National Institute for Health and Care Excellence

Draft for consultation

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

[19] Evidence review: Reducing the risk of seizure-related mortality, including SUDEP

NICE guideline

Evidence review underpinning 10.1.5 and 10.2.1 recommendations and the research recommendations 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 Reducing the risk of seizure-related mortality including SUDEP

1.1 Review question

What interventions are effective in reducing the risk of seizure-related mortality, including Sudden Unexpected Death in Epilepsy (SUDEP), in people with epilepsy?

1.1.1 Introduction

Epilepsy is a condition that associates with risk. There is a risk of injury, including head injury, and mortality in the form of drowning and accidents. One significant cause of epilepsy-related mortality is Sudden Unexpected Death in Epilepsy (SUDEP). Overall, the rate of SUDEP is around 1 in 1000 people with epilepsy per year. The risk increases in people with generalised tonic clonic seizures, those with more difficult to treat epilepsy; poor medication adherence and psychosocial comorbidities, including neurodevelopmental comorbidities such as learning disabilities. Here we examine what can be done to reduce the risk of SUDEP in people with epilepsy and how to apply such interventions across healthcare.

1.1.2 Summary of the protocol

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 epilepsy Strata: Pregnant women and women in the perinatal period
Interventions	Any interventions for the reduction or prevention of seizure-related mortality, including SUDEP. Interventions may include, but are not limited to, the following: • Seizure-monitoring devices (such as bed sensors, fall alarms, and tracking devices that alert a carer to potential seizure activity) • Education and information giving • Safety pillows • Nocturnal supervision (including listening devices) • SSRIs • Opiate antagonists • Adenosine antagonists Interventions may also include those covered in other reviews within the guideline, such as AEDs and other non-pharmacological treatments such as vagus nerve stimulation, ketogenic diet, epilepsy surgery and digital health technologies. In any analysis, interventions will be combined with other interventions of the same class or of a similar design or category
Comparisons	• Active interventions compared with each other • Usual care / no intervention • Placebo / sham Each of the above comparator categories will be kept separate in any analysis.
Outcomes	Critical • SUDEP at longest study follow-up • Total non-SUDEP seizure-related mortality (including other seizure-related causes such as accident-related mortality, status epilepticus-related mortality, and unexplained mortality) at longest study follow-up

	Important • Adverse events (total) at longest study follow-up
Study design	• Systematic reviews • Randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs. • Prospective non-randomised cohort controlled and uncontrolled studies. • Case-control studies. For a systematic review to be included, it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching.

1.1.3 Effectiveness evidence

1.1.3.1 Included studies

A search was conducted for randomised controlled trials (RCTs) and observational studies reporting interventions to reduce the risk of seizure-related mortality (including SUDEP) in people with epilepsy. Two studies were identified which were included in a Cochrane review.[55] One was a case-control study comparing three exposures: nocturnal in-person supervision, alternative nocturnal precautions, and no supervision.[47] The second was a case-control comparing nocturnal surveillance with no nocturnal surveillance.[73] The Cochrane review was excluded from this review as some of the included studies did not match the PICO requirements for this review.[55] The two studies included in this review[47, 73] are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (2).

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

1.1.3.2 Excluded studies

See the excluded studies list in Appendix I:.

1.1.4 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention/exposure and comparison	Population	Outcomes	Comments
Langan 2005[47] UK	Nocturnal supervision, n=190 The presence of an individual of normal intelligence and at least 10 years old present at night, in the same room in which the person with epilepsy is sleeping, versus special precautions supervision, n=53 Special precautions involved regular checks throughout the night or the use of a listening device Versus No supervision, n= 278	Epilepsies in children, young people and adults SUDEP cases were aged between 16 and 50 years of age at death. (Mean age 32 years) Reported that controls were age matched within 5 years.	SUDEP	Included in a Cochrane systematic review [54, 55]
Shankar 2016[73] UK	Nocturnal surveillance (the number exposed was not reported) versus no nocturnal surveillance (the number exposed was not reported).	SUDEP cases were identified from the local coroner's records. The mean age was 42.5 years (median 42 years with a range of 2–82 years). Controls attended outpatient epilepsy clinics. The mean age was 42.76 years and median 47.5 years with a range of 9–86 years.	SUDEP	Included in a Cochrane systematic review.[55]

See Appendix D: for full evidence tables.

1.1.5 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Nocturnal supervision versus no supervision (meta-analysis)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Nocturnal supervision versus no supervision (95% CI)
SUDEP	1056 (2 studies[2])	VERY LOW[3,4,5] due to risk of bias	Unadjusted OR 0.19 (0.05 to 0.76)	Not calculable[1]	Not calculable[1]

[1] Absolute risk difference not calculable from case-control studies.
[2] case-control
[3] One study had a very high risk of selection bias and no attempt to control for confounding; the other had a high risk of selection bias.
[4] Serious inconsistency was found. However, each study showed a large effect in the same direction. Inconsistency was itself, therefore, deemed unlikely to influence decisions about clinical importance.

Table 4: Clinical evidence summary: Special precautions supervision versus no supervision

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Special precautions versus no supervision (95% CI)
SUDEP	331 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.31 to 0.91)	392 per 1000	184 fewer per 1000 (from 35 fewer to 271 fewer)

[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

Table 5: Clinical evidence summary: Special precautions supervision versus nocturnal supervision

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Special precautions versus nocturnal supervision (95% CI)
SUDEP	243 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.16 (0.63 to 2.13)	179 per 1000	29 more per 1000 (from 66 fewer to 202 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: for full GRADE tables.

1.1.6 Economic evidence

1.1.6.1 Included studies

No health economic studies were included.

1.1.6.2 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:.

1.1.7 Health economic modelling

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

1.1.8 The committee's discussion of the evidence

1.1.8.1 The outcomes that matter most

The critical outcomes included in this review were SUDEP and total non-SUDEP seizure-related mortality, including accident-related mortality, status epilepticus-related mortality, and unexplained mortality, both reported at the longest study follow up.

