14 | or/2,4-13 |
| 15 | *medical specialist/ or exp *tertiary health care/ |
| 16 | 15 use emcr |
| 17 | *tertiary healthcare/ or (referral* and specialization*).sh. |
| 18 | 17 use ppez |

| # | Searches |
|---|---|
| 19 | ((referral or consultation) and (tertiary or (cep or epileptolog* or multidisciplin* or multi disciplin* or neurolog* or neurophysiolog* or neuro physiolog* or neuropsycholog* or neuro psychol* or neuroradiolog* or neuro radiolog* or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or social work* or speciali* or surgeon* or surger* or therapist* or triage*))).hw. |
| 20 | ((evaluat* or refer* or transition*) and (tertiary or (cep or epileptolog* or multidisciplin* or multi disciplin* or neurolog* or neurophysiolog* or neuro physiolog* or neuropsycholog* or neuro psychol* or neuroradiolog* or neuro radiolog* or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or social work* or speciali* or surgeon* or surger* or therapist* or triage*))).ti. or ((evaluat* or refer* or transition*) adj4 (tertiary or (cep or epileptolog* or multidisciplin* or multi disciplin* or neurolog* or neurophysiolog* or neuro physiolog* or neuropsycholog* or neuro psychol* or neuroradiolog* or neuro radiolog* or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or social work* or speciali* or surgeon* or surger* or therapist* or triage*))).ab. |
| 21 | ((consultation* or evaluat* or refer* or transition*) and (((comphrehensive epilepsy or multidisciplinary or multi disciplinary) adj program*) or ((advanced or complex or tertiary) adj2 (care or cent* or healthcare or hospital* or program* or setting)) or ((epilepsy or seizure) adj (cent* or clinic*)) or medical specialist*)).ti,ab. |
| 22 | ((speciali?ed adj (care or healthcare)) or transition program*).ti,ab. |
| 23 | or/16,18-22 |
| 24 | 14 and 23 |
| 25 | limit 24 to english language |
| 26 | ((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.) |
| 27 | 26 use emez |
| 28 | ((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.) |
| 29 | 28 use mesz |
| 30 | 27 or 29 |
| 31 | 25 not 30 |

## Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 05 of 12, May 2020; Cochrane Central Register of Controlled Trials, Issue 5 of 12, May 2020
Date of last search: 07 May 2020

| # | searches |
|---|---|
| 1 | mesh descriptor: [epilepsy] explode all trees |
| 2 | mesh descriptor: [seizures] explode all trees |
| 3 | (convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”):ti,ab |
| 4 | (((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or ”spasmus nutans” or “west syndrome*”):ti,ab |
| 5 | ((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) near/2 (seizure* or spasm*)):ti,ab |
| 6 | (bcects or bects or brec or “benign epilepsy” or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central |

| # | searches |
|---|---|
| | focal") next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab |
| 7 | (dravet or smei or "lennox gastaut" or lgs or (landau near/2 kleffner)):ti,ab |
| 8 | (dravet*1 or ("intractable childhood epilepsy" near/2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei):ti,ab |
| 9 | (((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near/3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) near/2 epilep*) or (epilepsy near/2 "eyelid myoclonia") or (ige near/2 "phantom absenc*") or "impulsive petit mal" or (janz near/3 (epilep* or "petit mal")) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near/2 (disease or syndrome)) or ((jme or jmes) and epilep*) or "perioral myoclon*"):ti,ab |
| 10 | (dravet*1 or ("intractable childhood epilepsy" near/2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei):ti,ab |
| 11 | ((drop or akinetic or atonic or tonic) near/2 (attack* or epileps* or seizure* or convulsion*)) or "brief seizure" or (tonic near/3 atonic near/3 (attack* or epileps* or seizure* or convulsion*)):ti,ab |
| 12 | {or #1-#11} |
| 13 | mesh descriptor: [tertiary healthcare ] this term only |
| 14 | (referral* and specialization*):kw |
| 15 | ((referral or consultation) and (tertiary or (cep or epileptolog* or multidisciplin* or "multi disciplin*" or neurolog* or neurophysiolog* or "neuro physiolog*" or neuropsycholog* or "neuro psychol*" or neuroradiolog* or "neuro radiolog*" or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or "social work*" or speciali* or surgeon* or surger* or therapist* or triage*))):kw. |
| 16 | ((evaluat* or refer* or transition*) and (tertiary or (cep or epileptolog* or multidisciplin* or "multi disciplin*" or neurolog* or neurophysiolog* or "neuro physiolog*" or neuropsycholog* or "neuro psychol*" or neuroradiolog* or "neuro radiolog*" or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or "social work*" or speciali* or surgeon* or surger* or therapist* or triage*))):ti |
| 17 | ((evaluat* or refer* or transition*) near/4 (tertiary or (cep or epileptolog* or multidisciplin* or "multi disciplin*" or neurolog* or neurophysiolog* or "neuro physiolog*" or neuropsycholog* or "neuro psychol*" or neuroradiolog* or "neuro radiolog*" or neurosurg* or nurs* or nutrition or psychiatr* or psychologist* or "social work*" or speciali* or surgeon* or surger* or therapist* or triage*))):ab |
| 18 | ((consultation* or evaluat* or refer* or transition*) and (((comphrehensive epilepsy" or multidisciplinary or "multi disciplinary") next program*) or ((advanced or complex or tertiary) near/2 (care or cent* or healthcare or hospital* or program* or setting)) or ((epilepsy or seizure) next (cent* or clinic*)) or "medical specialist*")):ti,ab |
| 19 | ((speciali?ed next (care or healthcare)) or "transition program*"):ti,ab |
| 20 | {or #13-#19} |
| 21 | #12 and #20 |

