National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults: diagnosis and management

[10] Evidence review: Anti-seizure medications for Repetitive/cluster seizures: Monotherapy and add-on therapies

NICE guideline

Evidence reviews underpinning recommendations 7.2.1 – 7.2.4 and a research recommendation in the NICE guideline.

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Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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1 Anti-seizure medications for repetitive/cluster seizures: Monotherapy and add-on therapies

1.1 Introduction

People with recurrent, prolonged or continuous seizures require urgent intervention to limit their risk of neurological harm and death Adherence to standard management protocols, including early intervention, is important to improve outcomes for repetitive/cluster seizures in adults and children. Such protocols need to be individualised and built upon the best evidence to guide the most effective and timely interventions in both community and hospital settings.

1.2 Review question: What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?

1.2.1 PICO table

For full details, see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Inclusion: children, young people and adults with acute repetitive seizures or clusters over a number of hours or days Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
Interventions	Brivaracetam Carbamazepine Chloral hydrate (trichlophos) Clobazam Clonazepam Diazepam Fenfluramine Levetiracetam Lorazepam Midazolam Nitrazepam Oxygen Paraldehyde Phenytoin Steroids / adrenocorticotropic hormone (ACTH) Topiramate Valproate (sodium valproate / valproic acid) Vigabatrin
Comparisons	Drug vs placebo/no treatment One drug vs another drug

Outcomes	**Critical**
	• mortality (including SUDEP)
	• time to seizure cessation, within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours 1 week
	• time to event seizure cessation
	• quality of life (QOLIE-31, QOLIE-AD-48)
	• length of hospital stay
	• adverse events
	  ○ respiratory depression
	  ○ hypotension
	  ○ frequency of endotracheal intubation
	  ○ ICU admission
	  ○ neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance
	• healthcare resource use

Study design	RCTs. Systematic reviews of RCTs. Non-randomised studies will be excluded as it is anticipated there will be sufficient RCTs evidence.

1.2.2 Clinical evidence

1.2.2.1 Included studies

Two studies were included in the review;[33, 48] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). Evidence was found for rectal diazepam versus placebo in people with convulsive seizures. Both studies were conducted in adults and children.

See also the study selection flow chart in Appendix C: section C.1, study evidence tables in Appendix D: section D.1, forest plots in Appendix E: section E.1 and GRADE tables in Appendix F: section F.1.

1.2.2.2 Excluded studies

See the excluded studies list in Appendix I:.

1.2.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention	Comparison	Population Age Top 3 reasons for SE	Outcomes	Comments
Cereghino, 1998[33] USA	Rectal Diazepam: Child and adult syringes were available in 3- and 5-ml sizes respectively and contained either 5 mg or 10 mg of diazepam in the child syringe. Or 10, 15 or 20 mg diazepam in the adult syringe. n=56	Placebo: Child and adult syringes were available in 3- and 5-ml sizes respectively and contained either 5 mg or 10 mg of placebo in the child syringe. Or 10, 15 or 20 mg placebo in the adult syringe. n=58	Children and adults ≥ 2 to <6 years = 25 ≥6 to <12 years = 25 ≥12 years = 64 No seizure cause information given	Seizure free at 12 hours Patients who required additional emergency treatment	No information given on setting
Dreifuss 1998[48] USA	Rectal Diazepam: 0.5 mg/kg of body weight for children 2 to 5 years of age, 0.3 mg /kg for children 6 to 11 years of age, and 0.2 mg/kg for patients 12 or older. n=64	Placebo: identical-looking placebo were supplied by the manufacturer in 2 ml syringes containing 0.5, 1.0, or 1.5 ml and 5 ml syringes containing 2.0, 2.5, 3.0, 3.5, or 4.0 ml. n=61	Children and adults (median age) Diazepam (8 years and 23 years) Placebo (8 years and 20.5 years) No seizure cause information given	Seizure free at 12 hours Adverse events	No information given on setting

See Appendix D: section D.1 for full evidence tables.

1.2.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: diazepam versus placebo

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Diazepam (95% CI)
Seizure free at 12 hours	205 (2 studies) 12 hours	MODERATE[1] due to risk of bias	RR 1.96 (1.4 to 2.75)	298 per 1000	286 more per 1000 (from 119 more to 522 more)
Nervous system adverse effects (including Abnormal coordination, Dizziness, Euphoria, Nervousness, Somnolence)	91 (1 study)	LOW[1] due to risk of bias	RR 3.07 (1.54 to 6.09)	174 per 1000	360 more per 1000 (from 94 more to 885 more)
Patients who required additional emergency treatment	114 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.44 (0.12 to 1.63)	121 per 1000	68 fewer per 1000 (from 106 fewer to 76 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See Appendix F: section F.1 for full GRADE tables.

1.2.5 Economic evidence

1.2.5.1 Included studies

No health economic studies were included.

1.2.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G: section **Error! Reference source not found.**.

1.2.6 Health economic modelling

This area was not prioritised for a new cost-effectiveness analysis.

1.2.7 Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness. The drugs reported in the included clinical evidence are reported here for an illustration of unit costs.

Table 4: UK costs of drugs used for Status Epilepticus

Drug	Description	Cost	Dose	Cost per dose	Cost source
Diazepam					
Rectal	10mg/2.5ml 5 tubes	£5.90	10mg	£1.48	BNF (drug tariff price)

Source: BNF Drug Tariff price, 21/02/20[21]. Sources of doses from the review.

1.2.8 Evidence statements

1.2.8.1 Clinical evidence statements

None.

1.2.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.3 Review question: What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?

1.3.1 PICO table

For full details, see the review protocol in Appendix A: section A.2.

Table 5: PICO characteristics of review question

Population	Inclusion: children, young people and adults with acute repetitive seizures or clusters over a number of hours or days who have not responded to first-line therapy

	Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
Interventions	Brivaracetam Carbamazepine Clobazam Clonazepam Diazepam Lacosamide Levetiracetam Lorazepam Midazolam Oxygen Paraldehyde Perampanel Phenytoin Steroids/ACTH Topiramate Valproate (sodium valproate / valproic acid) Vigabatrin Zonisamide
Comparisons	First-line drug vs same first-line add-on drug First-line drug plus add-on drug vs same first-line drug and different add-on drug Add-on drug vs failure on initial therapeutic management (for example 2 drugs previously administered)
Outcomes	**Critical** • Mortality (including SUDEP) • time to seizure cessation, within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours 1 week • time to event seizure cessation • quality of life (QOLIE-31, QOLIE-AD-48) • length of hospital stay • adverse events o respiratory depression o hypotension o frequency of endotracheal intubation o ICU admission o neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance • healthcare resource use
Study design	RCTs Systematic reviews of RCTs Non-randomised studies will be excluded as it is anticipated there will be sufficient RCTs evidence.

1.3.2 Clinical evidence

1.3.2.1 Included studies

Two studies were included in the review[49, 58] and these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). Evidence was found for diazepam, levetiracetam, midazolam, and phenytoin. One study was conducted in children and the second in adults. Both studies were in adults or children with convulsive epilepsy. No evidence could be pooled as no two studies reported on the same outcome for the same comparison.

See also the study selection flow chart in Appendix C: section C.2, study evidence tables in Appendix D: section D.2, forest plots in Appendix E: section E.2 and GRADE tables in Appendix F: section F.2.

1.3.2.2 Excluded studies

See the excluded studies list in Appendix I:.

1.3.3 Summary of clinical studies included in the evidence review

Table 6: Summary of studies included in the evidence review

Study	Intervention	Comparison	Population Age Top 3 reasons for SE	Outcomes	Comments
Fa Yyazi 2012[49] Iran	Intravenous midazolam: administered as an intravenous bolus dose (0.2 mg/kg), followed by continuous intravenous infusion (1-10 µg/kg per min) n=18	Intravenous diazepam: administered every 3 hours (0.2 mg /kg) n=20	Children (age range: 6 months to 15 years) Midazolam Idiopathic epilepsy: 39% Cryptogenic epilepsy: 5% Symptomatic epilepsy: 56% Diazepam Idiopathic epilepsy:45% Cryptogenic epilepsy: 15% Symptomatic epilepsy: 40%	Complete response to treatment for at least 48 hours Hospital stay Paediatric intensive care unit stay	Paediatric Intensive Care Unit (PICU) Inclusion criteria for the study stated only the patients who completely received first- and second line anticonvulsant medications based on their hospital's protocol for convulsive status epilepticus (i.e., refractory status epilepticus)
Gujjar 2017[58] Oman	Intravenous levetiracetam: 30 mg/kg over 30 min Maintenance treatment of 1 to 1.5 gm bid, starting 12 hours after first dose	Intravenous phenytoin: 20 mg/kg at a maximum rate of 50 mg/min Maintenance treatment of 300 mg/day 24 hours after initial dose	Adults Levetiracetam Epilepsy: 68.4% Remote symptoms: 21.1% Acute symptoms: 10.5%	Mortality after prolonged ICU stay Cessation of SE within 24 hours Good outcome at discharge mRS score	ED/high-dependence unit/ICU All patients received lorazepam (4 mg) or diazepam (5-10 mg) over 2 min, if seizure persisted patients were labelled as refractory

Study	Intervention	Comparison	Population Age Top 3 reasons for SE	Outcomes	Comments
	n=38	n=25	Phenytoin Epilepsy: 56% Remote symptoms: 16% Acute symptoms: 28%		

See Appendix D: for full evidence tables.

1.3.4 Quality assessment of clinical studies included in the evidence review

Table 7: Clinical evidence summary: Levetiracetam versus phenytoin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Phenytoin	Risk difference with Levetiracetam (95% CI)
Mortality after prolonged ICU stay	63 (1 study)	LOW[1] due to imprecision	Peto OR 0.08 (0 to 4.42)	40 per 1000	40 fewer per 1000 (from 140 fewer to 60 more)
Seizure cessation within 24 hours	63 (1 study) 24 hours	MODERATE[1] due to imprecision	RR 1.02 (0.8 to 1.31)	800 per 1000	16 more per 1000 (from 160 fewer to 248 more)
Good outcome at discharge: mRS	63 (1 study)	MODERATE[1] due to imprecision	RR 1.41 (0.96 to 2.07)	560 per 1000	230 more per 1000 (from 22 fewer to 599 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 8: Clinical evidence summary: midazolam versus diazepam

Outcomes	*No of Participants (studies) Follow up*	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Diazepam	Risk difference with Midazolam (95% CI)
Complete response to treatment (for at least 48 hours)	38 (1 study) 48 hours	LOW[1,2] due to risk of bias, imprecision	RR 1.33 (0.77 to 2.3)	500 per 1000	165 more per 1000 (from 115 fewer to 650 more)
Hospital stay (days)	38 (1 study)	LOW[1,2] due to risk of bias, imprecision		The mean hospital stay (days) in the control groups was 11.1 days	The mean hospital stay (days) in the intervention groups was 4.73 higher (2.77 lower to 12.23 higher)
Paediatric Intensive Care Unit stay (days)	38 (1 study)	LOW[1,2] due to risk of bias, imprecision		The mean paediatric intensive care unit stay (days) in the control groups was 3.2 days	The mean paediatric intensive care unit stay (days) in the intervention groups was 7.69 higher (2.58 to 12.8 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See Appendix F: for full GRADE tables.

1.3.5 Economic evidence

1.3.5.1 Included studies

No health economic studies were included.

1.3.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.3.6 Health economic modelling

This area was not prioritised for a new cost-effectiveness analysis.

1.3.7 Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness. The most commonly used drugs reported in the included clinical evidence are reported here for an illustration of unit costs.

Other resources may be required, such as an IV line and solution to dilute the drug for infusion.

