National Institute for Health and Care Excellence

FINAL

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

[17] Evidence review: Prediction of death, including SUDEP, in people with epilepsy

NICE guideline NG217

Evidence review underpinning research recommendations in the NICE guideline.

April 2022

FINAL

Developed by the National Guideline Centre

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ISBN: 978-1-4731-4513-9

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1.1 Review question

What are the most accurate tools to predicting death, including SUDEP, in people with epilepsy?

1.1.1 Introduction

Epilepsy is associated with risks of premature morbidity and mortality from a number of causes. These include a risk of injury, including head injury, and mortality in the form of drowning and accidents. One 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.

Prediction of which people are most at risk of these adverse outcomes would allow health care practitioners to work together with people with epilepsy, particularly those identified to be at higher risk of mortality, and better target education and management options on an individualised basis.

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: People with a diagnosis of epilepsy. Exclusion: New-born babies with acute symptomatic seizures.
Target condition	Epilepsy
Prediction test	Any risk prediction tools for death, including SUDEP, used clinically, performed at baseline.
Reference standard	Death/SUDEP during subsequent follow-up.
Statistical measures	Discrimination: sensitivity, specificity, C statistic. These measures assess how accurately the tool can predict those who will and will not get SUDEP/die from any cause. Calibration: tests how well the tool results predict the absolute risk of getting SUDEP/dying from any cause. Net classification Improvement: a sensitive method for evaluating the different levels of predictive accuracy accruing from a change in the prediction tool. Follow up: use all available but stratify: <1 yr,1-5 years, >5 years.
Study design	Internal or external validation studies of the prediction tools. External validation studies (tested on a different study sample to the derivation sample) are preferred, although internal derivation studies (where the validation samples are different, but still drawn from the identical population to the derivation sample) will still be included with a downgrade for indirectness. These validation studies will almost certainly be prospective cohort studies, but retrospective cohort studies will be used if available.

1.1.3 Methods and process

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

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

1.1.4 Predictive evidence

1.1.4.1 Included studies

A search was made for studies that measure the accuracy of tools for predicting SUDEP/death from any cause. Three prediction tool studies were included in the review.[4, 12, 19] The key characteristics of these studies are summarised in Table 2 below, while Table 3 summarises the predictions tools used in the studies. Evidence from these studies is summarised in the clinical evidence summary below in Table 4 to Table 7.

Stratification of studies was planned for age (<18/≥18), follow up time (<1 yr., 1-5 yrs., >5 yrs.), and whether the event outcome was specifically SUDEP or all-cause mortality (which could include SUDEP). Because there was >1 stratification strategy, studies were analysed in emergent strata that were permutations of the stratification categories. The two strata that emerged were:

- Adult/unclear follow up time/SUDEP
- Mixed age group/>5 years follow up/ all-cause mortality

Within each stratum, sub-grouping had been planned to try to 'explain' heterogeneity in meta-analyses according to the following strategies: Young subgroups: <2, 2-11, 11-18; Adults: 18-55, >55; Learning disability vs no learning disability; Head injury vs no head injury; Type of epilepsy; gender. However, these sub-grouping strategies were not required because in the absence of pooled data, no heterogeneity existed.

The assessment of the evidence quality was conducted with emphasis on discrimination measures such as sensitivity/specificity and the C statistic, as these were identified by the committee as the primary measures in guiding decision-making. The committee set clinical decision thresholds for

- Sensitivity: 0.9 above which a test would be recommended and 0.6 below which a test is of no clinical use.
- Specificity: 0.5 above which a test would be recommended and 0.1 below which a test is of no clinical use.
- C statistics: 0.7 above which a test would be recommended and 0.5 below which a test is of no clinical use.