**Database(s): DARE; HTA database - CRD** Date of last search: 07 May 2020

| | |
|---|---|
| 1 | mesh descriptor epilepsy explode all trees |
| 2 | mesh descriptor seizures explode all trees |
| 3 | (convulsion* or "dravet syndrome" or epilep* or "continous spike wave of slow sleep" or "landau kleffner syndrome" or "lennox gastaut syndrome" or "infant* spasm*" or seizure* or "west syndrome") |
| 4 | (((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or "generali?ed flexion epileps*" or hypsarrhythmia* or ((jacknife or "jack nife" or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epilepsy" or "propulsive petit mal" or "spasm in* flexion" or "spasmus nutans" or "west syndrome*") |
| 5 | ((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or "doose* syndrome" or mae or "generali?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near/2 (seizure* or spasm*)) |
| 6 | (bcects or bects or brec or "benign epilepsy" or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or "temporal-central focal") next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))) |
| 7 | (dravet or smei or "lennox gastaut" or lgs or (landau near/2 kleffner)) |
| 8 | (dravet*1 or ("intractable childhood epilepsy" near/2 ("generalised tonic clonic" or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei) |
| 9 | (((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near/3 (epilep* or seizure*)) or (("childhood absence" or "juvenile absence" or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) near/2 epilep*) or (epilepsy near/2 "eyelid myoclonia") or (ige |

| | |
|---|---|
| | near/2 “phantom absenc*”) or “impulsive petit mal” or (janz near/3 (epilep* or “petit mal”)) or “jeavons syndrome*” or ((janz or lafora or “lafora body” or lundborg or unverricht) near/2 (disease or syndrome)) or ((jme or jmes) and epilep*) or “perioral myoclon*”) |
| 10 | (dravet*1 or (“intractable childhood epilepsy” near/2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei) |
| 11 | ((drop or akinetic or atonic or tonic) near/2 (attack* or epileps* or seizure* or convulsion*)) or “brief seizure” or (tonic near/3 atonic near/3 (attack* or epileps* or seizure* or convulsion*)) |
| 12 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 |

## Economic

**Database(s): MEDLINE & Embase (Multifile) - OVID**
Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021
Date of last search: 31 March 2021

*Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily*

| # | searches |
|---|---|
| 1 | exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/ |
| 2 | 1 use emczd |
| 3 | exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/ |
| 4 | 3 use ppez |
| 5 | (epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab. |
| 6 | (seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab. |
| 7 | (atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab. |
| 8 | exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab. |
| 9 | exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez |
| 10 | (((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab. |
| 11 | infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab. |
| 12 | landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab. |
| 13 | lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez |
| 14 | (child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab. |
| 15 | myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab. |
| 16 | myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab. |

| # | searches |
|---|---|
| 17 | exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab. |
| 18 | severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez |
| 19 | (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab. |
| 20 | epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab. |
| 21 | or/2,4-20 |
| 22 | exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/ |
| 23 | 22 use ppez |
| 24 | budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/ |
| 25 | 24 use emczd |
| 26 | budget*.ti,ab. |
| 27 | cost*.ti. |
| 28 | (economic* or pharmaco economic* or pharmacoeconomic*).ti. |
| 29 | (price* or pricing*).ti,ab. |
| 30 | (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. |
| 31 | (financ* or fee or fees).ti,ab. |
| 32 | (value adj2 (money or monetary)).ti,ab. |
| 33 | or/23,25-32 |
| 34 | 21 and 33 |
| 25 | limit 34 to engish language |

**Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD**
Date of last search: 31 March 2021

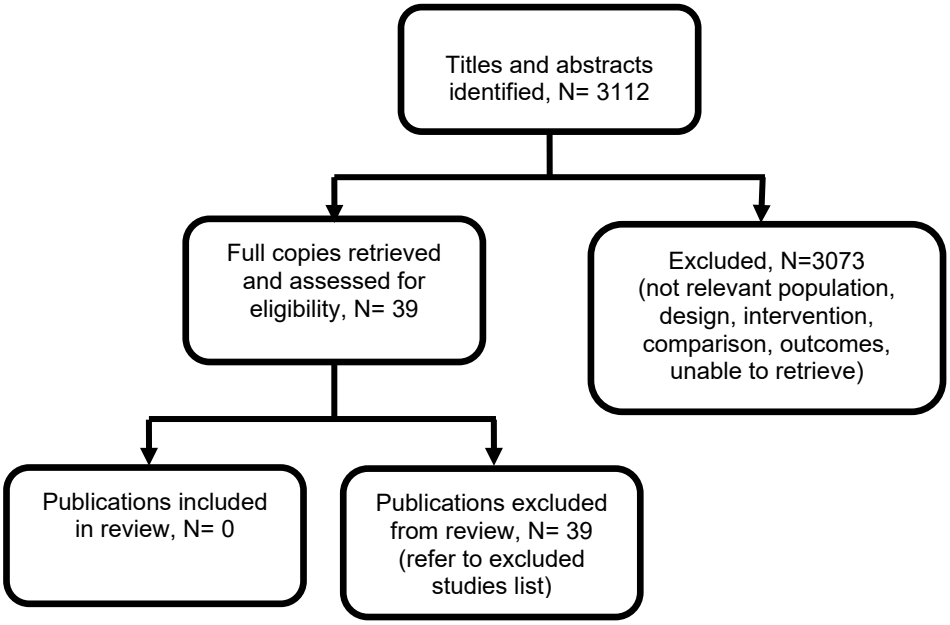
| # | searches |
|---|---|
| 1 | mesh descriptor epilepsy explode all trees |
| 2 | mesh descriptor seizures this term only |
| 3 | mesh descriptor seizures, febrile this term only |
| 4 | mesh descriptor status epilepticus explode all trees |
| 5 | (epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”) |
| 6 | ((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or “petit mal*” or pyknolepsy or “typical absence*”) |
| 7 | mesh descriptor seizures explode all trees |
| 8 | ((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or “brief seizure” or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*)) |
| 9 | mesh descriptor epilepsy, rolandic this term only |
| 10 | (bcects or bects or brec or “benign epilepsy” or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*))) |
| 11 | mesh descriptor epilepsy, generalized this term only |
| 12 | (((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or ((“childhood absence” or “juvenile absence” or myoclonic or myoclonia or “myoclonic astatic” or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 “eyelid myoclonia”) or (ige near2 phantom absenc*) or “impulsive petit mal” or (janz near3 (epilep* or “petit mal”)) or “jeavons syndrome*” or ((janz or lafora or “lafora body” or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or “perioral myoclon*”) |
| 13 | mesh descriptor spasms, infantile this term only |
| 14 | (((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal“or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”) |
| 15 | mesh descriptor landau kleffner syndrome this term only |
| 16 | (dravet or “lennox gastaut” or lgs or (landau near2 kleffner) or smei) |

| # | searches |
|---|---|
| 17 | mesh descriptor lennox gastaut syndrome this term only |
| 18 | mesh descriptor epileptic syndromes this term only |
| 19 | (“child* epileptic encephalopath*” or gastaut or lennox or lgs) |
| 20 | ((myoclon* near2 (absence* or epileps* or seizure* or jerk* or “progressive familial epilep*” or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or “muscle jerk”) |
| 21 | mesh descriptor epilepsies, myoclonic explode all trees |
| 22 | ((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) near2 (seizure* or spasm*)) |
| 23 | mesh descriptor epilepsies, partial explode all trees |
| 24 | ((focal or “focal onset” or local or partial or “simple partial”) near3 (epileps* or seizure*)) |
| 25 | mesh descriptor epilepsies, myoclonic this term only |
| 26 | (dravet*1 or (“intractable childhood epilepsy” near2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei) |
| 27 | mesh descriptor epilepsy, tonic-clonic this term only |
| 28 | mesh descriptor epilepsy, generalized this term only |
| 29 | (((clonic or “grand mal” or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*))) |
| 30 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 |