Table 9: UK costs of drugs used for Status Epilepticus

Drug	Description	Cost	Dose	Cost per dose	Cost source
Phenytoin					
Solution for injection	250mg/5ml 5 ampoules	£3.37	1g	£2.69	eMIT
Leveritacetam					
Solution for injection	500mg/5ml 10 infusion vials	£28.37	2g – 4g	£11.35 - £22.69	eMIT
Diazepam					
Solution for injection	10mg/2ml 10 ampoules	£3.95	10mg[(a)]	£0.40	eMIT
Buccal midazolam					
Solution for injection	10mg/5ml 10 ampoules	£7.26	10mg[(a)]	£0.73	BNF

Sources: Electronic Market Information Tool (eMIT), 09/01/20[41], British National Formulary (BNF)[21], 13/07/21.Sources of doses from the committee.

(a) 10mg and then an additional 10mg if required. Cost is presented for 10mg

1.3.8 Evidence statements

1.3.8.1 Clinical evidence statements

None.

1.3.8.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.4 Committee's discussion of the evidence

The summarised discussion of this evidence can be found in evidence review 09.

1.5 Recommendations supported by this evidence review

This evidence review supports recommendations 7.2.1 – 7.2.4 and the research recommendation on the effectiveness of anti-seizure drugs (monotherapy or add-on) in the treatment of repeated or cluster seizures.

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Appendices

Appendix A: Review protocols

A.1 Clinical review protocol: Monotherapy

Table 10: Review protocol: monotherapy treatment for repeated seizures of clusters of seizures

ID	Field	Content
1.	Review title	What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?
2.	Review question	What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?
3.	Objective	Some people with epilepsy can have repeated seizures or clusters of events which may, or may not, be triggered by stimuli such as fever. Such events are differentiated from status epilepticus as there is recovery in between the individual seizures. In this review we aim to determine if there is evidence to support the usage of specific medications to acutely abort repetitive seizures or clusters of seizures and the impact this may have on overall seizure control/the epilepsy as a whole.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Repeated seizures or cluster seizures are serious medical events and as such considered medical emergencies. They require medication as soon as possible.
6.	Population	Inclusion: children, young people and adults with acute repetitive seizures or clusters over a number of hours or days Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention/Exposure/Test	Brivaracetam Carbamazepine Chloral hydrate (trichlophos) Clobazam Clonazepam Diazepam Fenfluramine Levetiracetam Lorazepam Midazolam Nitrazepam Oxygen Paraldehyde Phenytoin Steroids / adrenocorticotropic hormone (ACTH) Topiramate Valproate (sodium valproate / valproic acid) Vigabatrin

8.	Comparator/Reference standard/Confounding factors	Drug vs placebo/no treatment One drug vs another drug
9.	Types of study to be included	RCTs Systematic reviews of RCTs Non-randomised studies will be excluded as it is anticipated there will be sufficient RCTs evidence
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
11.	Context	There is no definitive clinical definition for a cluster or series of seizures. Studies examining clinically defined seizure clustering patterns have used varying empiric definitions, including two to four seizures per <48 hours, 3 seizures per 24 hours or two generalized tonic–clonic or three complex partial seizures in 4 hours. Nonspecific definitions, such as "those having several convulsions within a day or two," have also been described. Seizure clusters, while not as life threatening as status epilepticus have a significant impact on patient health and well-being. Clusters frequently result in emergency department visits and, if left untreated, have been reported to evolve into status epilepticus.
12.	Primary outcomes (critical outcomes)	• mortality (including SUDEP) • time to seizure cessation, within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours 1 week • time to event seizure cessation • quality of life (QOLIE-31, QOLIE-AD-48) • length of hospital stay • adverse events – respiratory depression – hypotension – frequency of endotracheal intubation – ICU admission – neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance • healthcare resource use

13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was 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/

<table>
<tr><td></td><td></td><td colspan="3">• Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.

Heterogeneity between the studies in effect measures will be assessed using the I² statistic and visually inspected. An I² value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">In the presence of heterogeneity, sub-group analysis will be conducted:
1) according to the risk of bias of individual studies
2) by age (older people/adults/children)
3) study location (UK, US, Europe and rest of the world)
4) route of administration
5) drug dose</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
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<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
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<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td rowspan="4">23.</td><td rowspan="4">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
</table>

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact Angela Cooper National Guideline Centre Angela.cooper@rcplondon.ac.uk 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	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.	
28.	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/indevelopment/gid-ng10112	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • 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.	
32.	Keywords	Epilepsy, repeated seizures, clusters, anti-epileptic drugs	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		

36.	Details of final publication	www.nice.org.uk

A.2 Clinical review protocol: Add on therapies

Table 11: Review protocol: add on therapy for treatment of repeated seizures or clusters of seizures

ID	Field	Content
1.	Review title	What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?
2.	Review question	What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?
3.	Objective	Some people with epilepsy can have repeated seizures or clusters of events which may, or may not, be triggered by stimuli such as fever. Such events are differentiated from status epilepticus as there is recovery in between the individual seizures. However, some people do not respond to first line therapy. In this review we aim to determine if there is evidence to support the usage of specific add-on medications to abort/prevent repetitive seizures or clusters of seizures and the impact this may have on overall seizure control/the epilepsy as a whole.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Repeated seizures or cluster seizures are serious medical events and as such considered medical emergencies. They require medication as soon as possible. People can be at risk for repeated clusters or status epilepticus if: • Seizure clusters last longer than normal • Seizures occur closer together • A person doesn't recover as well between seizures or clusters • If rescue medicines given to stop the clusters don't work add-on therapy is required.
6.	Population	Inclusion: children, young people and adults with acute repetitive seizures or clusters over a number of hours or days who have not responded to first line therapy Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention/Exposure/Test	Brivaracetam Carbamazepine Clobazam Clonazepam Diazepam Lacosamide Levetiracetam Lorazepam Midazolam Oxygen Paraldehyde Perampanel Phenytoin Steroids/ACTH Topiramate

		Valproate (sodium valproate / valproic acid) Vigabatrin Zonisamide
8.	Comparator/Reference standard/Confounding factors	First line drug vs same first line add-on drug First line drug plus add-on drug vs same first line drug and different add-on drug Add-on drug vs failure on initial therapeutic management (for example 2 drugs previously administered)
9.	Types of study to be included	RCTs Systematic reviews of RCTs Non-randomised studies will be excluded as it is anticipated there will be sufficient RCTs evidence
10.	Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
11.	Context	There is no definitive clinical definition for a cluster or series of seizures. Studies examining clinically defined seizure clustering patterns have used varying empiric definitions, including two to four seizures per <48 hours, 3 seizures per 24 hours or two generalized tonic–clonic or three complex partial seizures in 4 hours. Nonspecific definitions, such as "those having several convulsions within a day or two," have also been described. Seizure clusters, while not as life threatening as status epilepticus have a significant impact on patient health and well-being. Clusters frequently result in emergency department visits and, if left untreated, have been reported to evolve into status epilepticus. When there is no resolution of seizures with a first drug an additional drug is required.
12.	Primary outcomes (critical outcomes)	• Mortality (including SUDEP) • time to seizure cessation, within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours 1 week • time to event seizure cessation • quality of life (QOLIE-31, QOLIE-AD-48)

		• length of hospital stay
		• adverse events
		  ○ respiratory depression
		  ○ hypotension
		  ○ frequency of endotracheal intubation
		  ○ ICU admission
		  ○ neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance
		• healthcare resource use

13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and

<table>
<tr><td></td><td></td><td colspan="4">imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome.

The risk of bias across all available evidence was 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/
• Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.

Heterogeneity between the studies in effect measures will be assessed using the I² statistic and visually inspected. An I² value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects.</td></tr>
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<tr><td>☐</td><td colspan="3">Diagnostic</td></tr>
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<tr><td>☐</td><td colspan="3">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="3">Other (please specify)</td></tr>
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<tr><td>19.</td><td>Language</td><td colspan="4">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="4">England</td></tr>
<tr><td>23.</td><td></td><td>Review stage</td><td colspan="2">Started</td><td>Completed</td></tr>
</table>

	Stage of review at time of this submission	Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact Angela Cooper National Guideline Centre Angela.cooper@rcplondon.ac.uk 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

27.	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.	
28.	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/indevelopment/gid-ng10112	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • 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.	
32.	Keywords	Epilepsy, repeated seizures, clusters, anti-epileptic drugs	
33.	Details of existing review of same topic by same authors		
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published

		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

A.3 Economic review protocol

Table 12: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[123] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The search strategy will be added here after rerun searches have been conducted.

This literature search strategy was used for the following reviews:

- What AEDs (monotherapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What AEDs (add-on therapy) are effective in the treatment of repeated seizures or clusters of seizures?
- What antiepileptic drugs (monotherapy) are effective in the treatment of status epilepticus?
- What antiepileptic drugs (add-on therapy) are effective in the treatment of status epilepticus?
- What AEDs (monotherapy) are effective in the treatment of prolonged seizures?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[123]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 13 May 2021	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue 5 of 12 CENTRAL to 2021 Issue 5 of 12	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.

6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	exp Anticonvulsants/
28.	exp Acetazolamide/
29.	exp Carbamazepine/
30.	exp Chloral hydrate/
31.	exp Clomethiazole/
32.	exp Clonazepam/
33.	exp Clorazepate Dipotassium/
34.	exp Diazepam/
35.	exp Ethosuximide/
36.	exp Levetiracetam/
37.	exp Lorazepam/
38.	exp Mephenytoin/
39.	exp Mephobarbital/
40.	exp Midazolam/
41.	exp Methazolamide/
42.	exp Nitrazepam/
43.	exp Paraldehyde/
44.	exp Pentobarbital/
45.	exp Phenobarbital/
46.	exp Phenytoin/
47.	exp Primidone/
48.	exp Propofol/
49.	exp Temazepam/
50.	exp Thiopental/
51.	exp Topiramate/
52.	exp Trimethadione/

53.	exp Valproic Acid/
54.	exp Vigabatrin/
55.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
56.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
57.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
58.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
59.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
60.	hyperbaric oxygen.ti,ab.
61.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
62.	*Adrenal Cortex Hormones/ or *adrenocorticotropic hormone/ or *cosyntropin/
63.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
64.	or/27-63
65.	randomized controlled trial.pt.
66.	controlled clinical trial.pt.
67.	randomi#ed.ti,ab.
68.	placebo.ab.
69.	randomly.ti,ab.
70.	Clinical Trials as topic.sh.
71.	trial.ti.
72.	or/65-71

73.	Meta-Analysis/
74.	exp Meta-Analysis as Topic/
75.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
76.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
77.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
78.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
79.	(search* adj4 literature).ab.
80.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
81.	cochrane.jw.
82.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
83.	or/73-82
84.	26 and 64
85.	84 and (72 or 83)

1 **Embase (Ovid) search terms**

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	exp Anticonvulsants/
26.	exp Acetazolamide/
27.	exp Carbamazepine/
28.	exp Chloral hydrate/
29.	exp Clomethiazole/

30.	exp Clonazepam/
31.	exp Clorazepate Dipotassium/
32.	exp Diazepam/
33.	exp Ethosuximide/
34.	exp Lorazepam/
35.	exp Mephenytoin/
36.	exp Mephobarbital/
37.	exp Midazolam/
38.	exp Methazolamide/
39.	exp Nitrazepam/
40.	exp Paraldehyde/
41.	exp Pentobarbital/
42.	exp Phenobarbital/
43.	exp Phenytoin/
44.	exp Primidone/
45.	exp Propofol/
46.	exp Temazepam/
47.	exp Thiopental/
48.	exp Topiramate/
49.	exp Trimethadione/
50.	exp Valproic Acid/
51.	exp Vigabatrin/
52.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline).ti,ab.
53.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*).ti,ab.
54.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide).ti,ab.
55.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or

	valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide).ti,ab.
56.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate).ti,ab.
57.	hyperbaric oxygen.ti,ab.
58.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids).ti,ab.
59.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin).ti,ab.
60.	*corticosteroid/ or *tetracosactide/
61.	or/25-60
62.	random*.ti,ab.
63.	factorial*.ti,ab.
64.	(crossover* or cross over*).ti,ab.
65.	((doubl* or singl*) adj blind*).ti,ab.
66.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
67.	crossover procedure/
68.	single blind procedure/
69.	randomized controlled trial/
70.	double blind procedure/
71.	or/62-70
72.	systematic review/
73.	meta-analysis/
74.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
75.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
76.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
77.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
78.	(search* adj4 literature).ab.
79.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
80.	cochrane.jw.
81.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
82.	or/72-81
83.	24 and 61
84.	83 and (71 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] explode all trees
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] explode all trees
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #1-#5)
#7.	MeSH descriptor: [Anticonvulsants] explode all trees