The important outcomes were adverse events reported at the longest study follow up.

No evidence was identified for total non SUDEP seizure-related mortality or adverse events.

1.1.8.2 The quality of the evidence

Evidence from two case-control studies was identified for this review. One study compared nocturnal supervision, special precautions supervision and no supervision. Nocturnal supervision was described as the presence of an individual at night in the same room as the person with epilepsy. Special precautions supervision was described as regular checks throughout the night or the use of a listening device. The other study included also included nocturnal supervision to no supervision, no details of the interventions given.

The evidence was very low or low quality, due to allocation concealment or imprecision.

1.1.8.3 Benefits and harms

The evidence showed a clinically important benefit for nocturnal supervision when compared to no supervision for SUDEP. When comparing the two supervision methods with each other, a clinically important benefit was shown for nocturnal supervision for SUDEP.

Although there was very little evidence and the only studies included were of low quality, it was noted by the committee there was an indication that nocturnal supervision of some sort is beneficial in reducing the occurrence of SUDEP. This corresponded with the view of the committee, who noted other studies have observed that approximately 90% of SUDEP cases occur in people who are alone.

The committee discussed the practicalities as well as the inappropriateness in many circumstances of making a strong recommendation for the type of supervision in the studies for people with epilepsy. The committee acknowledged parents sometimes sleep in the same room as their child or use night monitors and can gain some reassurance from doing this. However, they noted the challenges and suitability of supervising adolescents and that such

an intervention would not be feasible or acceptable for many adults who live on their own. The committee did acknowledge that for people living in supported accommodation night-time supervision is sometimes provided by 'awake carers' for people at risk of SUDEP. The committee discussed that the variability in levels of risk and range of domestic settings, without good evidence precluded making a recommendation. However, the committee stressed the importance of discussing risk factors associated with epilepsy-related mortality and SUDEP with the person and their family or carers in order to raise awareness and promote safe practices. This could include explaining how nocturnal supervision may be helpful for some people. The committee agreed that any discussion about SUDEP should include ways to reduce the risk, in particular, the need to adhere to medication regimens. The committee discussed the importance of preparing young people for adulthood and the transition from having adults in charge of their wellbeing and medication adherence to having sole responsibility for managing their own medication.

The committee agreed a recommendation for direct supervision could not be made from the evidence available. However, based on their clinical experience and expertise, the committee agreed that it was important to recommend a discussion of risk factors with people who have nocturnal seizures to promote safe practice (such as compliance with medication) where possible.

The committee noted that no evidence was found for seizure-monitoring devices, education and information giving, safety pillows, SSRIs, opiate antagonists or adenosine antagonists.

1.1.8.4 Cost effectiveness and resource use

No economic evaluations were identified for this question.

The type of interventions looked for in this review ranged from monitoring devices to pharmacological interventions. These can have very different costs ranging from one-off costs (for devices) to ongoing costs (drugs). The clinical review identified only very low-quality graded evidence for nocturnal supervision. No clinical evidence was found for the other interventions specified in the protocol. Overall, the committee felt that there was limited evidence to be able to recommend supervision for all people with epilepsy, specifically as the intervention in the included study in the clinical review was another person being in the room. The committee noted the significant costs associated with having an NHS staff member supervise an individual person during the night.

1.1.8.5 Other factors the committee took into account

The committee recognised there could be significant benefits to monitoring people with epilepsy who have seizures during their sleep and have been assessed to be at higher risk of mortality. Therefore, the committee made a recommendation to discuss introducing or increasing the degree of night-time supervision in these groups of people. For further discussions surrounding this recommendation, see the committee discussion of the evidence in Evidence Review R2 modifiable risk factors for epilepsy-related mortality, including SUDEP.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 10.1.5 and 10.2.1 in the NICE guideline and the research recommendations on identifying and mitigating SUDEP risk factors.

1.1.10 References

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: Reducing SUDEP

ID	Field	Content
0.	PROSPERO registration number	
1.	Review title	Reducing the risk of seizure-related mortality including SUDEP in people with epilepsy
2.	Review question	What interventions are effective in reducing the risk of seizure-related mortality, including Sudden Unexpected Death in Epilepsy (SUDEP), in people with epilepsy?
3.	Objective	Epileptic seizures can result in injury, and may also be associated with mortality, for example, because of sudden unexpected death in epilepsy (SUDEP). Optimal management reduces the risk of SUDEP. The aim of the review question is to identify effective treatments to reduce the risk of seizure-related mortality, including SUDEP.
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 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	Epilepsies in children, young people and adults
6.	Population	Inclusion: Children, young people and adults with epilepsy Strata: Pregnant women and women in perinatal period

		Exclusion: New-born babies (under 28 days) with acute symptomatic seizures.
7.	Intervention/Exposure/Test	Any intervention for the reduction or prevention of seizure-related mortality including SUDEP In any analysis, interventions will be combined with other interventions of the same class or of a similar design or category.
8.	Comparator/Reference standard/Confounding factors	• Active interventions compared with each other • Usual care / no intervention • Placebo / sham Each of the above comparator categories will be kept separate in any analysis.
9.	Types of study to be included	• Systematic reviews • Randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs. • Prospective non-randomised cohort controlled and uncontrolled studies. • Case-control studies. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching.
10.	Other exclusion criteria	Exclusions: • Non-English language studies • Conference abstracts
11.	Context	
12.	Primary outcomes (critical outcomes)	**Critical** • SUDEP at longest study follow-up • Total non-SUDEP seizure-related mortality (including other seizure-related causes such as accident-related mortality, status epilepticus-related mortality, and unexplained mortality) at longest study follow-up
13.	Secondary outcomes (important outcomes)	**Important** • Adverse events (total) at longest study follow-up
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. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

<table>
<tr><td></td><td></td><td colspan="2">• Randomised Controlled Trial: Cochrane RoB (2.0)
• Nonrandomised study, including cohort studies: Cochrane ROBINS-I
• Case control study: CASP case control checklist

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.</td></tr>
<tr><td>16.</td><td>Strategy for data synthesis</td><td colspan="2">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/

Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.