# Appendix C – Clinical evidence study selection

## Study selection for: What are the criteria for referral to specialist services?

**Figure 1: Study selection flow chart**



# Appendix D – Clinical evidence tables

## Evidence tables for review question: What are the criteria for referral to specialist services?

No evidence was identified which was applicable to this review question.

# Appendix E – Forest plots

## Forest plots for review question: What are the criteria for referral to specialist services?

No meta-analysis was conducted for this review question and so there are no forest plots.

# Appendix F – Modified GRADE tables

## Modified GRADE tables for review question: What are the criteria for referral to specialist services?

No evidence was identified which was applicable to the research question and so there are no evidence profiles

# Appendix G – Economic evidence study selection

## Economic evidence study selection for review question: What are the criteria for referral to specialist services?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

# Appendix H – Economic evidence tables

## Economic evidence tables for review question: What are the criteria for referral to specialist services?

No evidence was identified which was applicable to this review question.

# Appendix I – Economic evidence profiles

## Economic evidence profiles for review question: What are the criteria for referral to specialist services?

No economic evidence was identified which was applicable to this review question.

# Appendix J – Economic analysis

## Economic evidence analysis for review question: What are the criteria for referral to specialist services?

No economic analysis was conducted for this review question.

# Appendix K – Excluded studies

## Excluded studies for review question: What are the criteria for referral to specialist services?

### Clinical studies

**Table 3: Excluded studies and reasons for their exclusion**

| Study | Reason for Exclusion |
|---|---|
| Arkilo, D., Griesemer, D., Padulsky, K., Lam, D., Wang, S., Hyder, D., Urgent referrals for seizure evaluation to a tertiary care neurology center: A pilot study, Journal of Child Neurology, 27, 885-887, 2012 | No relevant outcomes were identified |
| Assadeck, H., Toudou Daouda, M., Moussa Konate, M., Mamadou, Z., Hassane Djibo, F., Douma Maiga, D., Sanoussi, S., Clinical and etiological characteristics of epilepsy in people from Niger: a hospital-based study from a tertiary care referral center of Niamey, Niger, Epilepsia Open, 4, 318-327, 2019 | No relevant outcomes were identified |
| Assadeck, H., Toudou-Daouda, M., Mamadou, Z., Moussa-Konate, M., Hassane-Djibo, F., Douma-Maiga, D., Clinical and etiological characteristics of epilepsy in the elderly: A hospital-based study from a tertiary care referral center of niamey, niger, Journal of Neurosciences in Rural Practice, 10, 571-575, 2019 | No relevant outcomes were identified |
| Bodde, N. M. G., Lazeron, R. H. C., Wirken, J. M. A., Van Der Kruijs, S. J., Aldenkamp, A. P., Boon, P. A. J. M., Patients with psychogenic non-epileptic seizures referred to a tertiary epilepsy centre: Patient characteristics in relation to diagnostic delay, Clinical Neurology and Neurosurgery, 114, 217-222, 2012 | Study population does not meet the inclusion criteria |
| Chen, J. J., Caller, T. A., Mecchella, J. N., Thakur, D. S., Homa, K., Finn, C. T., Kobylarz, E. J., Bujarski, K. A., Thadani, V. M., Jobst, B. C., Reducing severity of comorbid psychiatric symptoms in an epilepsy clinic using a colocation model: Results of a pilot intervention, Epilepsy and Behavior, 39, 92-96, 2014 | No relevant outcomes were identified |
| De Menezes, M. A. S., Rho, J. M., Clinical and electrographic features of epileptic spasms persisting beyond the second year of life, Epilepsia, 43, 623-630, 2002 | No relevant outcomes were identified |
| Dericioglu, N., Arsava, E. M., Topcuoglu, M. A., The clinical features and prognosis of patients with nonconvulsive status epilepticus in the neurological intensive care unit of a tertiary referral center in Turkey, Clinical EEG and Neuroscience, 45, 293-298, 2014 | Study population does not meet the inclusion criteria |
| Dericioglu, N., Saygi, S., Ciger, A., The value of provocation methods in patients suspected of having non-epileptic seizures, Seizure, 8, 152-156, 1999 | Study population does not meet the inclusion criteria |