#8.	MeSH descriptor: [Acetazolamide] explode all trees
#9.	MeSH descriptor: [Carbamazepine] explode all trees
#10.	MeSH descriptor: [Chloral Hydrate] explode all trees
#11.	MeSH descriptor: [Chlormethiazole] explode all trees
#12.	MeSH descriptor: [Clonazepam] explode all trees
#13.	MeSH descriptor: [Clorazepate Dipotassium] explode all trees
#14.	MeSH descriptor: [Diazepam] explode all trees
#15.	MeSH descriptor: [Ethosuximide] explode all trees
#16.	MeSH descriptor: [Lorazepam] explode all trees
#17.	MeSH descriptor: [Mephenytoin] explode all trees
#18.	MeSH descriptor: [Mephobarbital] explode all trees
#19.	MeSH descriptor: [Midazolam] explode all trees
#20.	MeSH descriptor: [Methazolamide] explode all trees
#21.	MeSH descriptor: [Nitrazepam] explode all trees
#22.	MeSH descriptor: [Paraldehyde] explode all trees
#23.	MeSH descriptor: [Pentobarbital] explode all trees
#24.	MeSH descriptor: [Phenobarbital] explode all trees
#25.	MeSH descriptor: [Phenytoin] explode all trees
#26.	MeSH descriptor: [Primidone] explode all trees
#27.	MeSH descriptor: [Propofol] explode all trees
#28.	MeSH descriptor: [Temazepam] explode all trees
#29.	MeSH descriptor: [Thiopental] explode all trees
#30.	MeSH descriptor: [Topiramate] explode all trees
#31.	MeSH descriptor: [Trimethadione] explode all trees
#32.	MeSH descriptor: [Valproic Acid] explode all trees
#33.	MeSH descriptor: [Vigabatrin] explode all trees
#34.	(antiepilep* or anti-epilep* or anticonvulsant* or AED*1 or Acetazolamide or Alodorm or Antilepsin or Arem or Ativan or Barbexaclone or Beclamide or Brivaracetam or Carbagen or Carbamazepine or Celontin or Cerebyx or Chlonazepam or Chloracon or Cloazepam or Clobazam or Clonazepamum or Clonex or Clonopin or Clorazepate or Convulex or Depacon or Depak* or Depamide or Desitin or Diacomit or Diamox or Diastat or Diazepam or Dilantin or Diphenin* or Diphenylhydantoin or Divalpr* or Dormicum or Ecovia or Emeside or Epanutin or Epiject or Epilim or Episenta or Epival or Eptoin or Ergenyl or Erimin or Eslicarbazepine or Ethadione or Ethosuximide or Ethotoin or Ethylphenacemide or Exalief or Excegran or Ezogabine or Fanatrex or Felbamate or Felbatol or Fosphenytoin or Frisium or Fycompa or Gabapentin or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Halogabide or Halogenide or Hibicon or Hypnovel or Iktorivil or Inovelon or Insoma or Intensl or isoflurane or Keppra or Klonopin or Kriadex or Lacosamide or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigine or Lamotrine or Landsen or Levetiracetam or Liskantin or Loraz or Lorazepam or Losigamone or Luminal or Lyrica or Mebaral or Mephenytoin or Mephobarbit* or Mephyltaletten or Mesantoin or Mesuximide or Methazolamide or Methsuximide or Methylphenobarbit* or Midazolam or Mogadon or Mylepsinum or Mysoline):ti,ab
#35.	(neogab or neptazane or neurontin or nimetazepam or nitrados or nitrazadon or nitrazepam or normison or novo-clopate or nupentin or nydrane or onfi or ofiril or orlept or ormodon or ospolot or oxcarbazepine or pacisyn or paraldehyde or paramethadione or paxadorm or paxam or peganone or pentobarbital or perampanel or petinutin or petril or phemiton or phenacemide or pheneturide or phenobarbit*):ti,ab
#36.	(Phenusuximide or phenytek or phenytoin or posedrine or potiga or pregabalin or primidone or prodilantin or progabide or prominal or propofol or prysoline or ravotril or remacemide or remnos or resimatil or restoril or retigabine or rivotril or rufinamide):ti,ab

#37.	(sabril or seclar or selenica or seletracetam or sertan or somnite of stavzor or stedesa or stiripentol or sulthiam* or sultiam* or talampanel or tegretol or temazepam or temesta or teril or thiopental or tiagabine or timonil or topamax or topiramate or tranzene or tridione or trileptal or trimethadione of trobalt or urbanol or valance or valcote or valium or valnoctamide or valparin or valpro* or versed or vigabatrin or vimpat or zalkote or zarontin or zebinix or zonegran or zonisamide):ti,ab
#38.	(benzodiaz* or chloral hydrate or clomethiazole or dexmedetomidine or melatonin or meprobamate or zolpidem or tartrate or zopiclone or diazolam or desflurane or methoxyflurane or nitrous oxide or sevoflurane or leviracetam or alprazolam or chlordiazepoxide or hydrochloride or flurazepam or loprazolam or lormetazepam or oxazepam or etomidate):ti,ab
#39.	hyperbaric oxygen:ti,ab
#40.	(Hydrocortisone or prednisolone or dexamethasone or methylprednisolone or corticosteroids):ti,ab
#41.	(Adrenocorticotropic hormone or adrenocorticotropin or corticotropin or cosyntropin or tetracosactrin):ti,ab
#42.	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#43.	MeSH descriptor: [Adrenocorticotropic Hormone] explode all trees
#44.	MeSH descriptor: [Cosyntropin] explode all trees
#45.	(or #7-#44)
#46.	#6 and #45

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/

5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.

49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

1 **Embase (Ovid) search terms**

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/

29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

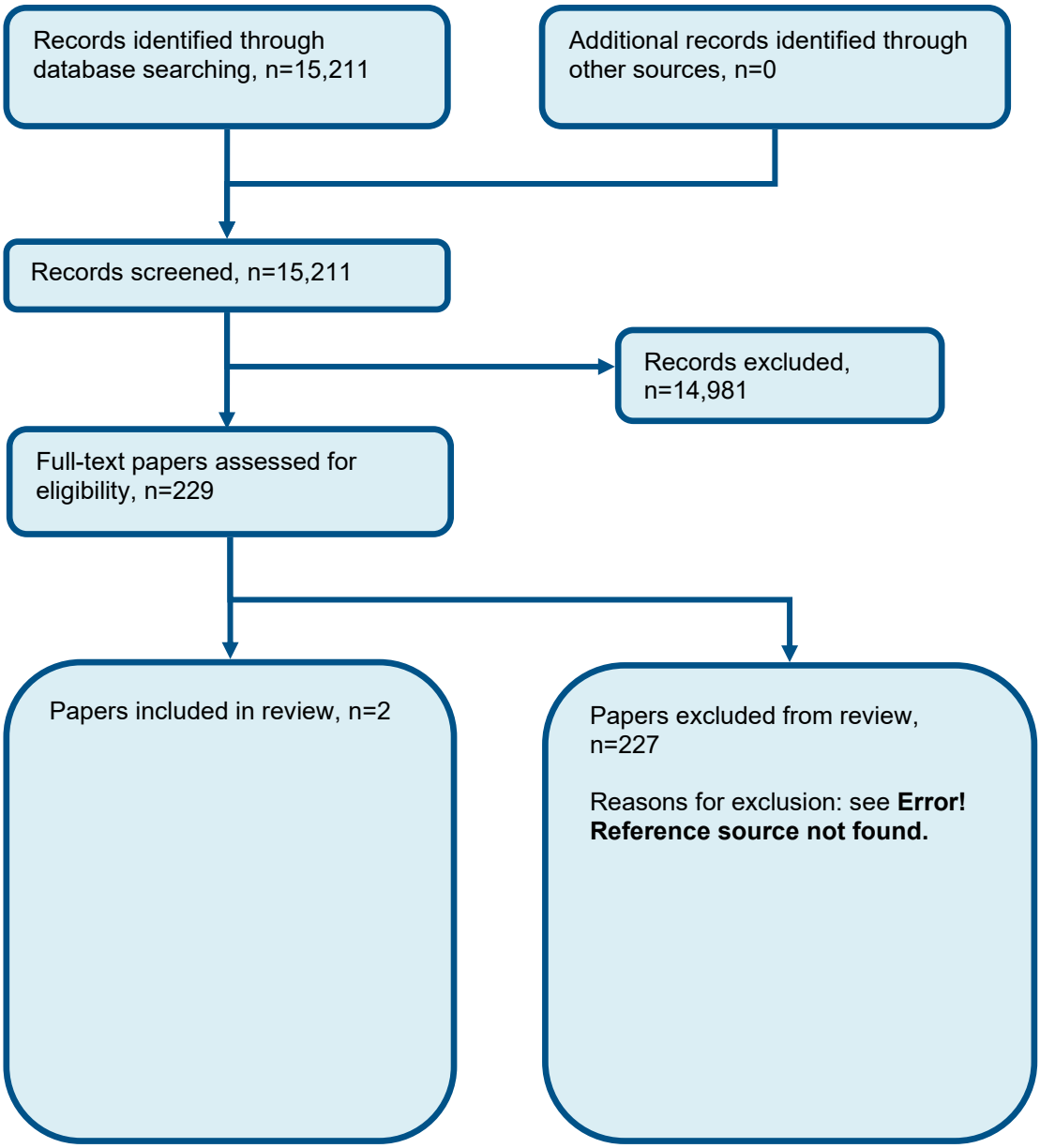
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