Statistically heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value of more than 50% indicating significant heterogeneity and an I^2 value of more than 75% indicating very significant heterogeneity).</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="2">In the event of heterogeneity, subgroup analysis will be undertaken based on the risk of bias of the included studies and the following possible modifiers of treatment effect:
• age (children, young people, adults, older people)
• seizure type (generalised tonic-clonic versus other)
• learning disabilities (people with learning disabilities and people without learning disabilities)
• ethnicity (BAME versus not BAME)
• socioeconomic background</td></tr>
<tr><td rowspan="4">18.</td><td rowspan="4">Type and method of review</td><td>✓</td><td>Intervention</td></tr>
<tr><td></td><td>Diagnostic</td></tr>
<tr><td></td><td>Prognostic</td></tr>
<tr><td></td><td>Qualitative</td></tr>
</table>

			Epidemiologic
			Service Delivery
			Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	TBC- after NICE sign-off	
22.	Anticipated completion date	TBC	
23.	Stage of review at time of this submission	Review stage	Started / Completed
		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 National Guideline Centre 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 Jacqui Real, Senior systematic reviewer Angela Cooper, Senior systematic reviewer Rafina Yarde, Systematic reviewer Margaret Constanti, 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: [NICE guideline webpage].	
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, mortality, SUDEP	
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	

1 **Table 8: 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).[61] **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.

1

Appendix B: Literature search strategies

This literature search strategy was used for the following review:

- What interventions are effective in reducing the risk of seizure-related mortality, including Sudden Unexpected Death in Epilepsy (SUDEP), in people with epilepsy?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[61]

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 the following approach:

- Population AND Study filter(s)

Table 3: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 May 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions
Embase (OVID)	1974 – 13 May 2021	Randomised controlled trials Systematic review studies Observational studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2021 Issue5 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 continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or west syndrome).ti,ab.
6.	(epilep* or seizure* or dravet syndrome or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or west syndrome).ti,ab.
7.	or/1-5
8.	or/1-4,6
9.	exp death, sudden/
10.	((seizure* or epilep*) adj4 (death* or died or dies or mortalit* or accident* or drown* or "adverse event*")).ti,ab.
11.	9 or 10
12.	7 and 11

13.	(SUDEP or "sudden unexp* death in epilepsy").ti,ab.
14.	12 or 13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case report/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Epidemiologic studies/
36.	Observational study/
37.	exp Cohort studies/
38.	(cohort adj (study or studies or analys* or data)).ti,ab.
39.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
40.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
41.	Controlled Before-After Studies/
42.	Historically Controlled Study/
43.	Interrupted Time Series Analysis/
44.	(before adj2 after adj2 (study or studies or data)).ti,ab.
45.	exp case control studies/
46.	case control*.ti,ab.
47.	Cross-sectional studies/
48.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
49.	or/35-48
50.	randomized controlled trial.pt.
51.	controlled clinical trial.pt.
52.	randomi#ed.ti,ab.
53.	placebo.ab.
54.	randomly.ti,ab.
55.	Clinical Trials as topic.sh.
56.	trial.ti.
57.	or/50-56
58.	Meta-Analysis/

59.	exp Meta-Analysis as Topic/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.
65.	(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.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	34 and (49 or 57 or 68)

1 **Embase (Ovid) search terms**

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or west syndrome).ti,ab.
6.	(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.
7.	or/1-5
8.	or/1-4,6
9.	exp sudden death/
10.	((seizure* or epilep*) adj4 (death* or died or dies or mortalit* or accident* or drown* or "adverse event*")).ti,ab.
11.	9 or 10
12.	7 and 11
13.	(SUDEP or "sudden unexp* death in epilepsy").ti,ab.
14.	12 or 13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	or/15-19
21.	randomized controlled trial/ or random*.ti,ab.
22.	20 not 21
23.	animal/ not human/
24.	nonhuman/
25.	exp Animal Experiment/
26.	exp Experimental Animal/
27.	animal model/
28.	exp Rodent/
29.	(rat or rats or mouse or mice).ti.

30.	or/22-29
31.	14 not 30
32.	limit 31 to English language
33.	random*.ti,ab.
34.	factorial*.ti,ab.
35.	(crossover* or cross over*).ti,ab.
36.	((doubl* or singl*) adj blind*).ti,ab.
37.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
38.	crossover procedure/
39.	single blind procedure/
40.	randomized controlled trial/
41.	double blind procedure/
42.	or/35-43
43.	systematic review/
44.	meta-analysis/
45.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
46.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
47.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
48.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
49.	(search* adj4 literature).ab.
50.	(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.
51.	cochrane.jw.
52.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
53.	or/45-54
54.	Clinical study/
55.	Observational study/
56.	family study/
57.	longitudinal study/
58.	retrospective study/
59.	prospective study/
60.	cohort analysis/
61.	follow-up/
62.	cohort*.ti,ab.
63.	63 and 64
64.	(cohort adj (study or studies or analys* or data)).ti,ab.
65.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
66.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
67.	(before adj2 after adj2 (study or studies or data)).ti,ab.
68.	exp case control study/
69.	case control*.ti,ab.
70.	cross-sectional study/
71.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
72.	or/56-62,65-73

73.	32 and (42 or 53 or 72)

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 continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or west syndrome):ti,ab
#6.	(epilep* or seizure* or dravet syndrome or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or west syndrome):ti,ab
#7.	(or #1-#5)
#8.	#1 or #2 or #3 or #4 or #6
#9.	MeSH descriptor: [Death, Sudden] explode all trees
#10.	((seizure* or epilep*) near/4 (death* or died or dies or mortalit* or accident* or drown* or "adverse event*")):ti,ab
#11.	#9 or #10
#12.	#7 and #11
#13.	(SUDEP or "sudden unexp* death in epilepsy"):ti,ab
#14.	#12 or #13