| Study | Reason for Exclusion |
|---|---|
| Escriba de la Fuente, A., Elorz Ibanez, A. C., Fernandez Santervas, Y., Quintilla Martinez, J. M., Ortez Gonzalez, C. I., Luaces Cubells, C., Emergency department management of epileptic seizures in children, Emergencias, 25, 116-118, 2013 | Article in Spanish |
| Fitzgerald, P., Herlihy, D., Sweeney, B., Cassidy, E. M., Neurology referrals to a liaison psychiatry service, Irish Medical Journal, 101, 271-273, 2008 | No relevant outcomes were identified |
| Gebauer-Bukurov, K., Bozic, K., Sekulic, S., Clinical characteristics and use of antiepileptic drugs among adolescents with uncomplicated epilepsy at a referral center in Novi Sad, Serbia, Acta Neurologica Belgica, 112, 147-54, 2012 | Study population does not meet the inclusion criteria: mixed population |
| Gigli, G. L., Maschio, M., Diomedi, M., Placidi, F., Silvestri, G., Marciani, M. G., Cognitive performances in newly referred patients with temporal lobe epilepsy: comparison with normal subjects in basal condition and after treatment with controlled-release carbamazepine, International Journal of Neuroscience, 88, 97-107, 1996 | Criteria for referral was not reported |
| Goldstein, L. H., Minchin, L., Stubbs, P., Fenwick, P. B. C., Are what people know about their epilepsy and what they want from an epilepsy service related?, Seizure, 6, 435-442, 1997 | No relevant outcomes were identified |
| Goodridge, D. M. G., Shorvon, S. D., Epileptic seizures in a population of 6000. I: Demography, diagnosis and classification, and role of the hospital services, British Medical Journal, 287, 641-644, 1983 | Study population does not meet the inclusion criteria: mixed population |
| Gronborg,S., Uldall,P., Mortality and causes of death in children referred to a tertiary epilepsy center, European Journal of Paediatric Neurology, 18, 66-71, 2014 | Study population does not meet the inclusion criteria: mixed population |
| Hauser, E., Freilinger, M., Seidl, R., Groh, C., Prognosis of childhood epilepsy in newly referred patients, Journal of Child Neurology, 11, 201-204, 1996 | No relevant outcomes were identified |
| Hogan, R. E., Mortality in Epilepsy: Referral to a Specialty Center Makes a Difference, Epilepsy Currents, 20, 16-18, 2020 | Study design does not meet the inclusion criteria: editorial comment |
| Hoyer, C., Stein, P., Rausch, H. W., Alonso, A., Nagel, S., Platten, M., Szabo, K., The use of a dedicated neurological triage system improves process times and resource utilization: A prospective observational study from an interdisciplinary emergency department, Neurological Research and Practice, 1, V, 2019 | No relevant outcomes were identified |
| Kong, S. T., Ho, C. S., Ho, P. C., Lim, S. H., Prevalence of drug resistant epilepsy in adults with epilepsy attending a neurology clinic of a tertiary referral hospital in Singapore, Epilepsy Research, 108, 1253-1262, 2014 | No relevant outcomes were identified |