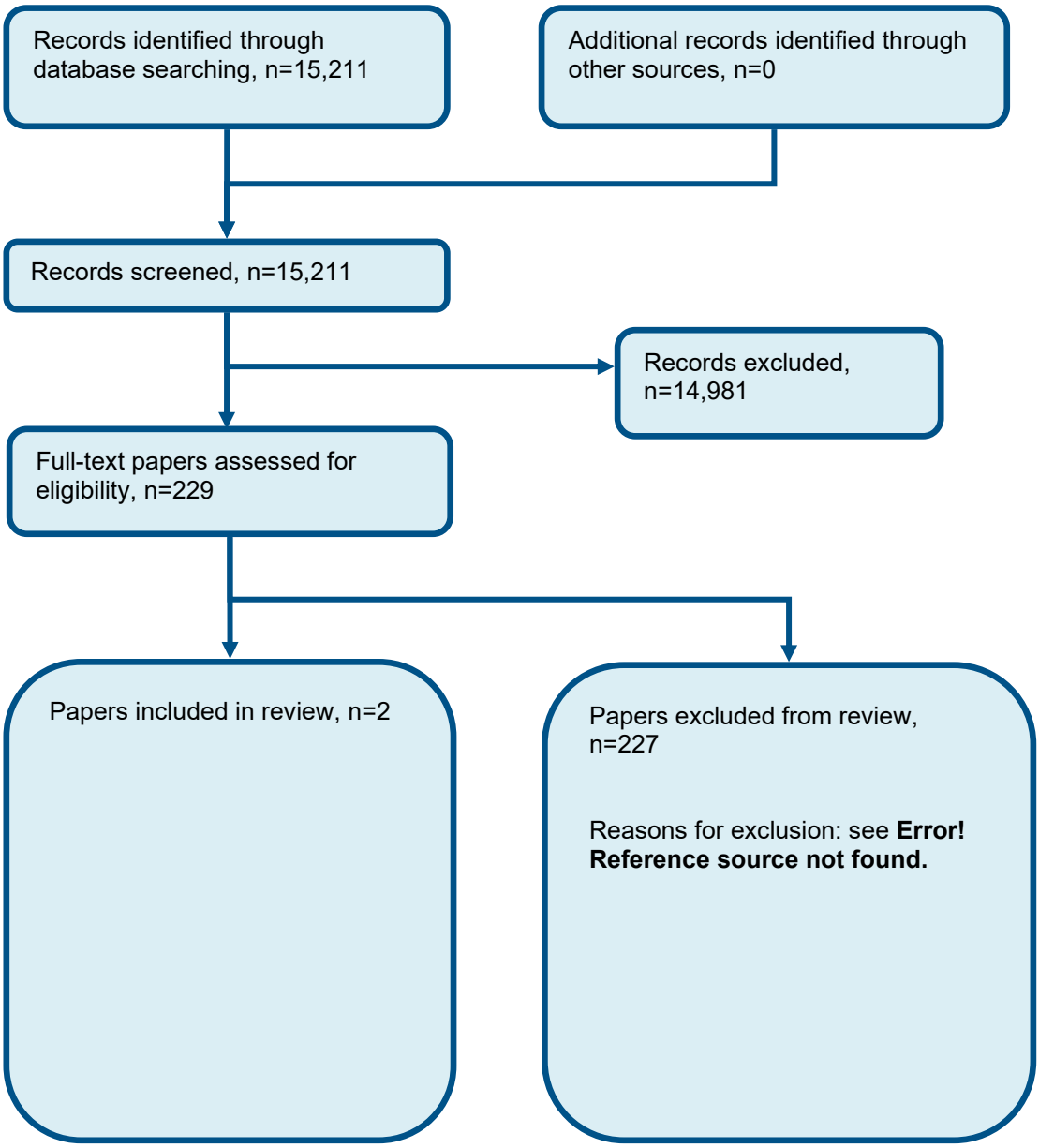
2
3

Appendix C: Evidence selection

C.1 Clinical evidence selection: Monotherapy



C.2 Clinical evidence selection: Add on therapies



Appendix D: Evidence tables

D.1 Clinical evidence tables: Monotherapy

Study	**Cereghino 1998[33]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=114)
Countries and setting	Conducted in USA: Setting not given
Line of therapy	1st line
Duration of study	Intervention + follow up: 72 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients or institutionalized patients aged 2 years or older with a documented history of ARS were selected for study. The epileptic seizure could be primary generalised, complex partial with or without becoming secondarily generalised or simple partial with a motor component as defined in the International classification of seizures. At least 2 episodes of ARS must have occurred within 1 year and one episode within 6 months of study entry. All concomitant AEDs had to remain at the same dosage for 2 weeks before study entry and could not be increased during the study.
Exclusion criteria	Patients who progressed habitually to status epilepticus despite therapeutic intervention were excluded. Patients who had received another investigational medication or device within 30 days of study entry were excluded.
Age, gender and ethnicity	Age - Other: ≥ 2 to <6 = 25, ≥6 to <12 = 25, ≥12 = 64. Gender (M:F): 57 male, 57 female. Ethnicity: 96 white, 8 black, 10 other

Study	**Cereghino 1998[33]**
Further population details	
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Drug - Diazepam. Diazepam - single administration of Diastat brand. Child and adult syringes were available in 3- and 5-ml sizes respectively and contained either 5 mg or 10 mg of diazepam or placebo in the child syringe. Or 10, 15 or 20 mg diazepam or placebo in the adult syringe. The prefilled syringes were packaged identically and supplied with a rectal tip and water-soluble lubricant. The target dose was based on patient age and weight, and the n rounded up. Duration N/A. Concurrent medication/care: Caregivers were instructed by use of video tape and illustrated written material on the paper methods of rectal administration and monitoring or patient respiration and response. Nurses maintained telephone contact with a caregiver every 2 weeks until an ARS episode occurred to review recognition, treatment and documentation of the event. Caregivers were seen every 3 months by the same nurse coordinator for review of training. 24-hour phone coverage was available. Seizure counts were initiated 15 mins after treatment and the observation period continued for 12 hours. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=58) Intervention 2: Placebo. Placebo - Child and adult syringes were available in 3- and 5-mL sizes respectively and contained either 5 mg or 10 mg of diazepam or placebo in the child syringe. Or 10, 15 or 20 mg diazepam or placebo in the adult syringe. The prefilled syringes were packaged identically and supplied with a rectal tip and water-soluble lubricant. The target dose was based on patient age and weight, and the n rounded up. Duration N/A. Concurrent medication/care: Caregivers were instructed by use of video tape and illustrated written material on the paper methods of rectal administration and monitoring or patient respiration and response. Nurses maintained telephone contact with a caregiver every 2 weeks until an ARS episode occurred to review recognition, treatment and documentation of the event. Caregivers were seen every 3 months by the same nurse coordinator for review of training. 24-hour phone coverage was available. Seizure counts were initiated 15 mins after treatment and the observation period continued for 12 hours. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Academic or government funding (Supported by a grant from Athena Neurosciences, Inc.)

Study	**Cereghino 1998[33]**
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus PLACEBO Protocol outcome 1: Time to seizure cessation, (within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours to 1 week) at Define - Actual outcome: Seizure free at 12 hours at 12 hours; Group 1: 31/56, Group 2: 20/58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: No details on cause of seizure; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Healthcare resource use at Define - Actual outcome: Patients who required additional emergency treatment at N/A; Group 1: 3/56, Group 2: 7/58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: No details on cause of seizure; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) at Define; Time to event seizure cessation at Define; Quality of life at Define; Length of hospital stay at Define; mean Glasgow outcome scale (% difference in the means between the two groups at Define; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at Define

1

Study	**Dreifuss 1998[48]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=125)
Countries and setting	Conducted in USA: Setting not given
Line of therapy	1st line
Duration of study	Intervention + follow up: 72 hours follow up

Study	Dreifuss 1998[48]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least four episodes of acute repetitive seizures during the preceding year and at least one in the preceding three months, acute repetitive seizures defined as an episode of multiple complex partial or generalized (tonic, clonic, tonic– clonic, atypical absence, or myoclonic) seizures occurring within a 24-hour period in adults or a 12-hour period in children, with a pattern distinguishable from the patient's usual seizure pattern, and with onset readily recognizable by a care giver, such as a parent, on a stable antiepileptic regimen for at least four weeks before enrolment
Exclusion criteria	Plasma phenobarbital concentrations greater than 30 mg/l (130 µmol/l), current treatment with drugs other than anticonvulsants, long-term use of benzodiazepines, use of central nervous system depressants or drugs interacting with diazepam, more than one previous treatment with rectal diazepam, nonepileptic seizures within the preceding five years, habitual progression to status epilepticus, clinically significant psychiatric disorder, lack of a suitable care giver, or use of an investigational drug or device within the preceding five months
Age, gender and ethnicity	Age - Median (range): median: Diazepam - 8 years (child), 23 years (adult) Placebo - 8 years (child), 20.5 years (adult). Gender (M:F): Diazepam group: 38/26, placebo group: 32/29. Ethnicity: 97 white, 21 black, 7 other
Further population details	
Indirectness of population	No indirectness
Interventions	(n=64) Intervention 1: Drug - Diazepam. Diazepam - 0.5 mg per kilogram of body weight for children 2 to 5 years of age, 0.3 mg/kg for children 6 to 11 years of age, and 0.2 mg/kg for patients 12 or older. These schedules were based on the results of clinical trials showing that diazepam clearance in children declines until about the age of 12 years, when adult values are reached. A second dose was given four hours after the first, and, for adults, a third dose was given eight hours after the second, since previous studies indicated that these schedules should maintain target plasma diazepam concentrations (150 to 300 mg/ml). Diazepam rectal gel (5 mg/ml) and identical-looking placebo were supplied by the manufacturer in 2 ml syringes containing 0.5, 1.0, or 1.5 ml and 5 ml syringes containing 2.0, 2.5, 3.0, 3.5-, or 4.0-ml. Diazepam doses

Study	Dreifuss 1998[48]
	ranged from 2.5 to 20 mg, in 2.5-mg increments. The doses were rounded up to the nearest 2.5 mg. The medication kits contained two syringes for children and three syringes for adults, with one dose per syringe. A syringe with half the regular dose was available to be used if the regular dose was expelled within five min. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location: (n=61) Intervention 2: Placebo. Placebo - Diazepam rectal gel (5mg/ml) and identical-looking placebo were supplied by the manufacturer in 2 ml syringes containing 0.5, 1.0, or 1.5 ml and 5 ml syringes containing 2.0, 2.5, 3.0, 3.5-, or 4.0-ml. Diazepam doses ranged from 2.5 to 20 mg, in 2.5-mg increments. The doses were rounded up to the nearest 2.5 mg. The medication kits contained two syringes for children and three syringes for adults, with one dose per syringe. A syringe with half the regular dose was available to be used if the regular dose was expelled within five minutes. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: 3. Risk of bias of studies: 4. Route of administration: 5. Study location:
Funding	Other (Supported by contracts with the National Institute of Neurological Disorders and Stroke and Athena Neurosciences.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus PLACEBO

Protocol outcome 1: Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) at Define
- Actual outcome: Nervous system adverse effects (including Abnormal coordination, Dizziness, Euphoria, Nervousness, Somnolence) at N/A; Group 1: 24/45, Group 2: 8/46
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Diazepam/placebo - median body weight; 23.6/22.4 child, 57.1/60.2 adult, male; 38/32, female - 26/29; Group 1 Number missing: 19, Reason: 8 had not yet had an episode of acute repetitive seizures, 11 had been withdrawn before receiving treatment (due to withdrawn consent, lack of a care giver, because of an added investigational drug, because of possible drug allergy, no acute repetitive seizures within a year or lost to follow up); Group 2 Number missing: 15, Reason: 7 had not yet had an episode of acute repetitive seizures, 8 had been withdrawn before receiving treatment (due to withdrawn consent, lack of a care giver, because of an added investigational drug, because of possible drug allergy, no acute repetitive seizures within a year or lost to follow up)

Study	Dreifuss 1998[48]
Protocol outcomes not reported by the study	Mortality (including SUDEP) at Define; Time to seizure cessation, (within 24 hours after drug administration, 24 to 72 hours, greater than 72 hours to 1 week) at Define; Time to event seizure cessation at Define; Quality of life at Define; Length of hospital stay at Define; mean Glasgow outcome scale (% difference in the means between the two groups at Define; Healthcare resource use at Define

D.2 Clinical evidence tables: Add on therapies

Study	Fa Yyazi 2012[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in Iran; Setting: Paediatric Intensive Care Unit (PICU)
Line of therapy	2nd line
Duration of study	Intervention + follow up: 48 hours follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	This study included all admitted children with refractory serial seizures in Mofid hospital, which is a referral centre for paediatric neurological diseases, aged from 6 months to 15 years, from October 2008 to May 2010. The diagnostic