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 4: 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

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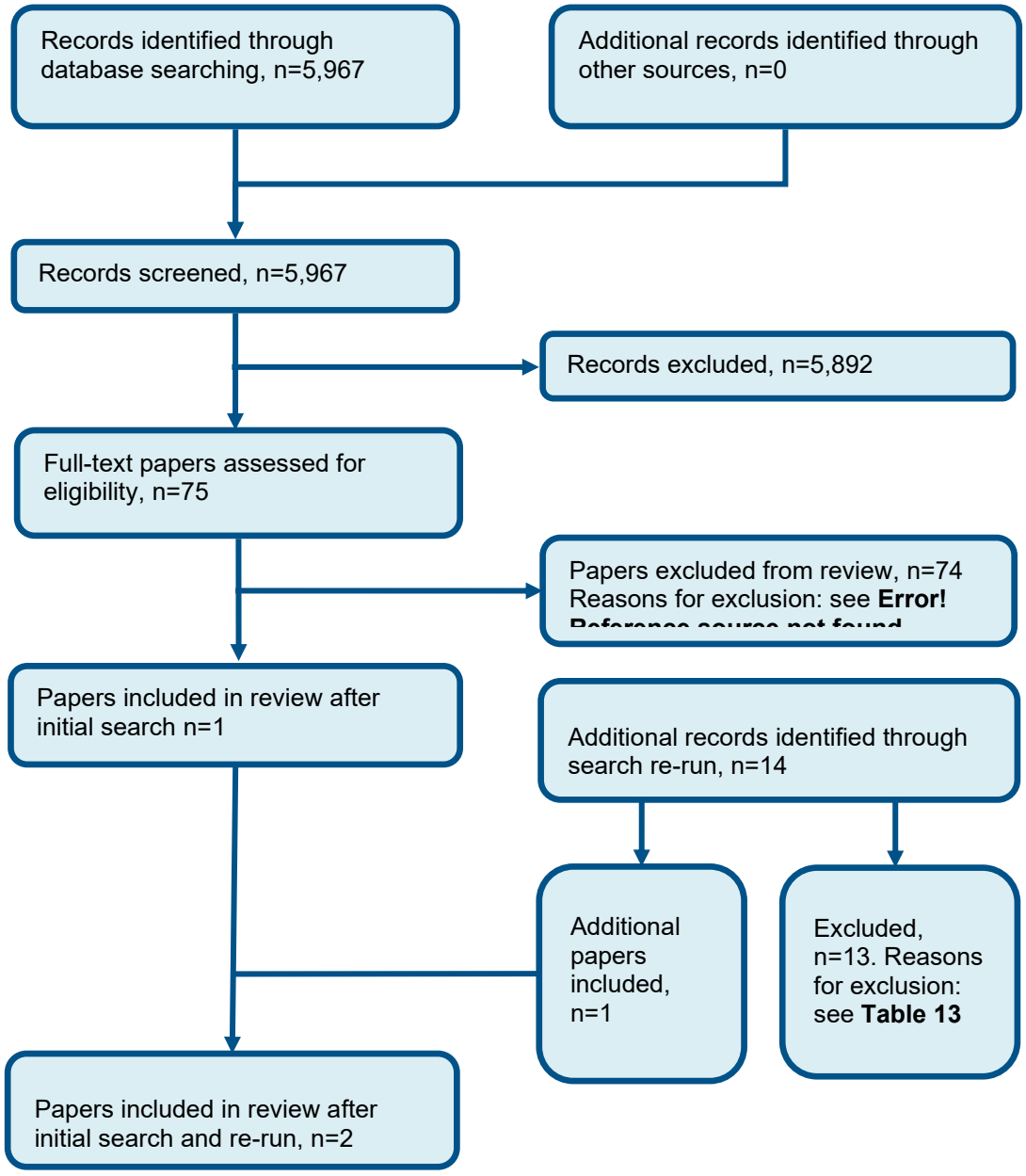
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of reducing SUDEP



2

1 # Appendix D: Clinical evidence tables

Study	**Langan 2005[47] (Maguire 2016[54])**
Study type	Case control study
Number of studies (number of participants)	1 (n=521)
Countries and setting	Conducted in United Kingdom; Setting:
Line of therapy	Adjunctive to current care
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with epilepsy who died suddenly between the ages of 16 and 50 years were identified by coroners and neurologists and by interviews with bereaved families. Deaths occurred between 1989 and 1998. Coroners in England and Wales were invited to notify neurologists of cases considered to be SUDEP. Neurologists were contacted via the British Neurologic Surveillance Unit. Cases were also identified through interviews with self-referred parents and partners of the deceased through Epilepsy Bereaved?, a UK support charity. Subjects were individuals with a history of active epilepsy (at least one seizure in the past in the past 5 years or taking an AED if in remission) whose death fulfilled the following definition: sudden, unexpected, witnessed, or unwitnessed, non-traumatic and non-drowning death in an individual with epilepsy, with or without evidence of a seizure.
Exclusion criteria	Excluding documented status epilepticus in which the post-mortem does not reveal a cause for death.
Age, gender and ethnicity	Age - Mean (SD): 32 years . Gender (M:F): 97 men, 57 women (case group only). Ethnicity: Not