| Study | Reason for Exclusion |
|---|---|
| Lowerison, M. W., Josephson, C. B., Jette, N., Sajobi, T. T., Patten, S., Williamson, T., Deardon, R., Barkema, H. W., Wiebe, S., Association of Levels of Specialized Care with Risk of Premature Mortality in Patients with Epilepsy, JAMA Neurology, 76, 1352-1358, 2019 | Criteria for referral was not reported |
| Mar, S., Dunkley, C., Alâ□□Ansari, I., Whitehouse, W. P., Comparison of a dedicated children's Seizure Clinic to mixed General Paediatric Clinics, Child: Care, Health & Development, 31, 597-602, 2005 | No relevant outcomes were identified |
| McFadyen, M. B., First seizures, the epilepsies and other paroxysmal disorders prospective audit of a first seizure clinic, Scottish Medical Journal, 49, 126-130, 2004 | Study population does not meet the inclusion criteria: mixed population |
| Minshall, I., Neligan, A., A review of people who did not attend an epilepsy clinic and their clinical outcomes, Seizure, 50, 121-124, 2017 | No relevant outcomes were identified |
| Monif, M., Seneviratne, U., Clinical factors associated with the yield of routine outpatient scalp electroencephalograms: A retrospective analysis from a tertiary hospital, Journal of Clinical Neuroscience, 45, 110-114, 2017 | No relevant outcomes were identified |
| Moore, J. L., McAuley, J. W., Mott, D., Reeves, A. L., Bussa, B., Referral characteristics of primary care physicians for seizure patients, Epilepsia, 41, 744-748, 2000 | No relevant outcomes were identified |
| Moran, N., Poole, K., Bell, G., Solomon, J., Kendall, S., McCarthy, M., McCormick, D., Nashef, L., Johnson, A., Sander, J., Shorvon, S., NHS services for epilepsy from the patient's perspective: a survey of primary, secondary and tertiary care access throughout the UK, Seizure, 9, 559-65, 2000 | No relevant outcomes were identified |
| Nolan, B., Plenk, K., Carr, D., Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis presenting to the emergency department with status epilepticus, Canadian Journal of Emergency Medicine, 16, 425-428, 2014 | Study design does not meet inclusion criteria: case study |
| Rana, K. S., Roy, S., Singh, D., Incidence and profile of intractable epilepsies in a pediatric neurology referral center, Journal of Pediatric Epilepsy, 1, 243-248, 2012 | Criteria for referral was not reported |
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| Study | Reason for Exclusion |
|---|---|
| W. O., Aldenkamp, A. P., Cryptogenic localization related epilepsy in children from a tertiary outpatient clinic: Is neurological and neuropsychological outcome predictable?, Clinical Neurology and Neurosurgery, 109, 422-430, 2007 | |
| Ristic, A. J., Sokic, D. V., Trajkovic, G., Jankovic, S., Vojvodic, N. M., Bascarevic, V., Popovic, L. M., Long-term survival in patients with status epilepticus: A tertiary referral center study, Epilepsia, 51, 57-61, 2010 | Criteria for referral was not reported |
| Sakpichaisakul, K., Saengow, V. E., Trenavit, P., Prolonged Convulsive Status Epilepticus in Thai Children: Mortality Rate and its Predictors, Journal of Pediatric Epilepsy, 6, 174-181, 2017 | Criteria for referral was not reported |
| Scevola, L., Sarudiansky, M., Lanzillotti, A., Oddo, S., Kochen, S., D'Alessio, L., To what extent does depression influence quality of life of people with pharmacoresistant epilepsy in Argentina?, Epilepsy and Behavior, 69, 133-138, 2017 | Criteria for referral was not reported |
| Seyer, F., Witt, J. A., Taube, J., Helmstaedter, C., The efficacy of a short-term multidisciplinary epilepsy program, Epilepsy and Behavior, 86, 98-101, 2018 | Criteria for referral was not reported |
| Stone, J., Carson, A., Duncan, R., Roberts, R., Warlow, C., Hibberd, C., Coleman, R., Cull, R., Murray, G., Pelosi, A., Cavanagh, J., Matthews, K., Goldbeck, R., Smyth, R., Walker, J., Sharpe, M., Who is referred to neurology clinics? - The diagnoses made in 3781 new patients, Clinical Neurology and Neurosurgery, 112, 747-751, 2010 | Study population does not meet inclusion criteria: mixed population |
| Thomas, S. V., Reghunath, B., Sankara Sarma, P., Mortality among epilepsy patients attending a tertiary referral center in a developing country, Seizure, 10, 370-373, 2001 | Criteria for referral was not reported |
| Uijl, S. G., Leijten, F. S., Parra, J., Arends, J. B., van Huffelen, A. C., Moons, K. G., What is the current evidence on decision-making after referral for temporal lobe epilepsy surgery? A review of the literature, Seizure, 14, 534-40, 2005 | Study design does not meet inclusion criteria: literature review. No relevant outcomes were reported |
| Uldall, P., Alving, J., Hansen, L. K., Kibaek, M., Buchholt, J., The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events, Archives of Disease in Childhood, 91, 219-221, 2006 | Study population does not meet inclusion criteria: mixed population |

### Economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

# Appendix L – Research recommendations

## Research recommendations for review question: What are the criteria for referral to specialist services?

No research recommendations were made for this review question.