Study	Fa Yyazi 2012[49]
	criteria for refractory serial seizures in this study was defined as four generalized tonic-clonic or complex partial seizures per day with a three-fold increase over usual seizure frequency within a two-day period that received at least two appropriate intravenous, intramuscular or oral antiepileptic drugs with no decrease to less than the pre-treatment level in seizure frequency.
Exclusion criteria	Occurrence of status epilepticus due to convulsive seizure longer than 30 minutes was considered as exclusion criteria, in addition to critical diseases such as meningitis and intracranial haemorrhage.
Age, gender and ethnicity	Age - Range: 6 months to 15 years. Gender (M:F): 18 male, 20 female. Ethnicity: Not stated.
Further population details	1. Age: Children
Indirectness of population	No indirectness
Interventions	(n=18) Intervention 1: Drug - Midazolam. Midazolam - midazolam was administered as an intravenous bolus dose (0.2mg/kg), followed by continuous intravenous infusion (1-10 µg/kg per min). Duration N/A. Concurrent medication/care: All children were monitored for the development of side effects of midazolam and diazepam, such as hypotension and respiratory depression. Routine laboratory examinations and EEG were performed in all patients. Brain CT or MRI was performed if needed. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: N/A 3. Risk of bias of studies: N/A 4. Route of administration: N/A 5. Study location: N/A (n=20) Intervention 2: Drug - Diazepam. Diazepam - intravenous diazepam was administered every 3 hours (0.2 mg /kg). Duration N/A. Concurrent medication/care: All children were monitored for the development of side effects of midazolam and diazepam, such as hypotension and respiratory depression. Routine laboratory examinations and EEG were performed in all patients. Brain CT or MRI was performed if needed. Indirectness: No indirectness Further details: 1. Dose: 2. Non convulsive by type: N/A 3. Risk of bias of studies: N/A 4. Route of administration: N/A 5. Study location: N/A
Funding	Other (The authors were supported by the Paediatric Neurology Research Centre of Shahid Beheshti University of Medical Sciences. Iranian Clinical Trial Registry code: IRCT 20120822106034N1 (www.IRCT.ir).)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIDAZOLAM versus DIAZEPAM Protocol outcome 1: Time to seizure cessation, (within 24hrs after drug administration, 24 to 72 hours, greater than 72 hours to 1 week)	

Study	Fa Yyazi 2012[49]
- Actual outcome: Complete response to treatment (for at least 48 hours) at N/A; Group 1: 12/18, Group 2: 10/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Category of seizure midazolam/diazepam; idiopathic - 7/9, cryptogenic - 1/3, symptomatic - 10/8; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Length of hospital stay - Actual outcome: Hospital stay (days) at N/A; Group 1: mean 15.83 (SD 14.46); n=18, Group 2: mean 11.1 (SD 7.779); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Category of seizure midazolam/diazepam; idiopathic - 7/9, cryptogenic - 1/3, symptomatic - 10/8; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A - Actual outcome: Paediatric Intensive Care Unit stay (days) at N/A; Group 1: mean 10.89 (SD 9.305); n=18, Group 2: mean 3.2 (SD 6.305); n=20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Category of seizure midazolam/diazepam; idiopathic - 7/9, cryptogenic - 1/3, symptomatic - 10/8; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Mortality (including SUDEP) ; Time to event seizure cessation ; Quality of life ; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) ; Healthcare resource use

1

Study	Gujjar 2017[58]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Oman ED/high-dependence unit/ICU
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Study	**Gujjar 2017[58]**
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (>15 years) with cluster seizures defined as recurrent episodes of seizures- two or more over last 24 hours (partial or generalised) with return to consciousness between episodes, with the last episode occurring within 2 hours
Exclusion criteria	Known allergy to drugs used, immediate surgery required, haemodynamic compromise, serious arrhythmias, pregnancy, cardiac failure or pulmonary oedema, in pre terminal states subtle SE, pseudo seizures
Age, gender and ethnicity	Age - Mean (SD): 39.3 (20). Gender (M:F): 44/19. Ethnicity: Not stated
Further population details	1. Age: Adults
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Drug - Levetiracetam. Intravenous levetiracetam: 30 mg/kg over 30 min Duration 30 min. Concurrent medication/care: None stated. Previously all patients received lorazepam (4 mg) or diazepam (5-10 mg) over 2 min. Indirectness: No indirectness Further details: 1. Dose: Define (30 mg/kg over 30 min). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: N/A 4. Route of administration: intravenous 5. Study location: N/A (n=25) Intervention 2: Drug - Phenytoin. Intravenous phenytoin: 20 mg/kg at a maximum rate of 50 mg/min Duration Immediately. Concurrent medication/care: None stated. Previously all patients received lorazepam (4 mg) or diazepam (5-10 mg) over 2 min. Indirectness: No indirectness Further details: 1. Dose: Define (20 mg/kg). 2. Non convulsive by type: Not applicable 3. Risk of bias of studies: Low risk of bias 4. Route of administration: intravenous 5. Study location: N/A
Funding	Academic or government funding (Dean's Fund, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LEVETIRACETAM versus PHENYTOIN Protocol outcome 1: Mortality (including SUDEP) - Actual outcome: At discharge at Discharge; Group 1: 0/38, Group 2: 1/25	

Study	Gujjar 2017[58]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Levetiracetam vs phenytoin: epilepsy- 68.4% vs 56%, remote symptoms- 21.1% vs 16%, acute symptoms- 10.5% vs 28% ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Time to seizure cessation, (within 24hrs after drug administration, 24 to 72 hours, greater than 72 hrs to 1 week) - Actual outcome: Seizure cessation at 24 hour; Group 1: 16/38, Group 2: 22/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Levetiracetam vs phenytoin: epilepsy- 68.4% vs 56%, remote symptoms- 21.1% vs 16%, acute symptoms- 10.5% vs 28% ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Quality of life - Actual outcome: Good outcome at discharge: mRS at Discharge; Group 1: 30/38, Group 2: 14/25 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Levetiracetam vs phenytoin: epilepsy- 68.4% vs 56%, remote symptoms- 21.1% vs 16%, acute symptoms- 10.5% vs 28% ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Time to event seizure cessation ; Length of hospital stay ; Adverse events (respiratory depression, hypotension, frequency of endotracheal intubation, ICU admission, neuropsychological events such as confusion, anxiety, challenging behaviour, mood disturbance) ; Healthcare resource use

Appendix E: Forest plots

E.1 Forest plots: Monotherapy

E.1.1 Diazepam versus placebo

Figure 1: Seizure free at 12 hours

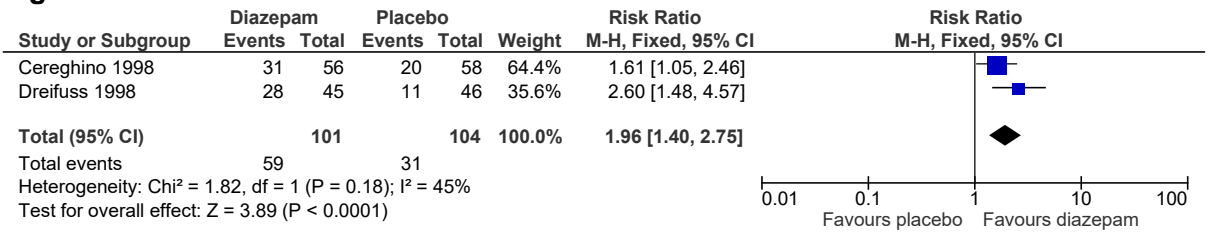


Figure 2: Nervous system adverse effects (including abnormal coordination, dizziness, euphoria, nervousness, somnolence)

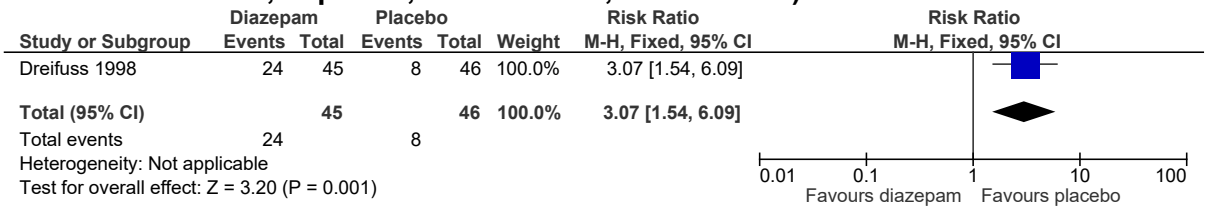
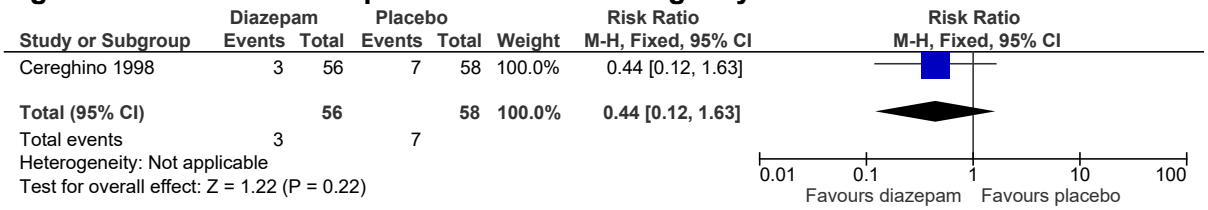


Figure 3: Patients who required additional emergency treatment



E.2 Forest plots: Add on therapies

E.2.1 Levetiracetam vs phenytoin

Figure 4: Mortality after prolonged ICU stay

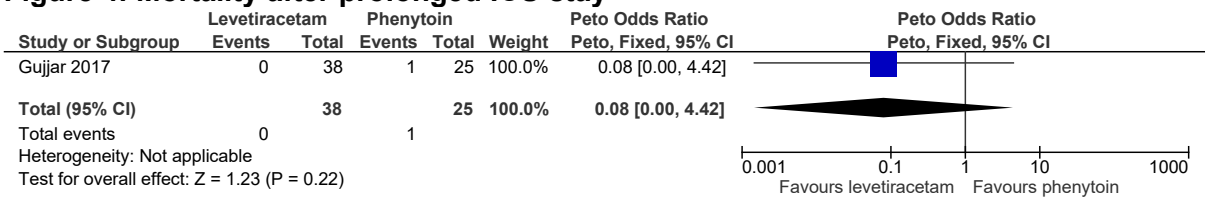


Figure 5: Seizure cessation within 24 hours

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Gujjar 2017	31	38	20	25	100.0%	1.02 [0.80, 1.31]
Total (95% CI)		**38**		**25**	**100.0%**	**1.02 [0.80, 1.31]**
Total events	31		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

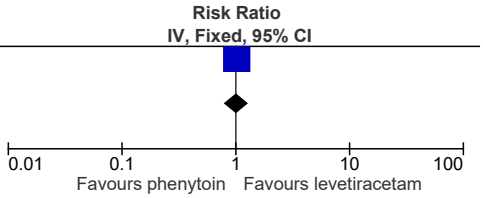
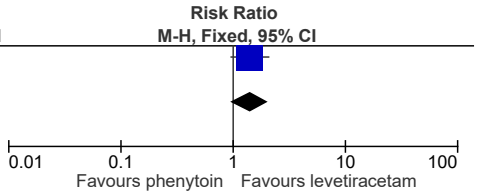


Figure 6: Good outcome at discharge: mRS

Study or Subgroup	Levetiracetam Events	Total	Phenytoin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gujjar 2017	30	38	14	25	100.0%	1.41 [0.96, 2.07]
Total (95% CI)		**38**		**25**	**100.0%**	**1.41 [0.96, 2.07]**
Total events	30		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)



E.2.2 Midazolam vs diazepam

Figure 7: Complete response to treatment (for at least 48 hours)

Study or Subgroup	Midazolam Events	Total	Diazepam Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fa yyazi 2012	12	18	10	20	100.0%	1.33 [0.77, 2.30]
Total (95% CI)		**18**		**20**	**100.0%**	**1.33 [0.77, 2.30]**
Total events	12		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

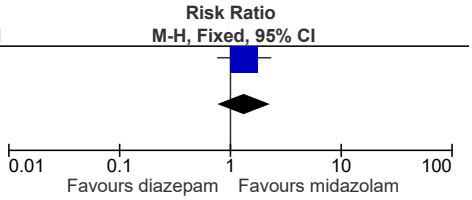


Figure 8: Hospital stay (days)

Study or Subgroup	Midazolam Mean	SD	Total	Diazepam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fa yyazi 2012	15.83	14.46	18	11.1	7.779	20	100.0%	4.73 [-2.77, 12.23]
Total (95% CI)			**18**			**20**	**100.0%**	**4.73 [-2.77, 12.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.22)