Study	**Langan 2005[47] (Maguire 2016[54])**
	stated.
Further population details	1. Age (children, yong people, adults, older people): 2. Ethnicity: 3. Learning disabilities: 4. Socioeconomic background:
Extra comments	Interviews involved a semi-structured questionnaire that examined aspects of the patient's epilepsy, medical and social background, and the circumstances of death.
Indirectness of population	No indirectness
Interventions	(n=190) Intervention 1: Intervention to reduce or prevent seizure related mortality including SUDEP - Nocturnal supervision . Nocturnal supervision - supervision at night defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions. . Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Seizure type (generalised tonic-clonic versus other): (n=53) Intervention 2: Intervention to reduce or prevent seizure related mortality including SUDEP - Seizure-monitoring devices . Special precautions - involved regular checks throughout the night or the use of a listening device. . Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Seizure type (generalised tonic-clonic versus other): (n=278) Intervention 3: No intervention. No supervision. Duration N/A. Concurrent medication/care: N/A. Indirectness: No indirectness Further details: 1. Seizure type (generalised tonic-clonic versus other):
Funding	Academic or government funding (Supported by the Epilepsy Research Foundation and Epilepsy Bereaved)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NOCTURNAL SUPERVISION versus NO INTERVENTION

Protocol outcome 1: SUDEP at longest follow-up at N/A
- Actual outcome: SUDEP at N/A; Group 1: 34/190, Group 2: 109/278
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: history of generalised tonic-clonic seizures - 120 (case group), 108 (control group), total no. of AEDs 1-2 - 42 (case group), 400 (control group); Group 1 Number missing: 0; Group 2 Number missing: 0

Study	**Langan 2005[47] (Maguire 2016[54])**
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEIZURE-MONITORING DEVICES versus NOCTURNAL SUPERVISION Protocol outcome 1: SUDEP at longest follow-up at N/A - Actual outcome: SUDEP at N/A; Group 1: 11/53, Group 2: 34/190 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: history of generalised tonic-clonic seizures - 120 (case group), 108 (control group), total no. of AEDs 1-2 - 42 (case group), 400 (control group); Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEIZURE-MONITORING DEVICES versus NO INTERVENTION Protocol outcome 1: SUDEP at longest follow-up at N/A - Actual outcome: SUDEP at N/A; Group 1: 11/53, Group 2: 109/278 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: history of generalised tonic-clonic seizures - 120 (case group), 108 (control group), total no. of AEDs 1-2 - 42 (case group), 400 (control group); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Total non-SUDEP seizure related mortality at longest follow up at N/A; Adverse events at N/A; Quality of life at N/A

1

Study	Shankar 2016 trial (Shankar 2016[73])
Study type	Case control study
Number of studies (number of participants)	1 (n=268)
Countries and setting	Conducted in United Kingdom; Setting: Controls drawn from a specialist epilepsy outpatient clinic in Cornwall, UK
Line of therapy	Not applicable
Duration of study	Other: Retrospective

Study	Shankar 2016 trial (Shankar 2016[73])
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Deaths registered by coroner within Cornwall, UK, from 2004 to 2012 with epilepsy recorded as primary or secondary cause, which met SUDEP criteria.
Exclusion criteria	Define
Recruitment/selection of patients	Consent of controls sought from consecutive patients
Age, gender and ethnicity	Age - Median (range): Cases: 42 (2 to 82); controls: 47.5 (9 to 86). Gender (M:F): Cases: 33 male, 15 female; controls: 115 male, 105 female. Ethnicity: Not stated
Further population details	1. Age (children, yong people, adults, older people): 2. Ethnicity: 3. Learning disabilities: 4. Socioeconomic background:
Indirectness of population	No indirectness
Interventions	(n=268) Intervention 1: Intervention to reduce or prevent seizure related mortality including SUDEP - Nocturnal supervision . dose/quantity, brand name, extra details. Duration Not applicable: retrospective. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Seizure type (generalised tonic-clonic versus other): (n=268) Intervention 2: Usual care. dose/quantity, brand name, extra details. Duration Not applicable: retrospective. Concurrent medication/care: Not stated. Indirectness: No indirectness Further details: 1. Seizure type (generalised tonic-clonic versus other):
Funding	Funding not stated

Study	Shankar 2016 trial (Shankar 2016[73])
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NOCTURNAL SUPERVISION versus USUAL CARE Protocol outcome 1: SUDEP at longest follow-up at N/A - Actual outcome: SUDEP at Not applicable: retrospective; Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - NO ADJUSTMENT FOR POTENTIAL CONFOUNDING, WHICH WAS LIKELY. Cases and controls were sampled from different time periods. Low numbers and missing data are cited as reasons for not conducting multivariate analysis, but no data were provided. ; Indirectness of outcome: No indirectness ; Baseline details: Cases more predominantly male (69%) than controls (52%). Similar for age. No other baseline comparisons were available. Cases and controls were sampled from different time periods.; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Total non-SUDEP seizure related mortality at longest follow up at N/A; Adverse events at N/A; Quality of life at N/A

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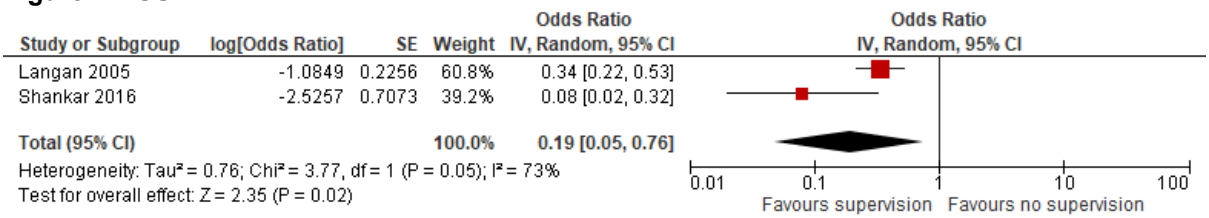
Appendix E: Forest plots

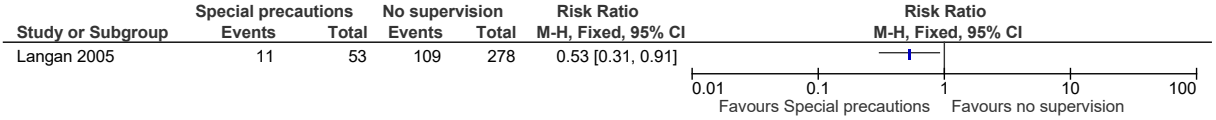
E.1 Nocturnal supervision versus no supervision (meta-analysis)