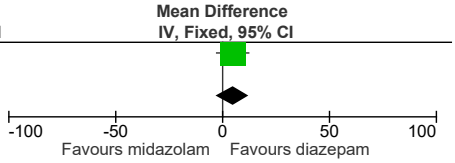
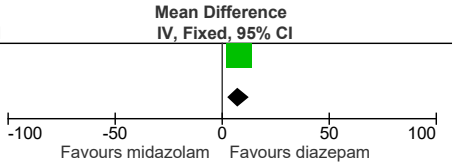


Figure 9: Paediatric Intensive Care Unit stay (days)

Study or Subgroup	Midazolam Mean	SD	Total	Diazepam Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fa yyazi 2012	10.89	9.305	18	3.2	6.305	20	100.0%	7.69 [2.58, 12.80]
Total (95% CI)			**18**			**20**	**100.0%**	**7.69 [2.58, 12.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.95 (P = 0.003)



Appendix F: GRADE tables

F.1 GRADE tables: Monotherapy

Table 15: Clinical evidence profile: Diazepam versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam	Placebo	Relative (95% CI)	Absolute		
Seizure free at 12 hours (follow-up 12 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	59/101 (58.4%)	31/104 (29.8%)	RR 1.96 (1.4 to 2.75)	286 more per 1000 (from 119 more to 522 more)	⊕⊕⊕O MODERATE	CRITICAL
Nervous system adverse effects (including Abnormal coordination, Dizziness, Euphoria, Nervousness, Somnolence)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/45 (53.3%)	8/46 (17.4%)	RR 3.07 (1.54 to 6.09)	360 more per 1000 (from 94 more to 885 more)	⊕⊕OO LOW	IMPORTANT
Patients who required additional emergency treatment												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/56 (5.4%)	7/58 (12.1%)	RR 0.44 (0.12 to 1.63)	68 fewer per 1000 (from 106 fewer to 76 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

F.2 GRADE tables: Add on therapies

Table 16: Clinical evidence profile: Levetiracetam versus phenytoin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Phenytoin	Relative (95% CI)	Absolute		
Mortality after prolonged ICU stay												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/38 (0%)	1/25 (4%)	Peto OR 0.08 (0 to 4.42)	40 fewer per 1000 (from 140 fewer to 60 more)	⊕⊕OO LOW	CRITICAL
Seizure cessation within 24 hours												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31/38 (81.6%)	20/25 (80%)	RR 1.02 (0.8 to 1.31)	16 more per 1000 (from 160 fewer to 248 more)	⊕⊕⊕O MODERATE	CRITICAL
Good outcome at discharge: mRS												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	30/38 (78.9%)	14/25 (56%)	RR 1.41 (0.96 to 2.07)	230 more per 1000 (from 22 fewer to 599 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

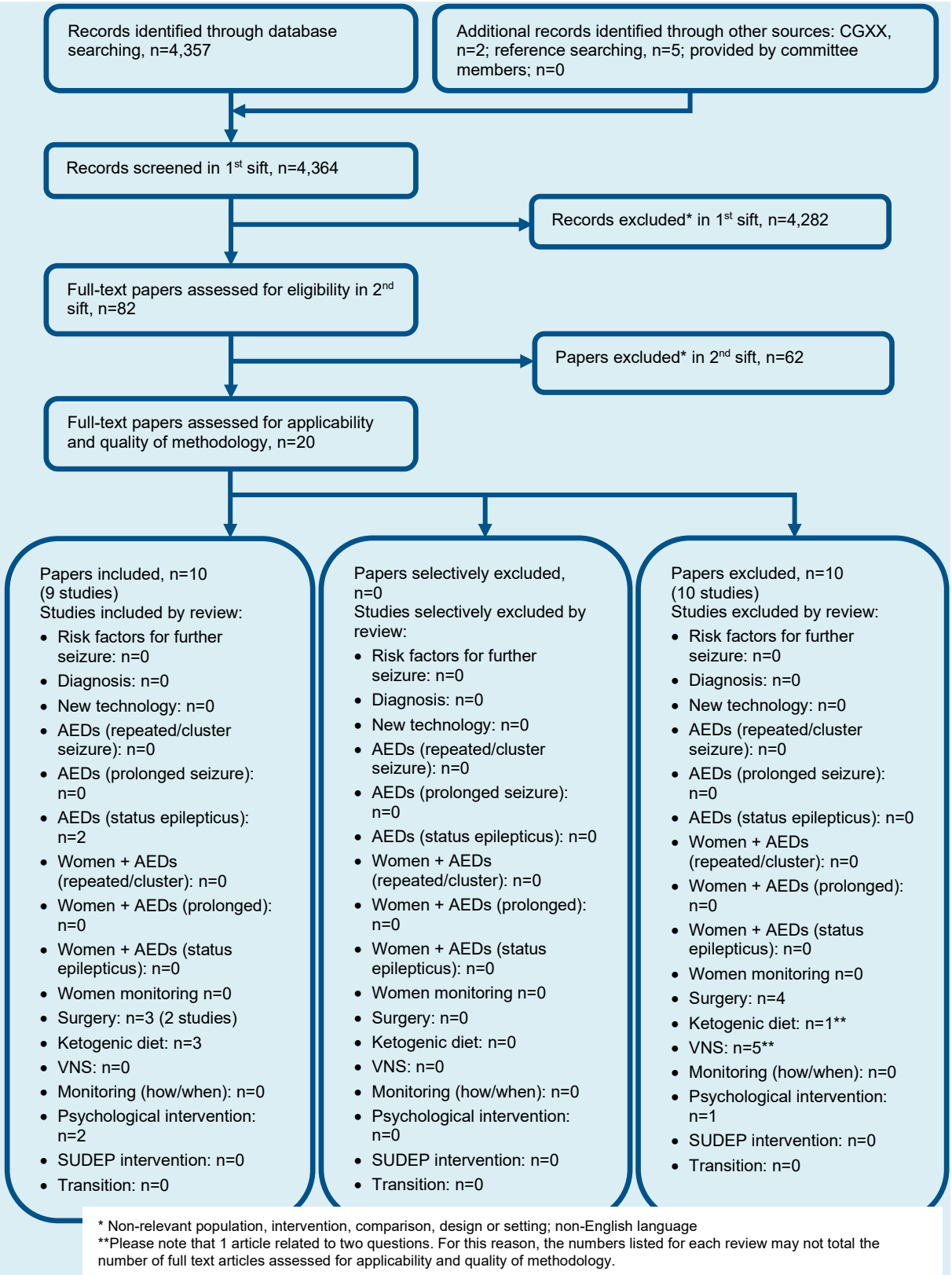
Table 17: Clinical evidence profile: midazolam versus diazepam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Midazolam	Diazepam	Relative (95% CI)	Absolute		

Complete response to treatment for at least 48 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/18 (66.7%)	10/20 (50%)	RR 1.33 (0.77 to 2.3)	165 more per 1000 (from 115 fewer to 650 more)	⊕⊕OO LOW	CRITICAL
Hospital stay (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	20	-	MD 4.73 higher (2.77 lower to 12.23 higher) [3]	⊕⊕OO LOW	IMPORTANT
Paediatric Intensive Care Unit stay (days) (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	20	-	MD 7.69 higher (2.58 to 12.8 higher) [3]	⊕⊕OO LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias 3 MID for hospital stay: +/- 3.9; MID for paediatric intensive care unit stay: +/- 3.152 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection



Appendix H: Health economic evidence tables

H.1 Monotherapy

None.

H.2 Add on therapies

None.

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Appendix I: Excluded studies

I.1 Excluded clinical studies: Monotherapy

Table 18: Studies excluded from the clinical review

Reference	Exclusion reason
Abou-Khalil 2013[1]	Comparison does not match protocol: autoinjector placebo
Ag Sguder 2016[2]	Incorrect study design retrospective cohort
Agarwal 2007[3]	Incorrect population
Ahmad 2006[4]	Incorrect population
Alldredge 2001[5]	Incorrect population
Amiri-Nikpour 2018[6]	Incorrect population
Amouian 2014[7]	Non-English language publication (Arabic)
Appleton 1995[8]	Incorrect population
Appleton 2004[9]	NMA; incorrect population
Arya 2015[10]	NMA; incorrect population
Ashrafi 2010[11]	Incorrect population
Banta- Banzali 2012[12]	Conference abstract
Bauerschmidt 2017[13]	Incorrect study design; non-systematic review
Bayrlee 2015[14]	Incorrect study design; non-systematic review
Baysun 2005[15]	Incorrect population
Bebin 1994[16]	Conference abstract
Beghi 2018[17]	Incorrect study design; health economic study
Bergin 2008[18]	Incorrect study design; non-systematic review
Bhattacharyya 2006[19]	Study analysed according to seizure number not patient data
Bleck 2013[20]	Incorrect study design; study protocol of unpublished study
Brigo 2012[31]	Systematic review; incorrect population
Brigo 2013[26]	Systematic review; incorrect population
Brigo 2015[29]	Incorrect population
Brigo 2015[30]	Systematic review; incorrect population
Brigo 2016[22]	Systematic review; incorrect population
Brigo 2016[23]	Systematic review; incorrect population
Brigo 2017[24]	Systematic review; incorrect population
Brigo 2018[25]	Systematic review; incorrect population
Brigo 2018[28]	Systematic review; incorrect population
Brigo 2019[27]	Systematic review; incorrect population
Cereghino 2002 [32]	Incorrect population
Chakravarthi 2014[35]	Incorrect population
Chakravarthi 2015[34]	Incorrect population
Chamberlain 1997[36]	Incorrect population
Chamberlain 2014[37]	Incorrect population
Chen 2011[38]	Incorrect population
Chitsaz 2013[39]	Incorrect population
Collins 2003[40]	Incorrect population
Dalziel 2017[43]	Incorrect population

Reference	Exclusion reason
Dalziel 2019[42]	Incorrect population
de 2010[45]	Incorrect study design; longitudinal cross over
de Assis 2012[44]	Incorrect study design; non-systematic review
DeToledo 2000[46]	Incorrect study design; narrative review
Doshi 2010[47]	Systematic review; incorrect population
Fa Yyazi 2012[49]	Incorrect intervention
Fallah 2007[50]	Incorrect population
Farrokh 2019[51]	Systematic review; incorrect population
Fisgin 2002[52]	Incorrect population
Fitzgerald 2003[53]	Incorrect study design; retrospective observational study
Gathwala 2012[54]	Incorrect population
Gilad 2008[55]	Incorrect population
Glauser 2016[56]	Systematic review; incorrect population
Gomes 2018[57]	Systematic review; incorrect population
Gujjar 2017[58]	Incorrect population
Gunawan 2015[59]	Incorrect population
Gunawan 2015[59]	Incorrect population
Hofler 2013[60]	Systematic review of non-randomised studies
Holsti 2010[61]	Incorrect population
Holsti 2010[62]	Incorrect population
Huertas Gonzalez 2019[63]	Non-English language publication (Spanish)
Husain 2015[64]	Unavailable
Isguder 2014[65]	Incorrect study design; retrospective cohort
Jain 2016[66]	Systematic review; incorrect population
Javadzadeh 2012[67]	Incorrect population
Jenkinson 2011[68]	Incorrect study design; non-systematic review
Kapur (ESETT Trial) 2019[69]	Incorrect population
Kellinghaus 2015[70]	Incorrect population
Kellinghaus 2018[71]	Incorrect study design; registry data
Khajeh 2018[72]	Incorrect population
Kinirons 2008[73]	Incorrect study design; literature review
Knake 2008[74]	Incorrect study design; retrospective cohort
Kriel 1991 [76]	Incorrect study design; questionnaire results
Kriel 1999[77]	Incorrect population
Kriel 2009[75]	Incorrect study design; commentary
Ku 2018[78]	Incorrect population
Lahat 2000[79]	Incorrect population
Lalji 1967[80]	Incorrect study design; non-randomised study
Lambrechtsen 2008[81]	Incorrect study design; retrospective cohort
Langer 2014[82]	Incorrect study design; retrospective cohort
Lee 2005[83]	Incorrect population
Lee 2016[84]	Commentary on discontinued study
Legros 2014[85]	Incorrect population
Leppik 1983[86]	Incorrect intervention
Liu 2012[87]	Systematic review; incorrect population

Reference	Exclusion reason
Lombroso 1989[88]	Incorrect study design; non-randomised study
Lowenstein 1988[93]	Incorrect study design; retrospective and prospective cohort
Lowenstein 1999[92]	Unavailable abstract
Lowenstein 2001[91]	Incorrect study design; protocol
Lowenstein 2003[89]	Unavailable
Lowenstein 2005[90]	Incorrect study design; literature review
Lyttle 2017[94]	Incorrect population
Lyttle 2019[95]	Incorrect population
Mahmoud 2018[96]	Systematic review; incorrect population
Mahmoudian 2004[98]	Incorrect population
Mahmoudian 2006[97]	Incorrect study design; case control study
Malamiri 2012[99]	Incorrect population
Malu 2014[100]	Incorrect population
Masapu 2018[101]	Incorrect population
Mayer 2002[102]	Incorrect study design; retrospective cohort study
McIntyre 2005[103]	Incorrect population
McKee 2015[104]	Incorrect study design; review
McMullan 2010[105]	Systematic review; incorrect population
McTague 2012[106]	Incorrect study design; observational study
McTague 2018[107]	Systematic review; incorrect population
Mehta 2007[108]	Incorrect population
Menon 2013[109]	Incorrect study design; literature review
Misra 2006[114]	Incorrect population
Misra 2012[113]	Incorrect population
Misra 2016[112]	Incorrect population
Misra 2017[111]	Unavailable
Misra 2017[110]	Incorrect population
Mittal 2006[115]	Incorrect population
Momen 2015[116]	Incorrect population
Morales 2015[117]	Incorrect study design; observational study
Mpimbaza 2008[118]	Incorrect population
Muhlhofer 2019[119]	Incorrect study design; observational study
Mundlamuri 2015[120]	Incorrect population
Murdoch 2007[121]	Incorrect population
Murthy 2006[122]	Incorrect study design; literature review
Navarro 2011[124]	Incorrect population
Navarro 2016[125]	Incorrect population
Neligan 2010[126]	Systematic review; incorrect population
Nene 2019[127]	Incorrect population
Newey 2017[128]	Incorrect population
Ngampoopun 2018[129]	Incorrect study design; observational study
Niermeijer 2003[130]	Incorrect study design; narrative review
Otto 1968[131]	Incorrect study design; abstract only
Owusu 2019[132]	Incorrect study design; retrospective cohort
Pang 2005[133]	Incorrect study design; literature review

Reference	Exclusion reason
Papavasiliou 2004[134]	Incorrect study design; case series
Parviainen 2007[135]	Incorrect population
Pinto 2016[136]	Incorrect population
Poplawska 2015[137]	Incorrect study design; narrative review
Portela 2015[138]	Incorrect population
Prabhakar 2013[139]	Systematic review; incorrect population
Prasad 2001[140]	Incorrect study design; retrospective cohort
Prasad 2007[141]	Systematic review; incorrect population
Prasad 2013[143]	Incorrect population
Prasad 2014[142]	Systematic review; incorrect population
Qureshi 2002[144]	Incorrect study design; comparative audit
Rajiv 2019[145]	Systematic review; incorrect population
Rantsch 2011[146]	Incorrect study design; retrospective cohort
Rantsch 2013[147]	Incorrect study design; retrospective cohort
Raspall-Chaure 2006[148]	Systematic review; incorrect population
Reif 2018[149]	Incorrect study design; case report
Remy 1992[150]	Incorrect population
Reznik 2016[151]	Incorrect study design; narrative review
Rosenow 2002[152]	Incorrect study design; narrative review
Rossetti 2004[156]	Incorrect study design; retrospective cohort
Rossetti 2008[154]	Incorrect study design; observational study
Rossetti 2011[155]	Incorrect population
Rossetti 2018[153]	Incorrect study design; narrative review
Ruegg 2003[157]	Incorrect study design; narrative review
Sabers 2013[158]	Incorrect population
Sanchez Fernandez 2014[159]	Incorrect study design; literature review
Sanchez Fernandez 2019[160]	Incorrect study design; economic analysis
Santamarina 2013[161]	Incorrect study design; retrospective cohort
Scott 1999[162]	Incorrect population
Shah 2005 [163]	Incorrect population
Shaner 1985[164]	Incorrect study design; abstract only
Shaner 1988[165]	Incorrect population
Shibata 2016[166]	Incorrect study design; non-randomised study
Shorvon 2011[168]	Incorrect study design; narrative review
Shorvon 2011[169]	Incorrect study design; narrative review
Shorvon 2012[167]	Incorrect study design; narrative review
Silbergleit 2011[172]	Systematic review; incorrect population
Silbergleit 2012[170]	Incorrect population
Silbergleit 2013[171]	Incorrect population
Singh 2009[173]	Incorrect population
Singhi 2002[174]	Incorrect population
Sirven 2003[175]	Incorrect study design; narrative review
Sivakumar 2015[176]	Incorrect study design; retrospective cohort
Skinner 2010[177]	Incorrect study design; case series
Smith 1971[179]	Incorrect study design, case series

Reference	Exclusion reason
Smith 2001[178]	Incorrect study design; narrative review
Sofou 2009[180]	Systematic review; incorrect population
Sorel 1981[181]	Incorrect study design; non-randomised study
Sreenath 2010[182]	Incorrect population
Stecker 1998[183]	Incorrect study design; retrospective and prospective cohort
Strzelczyk 2015[185]	Incorrect population
Strzelczyk 2016[184]	Incorrect population
Strzelczyk 2017[186]	Systematic review; incorrect population
Su 2016[187]	Incorrect population
Sutter 2013[192]	Incorrect study design; cohort study
Sutter 2014[191]	Incorrect study design; cohort study
Sutter 2015[190]	Incorrect study design; narrative review
Sutter 2017[188]	Incorrect study design; cohort study
Sutter 2018[189]	Systematic review; incorrect population
Talukdar 2009 [193]	Incorrect population
Tan 2010[194]	Incorrect population
Tanabe 2011[195]	Incorrect population
Tasker 2014[196]	Incorrect study design; narrative review
Thakker 2013[197]	Incorrect population
Thomson 2005[198]	Incorrect study design; literature review of cohort studies
Tonekaboni 2012[199]	Incorrect population
Towne 1999[200]	Incorrect study design; non-randomised study
Treiman 1985[201]	Incorrect study design; abstract only
Treiman 1991[202]	Unavailable abstract
Treiman 1998[203]	Incorrect population
Treiman 1998[204]	Incorrect population
Trinka 2009[205]	Unavailable
Trinka 2009[207]	Incorrect study design; narrative review
Trinka 2011[206]	Incorrect study design; narrative review
Trinka 2014[210]	Systematic review; incorrect population
Trinka 2015[208]	Incorrect study design; narrative review
Trinka 2016[209]	Incorrect study design; narrative review
Trinka 2017[211]	Incorrect study design; narrative review
Tripathi 2010 [212]	Incorrect population
Uges 2009[213]	Incorrect population
Uppal 2018[214]	Incorrect population
Vasquez 2019[215]	Incorrect study design, narrative review
Vohra 2015[216]	Incorrect population
Vossler 2019[217]	Incorrect study design; commentary
Walker 2003[219]	Incorrect study design; narrative review
Walker 2005[218]	Incorrect study design; guide
Welch 2015[220]	Incorrect population
Wheless 2008[223]	Incorrect study design; narrative review
Wheless 2010[221]	Incorrect study design, narrative review
Wheless 2019[222]	Incorrect population

Reference	Exclusion reason
Wilkes 2013[225]	Incorrect study design; narrative review
Wilkes 2014[224]	Systematic review; incorrect population
Willems 2019[226]	Systematic review; incorrect population
Won 2019[227]	Incorrect study design; retrospective cohort
Wongjirattikarn 2019[228]	Incorrect population
Yasiry 2014[229]	Systematic review; incorrect population
Zelano 2012[230]	Systematic review; incorrect population
Zhang 2019[231]	Systematic review; incorrect comparisons
Zhao 2016[232]	NMA; incorrect population

I.2 Excluded clinical studies: Add on therapies

Table 19: Studies excluded from the clinical review

Reference	Exclusion reason
Abou-Khalil 2013[1]	Comparison does not match protocol: autoinjector placebo
Ag Sguder 2016[2]	Incorrect study design retrospective cohort
Agarwal 2007[3]	Incorrect population
Ahmad 2006[4]	Incorrect population
Alldredge 2001[5]	Incorrect population
Amiri-Nikpour 2018[6]	Incorrect population
Amouian 2014[7]	Non-English language publication (Arabic)
Appleton 1995[8]	Incorrect population
Appleton 2004[9]	NMA; incorrect population
Arya 2015[10]	NMA; incorrect population
Ashrafi 2010[11]	Incorrect population
Banta- Banzali 2012[12]	Conference abstract
Bauerschmidt 2017[13]	Incorrect study design; non-systematic review
Bayrlee 2015[14]	Incorrect study design; non-systematic review
Baysun 2005[15]	Incorrect population
Bebin 1994[16]	Conference abstract
Beghi 2018[17]	Incorrect study design; health economic study
Bergin 2008[18]	Incorrect study design; non-systematic review
Bhattacharyya 2006[19]	Study analysed according to seizure number not patient data
Bleck 2013[20]	Incorrect study design; study protocol of unpublished study
Brigo 2012[31]	Systematic review; incorrect population
Brigo 2013[26]	Systematic review; incorrect population
Brigo 2015[29]	Incorrect population
Brigo 2015[30]	Systematic review; incorrect population
Brigo 2016[22]	Systematic review; incorrect population
Brigo 2016[23]	Systematic review; incorrect population
Brigo 2017[24]	Systematic review; incorrect population
Brigo 2018[25]	Systematic review; incorrect population
Brigo 2018[28]	Systematic review; incorrect population
Brigo 2019[27]	Systematic review; incorrect population

Reference	Exclusion reason
Cereghino 2002 [32]	Incorrect population
Cereghino, 1998[33]	Incorrect population
Chakravarthi 2014[35]	Incorrect population
Chakravarthi 2015[34]	Incorrect population
Chamberlain 1997[36]	Incorrect population
Chamberlain 2014[37]	Incorrect population
Chen 2011[38]	Incorrect population
Chitsaz 2013[39]	Incorrect population
Collins 2003[40]	Incorrect population
Dalziel 2017[43]	Incorrect population
Dalziel 2019[42]	Incorrect population
de 2010[45]	Incorrect study design; longitudinal cross over
de Assis 2012[44]	Incorrect study design; non-systematic review
DeToledo 2000[46]	Incorrect study design; narrative review
Doshi 2010[47]	Systematic review; incorrect population
Dreifuss 1998[48]	Incorrect population
Fallah 2007[50]	Incorrect population
Farrokh 2019[51]	Systematic review; incorrect population
Fisgin 2002[52]	Incorrect population
Fitzgerald 2003[53]	Incorrect study design; retrospective observational study
Gathwala 2012[54]	Incorrect population
Gilad 2008[55]	Incorrect population
Glauser 2016[56]	Systematic review; incorrect population
Gomes 2018[57]	Systematic review; incorrect population
Gunawan 2015[59]	Incorrect population
Gunawan 2015[59]	Incorrect population
Hofler 2013[60]	Systematic review of non-randomised studies
Holsti 2010[61]	Incorrect population
Holsti 2010[62]	Incorrect population
Huertas Gonzalez 2019[63]	Non-English language publication (Spanish)
Husain 2015[64]	Unavailable
Isguder 2014[65]	Incorrect study design; retrospective cohort
Jain 2016[66]	Systematic review; incorrect population
Javadzadeh 2012[67]	Incorrect population
Jenkinson 2011[68]	Incorrect study design; non-systematic review
Kapur (ESETT Trial) 2019[69]	Incorrect population
Kellinghaus 2015[70]	Incorrect population
Kellinghaus 2018[71]	Incorrect study design; registry data
Khajeh 2018[72]	Incorrect population
Kinirons 2008[73]	Incorrect study design; literature review
Knake 2008[74]	Incorrect study design; retrospective cohort
Kriel 1991 [76]	Incorrect study design; questionnaire results
Kriel 1999[77]	Incorrect population
Kriel 2009[75]	Incorrect study design; commentary
Ku 2018[78]	Incorrect population