Figure 1: SUDEP



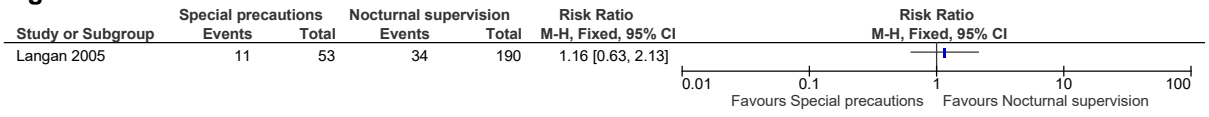
E.2 Special precautions supervision versus no supervision

Figure 3: SUDEP



E.3 Special precautions supervision versus nocturnal supervision

Figure 2: SUDEP



Appendix F: GRADE tables

Table 9: Clinical evidence profile: Nocturnal supervision versus no supervision (meta-analysis)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nocturnal surveillance versus no nocturnal surveillance	Control	Relative (95% CI)	Absolute		
SUDEP												
2	observational studies[1]	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	191 cases 865 controls		OR 0.19 (0.05 to 0.76)	- -[4]	⊕OOO VERY LOW	CRITICAL

[1] Case-control
[2] One study had a very high risk of selection bias and no attempt to control for confounding; the other had a high risk of selection bias.
[3] Serious inconsistency was found. However, each study showed a large effect in the same direction. Inconsistency was itself, therefore, deemed unlikely to influence decisions about clinical importance.
[4] Absolute risk difference not calculable from case-control studies.

Table 10: Clinical evidence profile: Special precautions supervision versus no supervision

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Special precautions versus no supervision	Control	Relative (95% CI)	Absolute		
SUDEP												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/53 (20.8%)	109/278 (39.2%)	RR 0.53 (0.31 to 0.91)	184 fewer per 1000 (from 35 fewer to 271 fewer)	⊕OOO VERY LOW	CRITICAL

[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

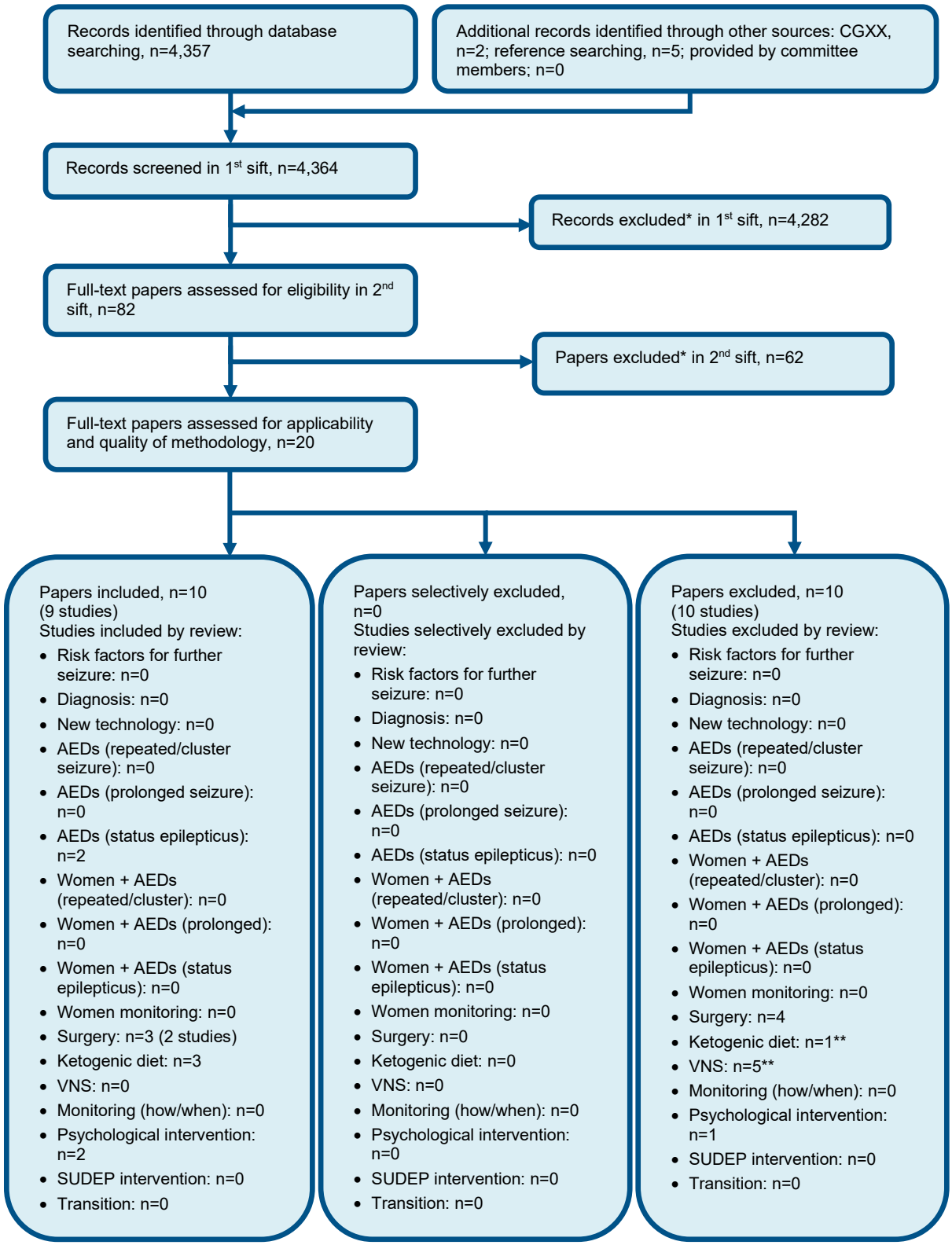
Table11: Clinical evidence profile: Special precautions supervision versus nocturnal supervision

Quality assessment	No of patients	Effect	Quality	Importan

											y	ce
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Special precautions versus nocturnal supervision**	**Control**	**Relative (95% CI)**	**Absolute**		
SUDEP												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/53 (20.8%)	34/190 (17.9%)	RR 1.16 (0.63 to 2.13)	29 more per 1000 (from 66 fewer to 202 more)	⊕OOO VERY LOW	CRITICAL

[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

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language
**Please note that 1 article related to two questions. For this reason, the numbers listed for each review may not total the number of full text articles assessed for applicability and quality of methodology.