Reference	Exclusion reason
Lahat 2000[79]	Incorrect population
Lalji 1967[80]	Incorrect study design; non-randomised study
Lambrechtsen 2008[81]	Incorrect study design; retrospective cohort
Langer 2014[82]	Incorrect study design; retrospective cohort
Lee 2005[83]	Incorrect population
Lee 2016[84]	Commentary on discontinued study
Legros 2014[85]	Incorrect population
Leppik 1983[86]	Incorrect intervention
Liu 2012[87]	Systematic review; incorrect population
Lombroso 1989[88]	Incorrect study design; non-randomised study
Lowenstein 1988[93]	Incorrect study design; retrospective and prospective cohort
Lowenstein 1999[92]	Unavailable abstract
Lowenstein 2001[91]	Incorrect study design; protocol
Lowenstein 2003[89]	Unavailable
Lowenstein 2005[90]	Incorrect study design; literature review
Lyttle 2017[94]	Incorrect population
Lyttle 2019[95]	Incorrect population
Mahmoud 2018[96]	Systematic review; incorrect population
Mahmoudian 2004[98]	Incorrect population
Mahmoudian 2006[97]	Incorrect study design; case control study
Malamiri 2012[99]	Incorrect population
Malu 2014[100]	Incorrect population
Masapu 2018[101]	Incorrect population
Mayer 2002[102]	Incorrect study design; retrospective cohort study
McIntyre 2005[103]	Incorrect population
McKee 2015[104]	Incorrect study design; review
McMullan 2010[105]	Systematic review; incorrect population
McTague 2012[106]	Incorrect study design; observational study
McTague 2018[107]	Systematic review; incorrect population
Mehta 2007[108]	Incorrect population
Menon 2013[109]	Incorrect study design; literature review
Misra 2006[114]	Incorrect population
Misra 2012[113]	Incorrect population
Misra 2016[112]	Incorrect population
Misra 2017[111]	Unavailable
Misra 2017[110]	Incorrect population
Mittal 2006[115]	Incorrect population
Momen 2015[116]	Incorrect population
Morales 2015[117]	Incorrect study design; observational study
Mpimbaza 2008[118]	Incorrect population
Muhlhofer 2019[119]	Incorrect study design; observational study
Mundlamuri 2015[120]	Incorrect population
Murdoch 2007[121]	Incorrect population
Murthy 2006[122]	Incorrect study design; literature review
Navarro 2011[124]	Incorrect population

Reference	Exclusion reason
Navarro 2016[125]	Incorrect population
Neligan 2010[126]	Systematic review; incorrect population
Nene 2019[127]	Incorrect population
Newey 2017[128]	Incorrect population
Ngampoopun 2018[129]	Incorrect study design; observational study
Niermeijer 2003[130]	Incorrect study design; narrative review
Otto 1968[131]	Incorrect study design; abstract only
Owusu 2019[132]	Incorrect study design; retrospective cohort
Pang 2005[133]	Incorrect study design; literature review
Papavasiliou 2004[134]	Incorrect study design; case series
Parviainen 2007[135]	Incorrect population
Pinto 2016[136]	Incorrect population
Poplawska 2015[137]	Incorrect study design; narrative review
Portela 2015[138]	Incorrect population
Prabhakar 2013[139]	Systematic review; incorrect population
Prasad 2001[140]	Incorrect study design; retrospective cohort
Prasad 2007[141]	Systematic review; incorrect population
Prasad 2013[143]	Incorrect population
Prasad 2014[142]	Systematic review; incorrect population
Qureshi 2002[144]	Incorrect study design; comparative audit
Rajiv 2019[145]	Systematic review; incorrect population
Rantsch 2011[146]	Incorrect study design; retrospective cohort
Rantsch 2013[147]	Incorrect study design; retrospective cohort
Raspall-Chaure 2006[148]	Systematic review; incorrect population
Reif 2018[149]	Incorrect study design; case report
Remy 1992[150]	Incorrect population
Reznik 2016[151]	Incorrect study design; narrative review
Rosenow 2002[152]	Incorrect study design; narrative review
Rossetti 2004[156]	Incorrect study design; retrospective cohort
Rossetti 2008[154]	Incorrect study design; observational study
Rossetti 2011[155]	Incorrect population
Rossetti 2018[153]	Incorrect study design; narrative review
Ruegg 2003[157]	Incorrect study design; narrative review
Sabers 2013[158]	Incorrect population
Sanchez Fernandez 2014[159]	Incorrect study design; literature review
Sanchez Fernandez 2019[160]	Incorrect study design; economic analysis
Santamarina 2013[161]	Incorrect study design; retrospective cohort
Scott 1999[162]	Incorrect population
Shah 2005 [163]	Incorrect population
Shaner 1985[164]	Incorrect study design; abstract only
Shaner 1988[165]	Incorrect population
Shibata 2016[166]	Incorrect study design; non-randomised study
Shorvon 2011[168]	Incorrect study design; narrative review
Shorvon 2011[169]	Incorrect study design; narrative review
Shorvon 2012[167]	Incorrect study design; narrative review

Reference	Exclusion reason
Silbergleit 2011[172]	Systematic review; incorrect population
Silbergleit 2012[170]	Incorrect population
Silbergleit 2013[171]	Incorrect population
Singh 2009[173]	Incorrect population
Singhi 2002[174]	Incorrect population
Sirven 2003[175]	Incorrect study design; narrative review
Sivakumar 2015[176]	Incorrect study design; retrospective cohort
Skinner 2010[177]	Incorrect study design; case series
Smith 1971[179]	Incorrect study design, case series
Smith 2001[178]	Incorrect study design; narrative review
Sofou 2009[180]	Systematic review; incorrect population
Sorel 1981[181]	Incorrect study design; non-randomised study
Sreenath 2010[182]	Incorrect population
Stecker 1998[183]	Incorrect study design; retrospective and prospective cohort
Strzelczyk 2015[185]	Incorrect population
Strzelczyk 2016[184]	Incorrect population
Strzelczyk 2017[186]	Systematic review; incorrect population
Su 2016[187]	Incorrect population
Sutter 2013[192]	Incorrect study design; cohort study
Sutter 2014[191]	Incorrect study design; cohort study
Sutter 2015[190]	Incorrect study design; narrative review
Sutter 2017[188]	Incorrect study design; cohort study
Sutter 2018[189]	Systematic review; incorrect population
Talukdar 2009 [193]	Incorrect population
Tan 2010[194]	Incorrect population
Tanabe 2011[195]	Incorrect population
Tasker 2014[196]	Incorrect study design; narrative review
Thakker 2013[197]	Incorrect population
Thomson 2005[198]	Incorrect study design; literature review of cohort studies
Tonekaboni 2012[199]	Incorrect population
Towne 1999[200]	Incorrect study design; non-randomised study
Treiman 1985[201]	Incorrect study design; abstract only
Treiman 1991[202]	Unavailable abstract
Treiman 1998[203]	Incorrect population
Treiman 1998[204]	Incorrect population
Trinka 2009[205]	Unavailable
Trinka 2009[207]	Incorrect study design; narrative review
Trinka 2011[206]	Incorrect study design; narrative review
Trinka 2014[210]	Systematic review; incorrect population
Trinka 2015[208]	Incorrect study design; narrative review
Trinka 2016[209]	Incorrect study design; narrative review
Trinka 2017[211]	Incorrect study design; narrative review
Tripathi 2010 [212]	Incorrect population
Uges 2009[213]	Incorrect population
Uppal 2018[214]	Incorrect population

Reference	Exclusion reason
Vasquez 2019[215]	Incorrect study design, narrative review
Vohra 2015[216]	Incorrect population
Vossler 2019[217]	Incorrect study design; commentary
Walker 2003[219]	Incorrect study design; narrative review
Walker 2005[218]	Incorrect study design; guide
Welch 2015[220]	Incorrect population
Wheless 2008[223]	Incorrect study design; narrative review
Wheless 2010[221]	Incorrect study design, narrative review
Wheless 2019[222]	Incorrect population
Wilkes 2013[225]	Incorrect study design; narrative review
Wilkes 2014[224]	Systematic review; incorrect population
Willems 2019[226]	Systematic review; incorrect population
Won 2019[227]	Incorrect study design; retrospective cohort
Wongjirattikarn 2019[228]	Incorrect population
Yasiry 2014[229]	Systematic review; incorrect population
Zelano 2012[230]	Systematic review; incorrect population
Zhang 2019[231]	Systematic review; incorrect comparisons
Zhao 2016[232]	NMA; incorrect population

I.3 Excluded health economic studies: Monotherapy

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 20: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

I.4 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 21: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

Anti-seizure medications: cluster seizures

Research question:

What anti-seizure drugs (monotherapy or add-on) are effective in the treatment of repeated or cluster seizures?

Why this is important

Epilepsy is common in adults and children, affecting 1 in 140 of the population. Epileptic seizures presenting acutely may persist or recur. Early control of such seizures is important to prevent their progression to status epilepticus (seizures persisting or recurring beyond 5 minutes) as this is a life-threatening medical emergency. It is important to investigate the success, safety and complications of acute treatments (including benzodiazepines such as lorazepam by buccal or intravenous routes) for repeated or cluster seizures to prevent their persistence or progression. Despite there being clear evidence-based protocols for the management of acute seizures (those persisting for up to 3 minutes) and for status epilepticus (seizures persisting beyond 5 minutes) in both adults and children, there is no clear evidence for the management of seizures persisting for 3-5 minutes (repeated or cluster seizures). This time window offers an important opportunity to prevent progression to status epilepticus, and yet the balance of risks between the benefits and harms of treatment at this stage is currently unknown.

Structured standalone statement:

- A randomised-controlled trial should be undertaken to determine which benzodiazepine (administered buccally or intravenously) is the most clinically and cost-effective at reducing seizure recurrence in the treatment of repeated or cluster seizures in adults and children. The study should also consider the impact of treatments on quality of life.

Structured rationale:

- Benzodiazepines such as lorazepam (administered buccally or intravenously) are currently recommended by many experts as first-line treatment for repeated or cluster seizures (persisting for 3 to 5 minutes) in adults and children. However, the systematic review undertaken by NICE in 2021 did not identify any robust evidence to support their use.

Rationale for research recommendation

Importance to ‘patients’ or the population	Epilepsy is a common disorder, and yet there is little information about the effectiveness and safety of acute treatments of repeated or cluster seizures. New guidance on this issue would impact the safety and quality of life of patients who develop repeated seizures.
Relevance to NICE guidance	Acute treatment of repeated or cluster seizures has been considered in this guideline, and there is a lack of data on their effectiveness and safety. New data on this issue would help to shape future NICE guidance.
Relevance to the NHS	The outcome would affect the types of treatment for repeated or cluster seizures provided by the NHS and would impact the planning and financing of acute medical services.
National priorities	High
Current evidence base	Minimal data on acute seizure management of seizures persisting for 3-5 minutes. The current

	evidence base relates to the initial acute management of seizure (the first 3 minutes) and to the management of status epilepticus (currently defined as seizures persisting beyond 5 minutes).
Equality considerations	None known

Modified PICO table

Population	Adults and children presenting with repeated or cluster seizures (persisting for 3-5 minutes)
Intervention	Administration of benzodiazepine (lorazepam or midazolam) by buccal route
Comparator	Administration of benzodiazepine (lorazepam or midazolam) by intravenous route
Outcome	Seizure cessation; complications; pain; adverse events; subsequent seizure control, mortality
Study design	Randomised controlled trial
Timeframe	Short term
Additional information	None