1

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Abdel-mannan 2019[1]	Systematic review: references individually checked. Incorrect study designs
Ackers 2011[2]	Incorrect study design. Inappropriate comparison
Ali 2017[3]	Incorrect interventions
Allen 2019[4]	Incorrect study design
Almeida 2010[5]	Crossover study
Annegers 1999[6]	Incorrect study design
Annegers 2000[7]	Incorrect study design
Anonymous 2020[8]	abstract only
Appleton 1997[9]	Incorrect study design
Aurlien 2016[10]	Incorrect interventions
Bardai 2015[11]	Incorrect study design
Beghi 2005[12]	Incorrect study design
Beniczky 2019[13]	systematic literature review
Beran 2004[14]	Incorrect study design
Berg 2004[16]	Incorrect study design
Berg 2013[15]	Incorrect study design
Brotherstone 2020[17]	Pilot study looking at the detection of seizures using an algorithm device, the primary outcome are heart rate change and oxygen saturation
Camfield 2002[18]	Incorrect study design
Camfield 2005[19]	Incorrect study design
Carpio 2005[20]	Incorrect study design
Cheng 2016[21]	Incorrect study design. Incorrect interventions

Chungath 2008[22]	Incorrect study design
Degiorgio 2017[24]	Systematic review: study designs inappropriate
Degiorgio 2019[23]	Incorrect study design
Diop 2005[25]	Incorrect study design. Inappropriate comparison
Dlouhy 2016[26]	Incorrect study design
Edey 2014[27]	Incorrect study design
Escalaya 2015[28]	Systematic review: study designs inappropriate
Forsgren 2005[29]	Incorrect study design
Gilbert 1999[30]	Systematic review: study designs inappropriate
Gorton 2018[31]	Inappropriate comparison
Grau-lopez 2020[32]	Variables studied were not interventions to prevent seizure-related death or SUDEP.
Gronborg 2014[33]	Incorrect study design
Harden 2017[34]	Incorrect study design
Hawkes 2019[35]	Incorrect study design
Hefti 2016[36]	Incorrect study design
Hesdorffer 2015[37]	Incorrect study design
Hitiris 2007[38]	Incorrect study design
Jafarpour 2019[39]	Incorrect study design
Jallon 2004[40]	Incorrect study design
Johnston 2007[41]	Incorrect study design
Josephson 2017[42]	Not review population. Incorrect study design
Kiani 2014[43]	Incorrect study design
Lamberts 2012[44]	Incorrect study design
Lamichhane 2020[45]	literature review
Langan 1998[48]	Incorrect study design
Langan 2000[46]	Incorrect study design
Lee 2021[49]	a nationwide case–control
Levira 2017[50]	Systematic review: study designs inappropriate

Lhatoo 2010[51]	Incorrect study design
Liebenthal 2015[52]	Incorrect interventions
Lucchesi 2020[53]	literature review
Maguire 2016[54]	Systematic review excluded as some of the included studies did not match the PICO for this review, the references were checked, and appropriate studies included to the evidence review.
Maguire 2020[55]	Systematic review which included only studies already included or excluded from this review.
Mckee 2000[56]	Incorrect study design
Meyer 2011[57]	Incorrect study design
Monte 2007[58]	Systematic review: study designs inappropriate
Morse 2016[59]	Systematic review: study designs inappropriate
Mostacci 2015[60]	Incorrect study design
Neligan 2019[62]	Systematic review is not relevant to review question or unclear PICO
Nevalainen 2014[63]	Incorrect study design
Ochoa-urrea 2021[64]	Seizure clusters in drug-resistant epilepsy from a multi-centre study. A linear mixed effects model was used to study the difference between the first and subsequent seizures as a predictor of SUDEP Risk no multivariate
Odom 2018[65]	Incorrect study design
Papacostas 2015[66]	Incorrect study design
Radhakrishnan 2018[67]	No relevant outcomes
Ryvlin 2018[68]	No relevant results
Saetre 2018[69]	Incorrect study design
Sairanen 2020[70]	only univariate analysis. mortality prediction: status epilepticus and the predictive value of the EMSE and STESS scores: A prospective study
Sanya 2005[71]	Incorrect study design
Saxena 2018[72]	Systematic review: study designs inappropriate
Shmuely 2016[74]	Systematic review: study designs inappropriate
Shmuely 2016[75]	Inappropriate comparison
Shorvon 2011[76]	Incorrect study design

Sirikarn 2019[77]	Outcome (long-term mortality) was not exclusively seizure-related, and it was applied to the derivation and validation of a prediction model, rather than the effect of its implementation.
Sutter 2018[78]	Incorrect study design
Tellez-zenteno 2005[79]	Systematic review: study designs inappropriate
Thurman 2014[80]	Systematic review: study designs inappropriate
Thurman 2017[81]	Systematic review: study designs inappropriate
Tomson 2016[82]	Incorrect study design
Ufongene 2020[83]	systematic review but method not outlined
Van der lende 2018[84]	Incorrect study design
Verma 2019[85]	Outcome (mortality) was not exclusively seizure-related, and was applied to an evaluation of two prediction scales rather than the effect of their implementation.
Vilella 2019[86]	Incorrect study design
Watila 2018[87]	Systematic review: study designs inappropriate
Weber 2005[88]	Incorrect study design
Young 2015[89]	Incorrect study design
Zhang 2016[90]	Incorrect study design

I.2 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 13: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix J: Research recommendations

J.1 To identify and mitigate SUDEP risk factors

Why this is important

Epilepsy is a condition that associates with significant risk, risk of injury, head injury and a risk of mortality. An important cause of mortality in individuals who have seizures is Sudden Unexpected Death in Epilepsy (SUDEP). The cumulative risk of SUDEP in a population-based follow-up study of 40 years was estimated to be 7-12%. The risk of SUDEP is about 1 in 10,000 person-years in population-based studies of newly diagnosed epilepsy and 1 in 1,000 person-years in people with long-term epilepsy. SUDEP incidence, however, increases with less well controlled epilepsy and varies with the type of epilepsy population. SUDEP in epilepsy specialist clinics is nearly double of those in community (2/1000). For those in residential care such as people with intellectual disability the rates are 3.5/1000 increasing to 4.2/1000 in treatment refractory population and further rising to 6.2/1000 in those ineligible for surgery. SUDEP rates of 1 in 200-300 person-years are seen in cohorts in specialist centres and up to almost 1 in 100 person-years in those with severe treatment resistant epilepsy, being particularly high among those with uncontrolled tonic-clonic seizures. While recognised across the age span the highest prevalence of SUDEP is in 20–45-year-olds.

The pathophysiology of SUDEP is uncertain, but it is considered to be an early postictal phenomenon, usually triggered by a generalised tonic-clonic seizure, leading to a severe centrally mediated cardiac and respiratory dysfunction. An alternate related mechanism is terminal apnoea and cardiac arrest post partial recovery. In a majority of reported SUDEP cases, the person was discovered in a prone position, likely having been asleep, suggesting suffocation.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the risk factors associated with SUDEP. There is significant public and political concern about this, especially as SUDEP may be prevented in some people. The current lack of evidence as to which risk factors may be important to a specific individual prevents person centred risk assessments and empowerment of those with epilepsy with regard to their safety.
Relevance to NICE guidance	SUDEP has been considered in this guidance and there is a lack of data on type, nature and relative importance of risk factors for SUDEP.
Relevance to the NHS	There is increasing recognition that a constellation of factors big and small across various health and social roles and across timelines could influence SUDEP outcomes. The outcome of this research would better inform clinicians and those with epilepsy of SUDEP risk, enable self-empowerment and inform patient- clinician relationships. The work would help reduce risk factors for SUDEP leading to a reduction of epilepsy related mortality. In turn, this work will lead to broader positive socioeconomic impact.
National priorities	High – The NHS RightCare epilepsy tool kit 2021 identified investigating SUDEP and its risk factors as a Systems improvement critical priority. It is considered essential for the NHS to be responsive to identify those at most risk of SUDEP

	in particular in special populations such as people with intellectual disability and pregnant women. The RightCare Toolkit recommends the need to develop and implement use of a standard risk template for people living with epilepsy that crosses organisational boundaries. In addition, the NHSE guidance highlights the need for population and whole system approach to risk mitigation particularly SUDEP. The optimal clinical epilepsy pathway published in December 2019 as part of NHS England's specialised neurology programme highlights the need for regular between appointments risk monitoring using self-empowerment technology and regular risk communication to ensure better outcomes. The currently underway National Confidential Inquiry into Epilepsy Deaths is keen to focus and understand on core goals of physical, psychological and social contributors and influencers to epilepsy related mortality including SUDEP. This inquiry will also assess organisational aspects of care including education, local and national guidelines, and delivery of care with a view to give strong recommendations to improve epilepsy mortality related outcomes.
Current evidence base	Work done to date has largely focused on seizure related factors. The strongest association identified is with frequency of generalised tonic-clonic seizures and refractory epilepsy. There is evidence to suggest good concordance with ASMs and nocturnal surveillance can be protective factors in mitigating SUDEP. SUDEP is a rare outcome and at present it is difficult to predict in a new presentation of epilepsy as to who is at increased risk of epilepsy associated mortality. A further challenge in the UK is that the diagnosis of SUDEP relies on the Coronial system, and not the medical system, making it potentially more difficult to establish the diagnosis if an index of suspicion is not raised for the consideration of SUDEP in a death involving a person with epilepsy. Further, a definite diagnosis of SUDEP cannot be made unless a neuropathological autopsy is requested. SUDEP is being increasingly being recognised as a fatal culmination of various potentially modifiable risk factors which could include seizure, physical, psychological and psychological health factors influenced by cultural perspectives. Current evidence does not recognise these multi-dimensional risk factors or how they may evolve over time. It has, though, been shown that person-centred empowerment can reduce risk factors leading to better seizure outcomes with the possibility of reducing SUDEP.
Equality considerations	There is little research on the nature and associations of risk factors in specific populations – particularly ethnic minorities, those from lower socioeconomic groupings, and those with intellectual and/or developmental disabilities. These populations are either more impacted by SUDEP or poorly studied thus require careful consideration.

Modified PICO table

Population	All people with epilepsy
Intervention	Identification and establishing the risk factors for SUDEP
Comparator	General population
Outcome	Death
Study design	Prospective Cohort study – Research Register
Timeframe	Long term
Additional information	The registry in addition to basic demographics (age/sex/ethnicity) should look to collect all available relevant information on seizure factors, other physical health factors (chronic conditions particularly respiratory/cardiac/metabolic), psychological and neurodevelopmental co-morbidity, medication (ASMs/psychotropics/others), sleep habits, social issues (compliance/alcohol & recreational drug use/relationships). To set up sub-studies as prospective cohort registers for high-risk populations particularly – • Treatment resistant and refractory generalised tonic-clonic seizures • Neurodevelopmental conditions • Genetic conditions