See also the study selection flow chart in Appendix C, and study evidence tables in Appendix D.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the predictive evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Predictive test	Reference standard (outcome event) definition	Number of outcome events	Follow up duration
Baysal-Kirac, 2017[4]	Adults of mean age 34.6 from secondary care in Turkey; AED resistant epilepsy; 21 M, 26F; TLE (n=20), extratemporal or multifocal epilepsy (n=27)	SUDEP-7 inventory score	SUDEP on autopsy	1	Unclear
Novak, 2015[19]	Adults of mean age 33, from unclear setting in USA; AED resistant epilepsy; 10M, 15F; Type of epilepsy unclear	SUDEP-7 inventory score (revised)	SUDEP on autopsy	2	Unclear
Keezer, 2015[12]	Adults and children of median age 24.4 (13.8 – 56.1) in UK; people with newly suspected recurrent unprovoked epileptic seizures; 291M,267F; idiopathic/cryptogenic epilepsy 76.3%, remote symptomatic epilepsy 23.7%;	Charlson Index The Elixhauser Index The Epilepsy-specific index	Any mortality (on death certificate)	unclear	23.3 years

Table 3: Summary of prediction tools used in the included studies and constituent variables and cut-offs (where available)

Risk tool	Variables and scoring
SUDEP-7 inventory score (original)	SUDEP – 7 inventory score from 1 to 10, scored as follows: >3 generalised tonic clonic (GTCs) seizures in the past year (2 points), one or more GTCs in the past year (1 point), one or more seizures of any type over last 12 months (1 point), >50 seizures of any type per month over the last 12 months (2 points), >=30 years of epilepsy (3 points), currently using >=3 AEDs (1 point), IQ<70 (2 points); the standard threshold for higher/lower risk not provided in paper
SUDEP-7 inventory score (revised to prevent score inflation)	SUDEP – 7 inventory score from 1 to 10, scored as follows: >3 generalised tonic clonic (GTCs) seizures in past year (2 points), one or more GTCs in past year (1 point, but 0 points if already scored 2 points for >3 GTCs in past year), one or more seizures of any type over last 12 months (1 point, but 0 points if >50 seizures of any type per month), >50 seizures of any type per month over the last 12 months (2 points), >=30 years of epilepsy (3 points), currently using >=3 AEDs (1 point), IQ<70 (2 points); the standard threshold for higher/lower risk not provided in paper
Charlson Index (for mortality generally, not SUDEP specifically)	Weighted scores were given to each of 19 co-morbidities: Myocardial infarct (1), Congestive heart failure (1), Peripheral vascular disease (1), Cerebrovascular disease (1), Dementia (1), Chronic pulmonary disease (1), Connective tissue disease (1), Ulcer disease (1), Mild liver disease (1), Diabetes (2), Hemiplegia (2), Moderate or severe renal disease (2), Diabetes with end-organ damage (2), Any tumour (2), Leukaemia (2), Lymphoma (2), moderate or severe liver disease (3), metastatic solid tumour (6), AIDS (6). Thresholds: low risk of death=0, low-medium=1, medium high=2, high>3
The Elixhauser index (for mortality generally, not SUDEP specifically)	A weighted score is assigned to each of the 21 comorbid conditions, as follows: Drug abuse (-7), Obesity (-4), Depression (-3), Blood loss anaemia (-2), Deficiency anaemia (-2), Valvular disease (-1), Peripheral vascular disorders (2), Chronic pulmonary disease (2), Coagulopathy (3), Solid tumour without metastasis (3), Pulmonary circulation disorders (4), Renal failure (4), Cardiac arrhythmias (4), Fluid and electrolyte disorders (5), Neurodegenerative disorders (5), Weight loss (6), Paralysis (6), Congestive heart failure(7), Lymphoma (9), Liver disease (11), Metastatic cancer(12). Thresholds: low risk of death<0, low-medium=0, medium high=1-4, high≥5
The Epilepsy-specific index (for mortality generally, not SUDEP specifically)	There are 14 comorbid conditions, in addition to age and sex, deemed to be significant predictors of mortality. These are as follows: Pulmonary circulation disorders (1), Hypertension (1), Cardiac arrhythmias (1), Congestive heart failure (2), Peripheral vascular disease (2), Renal disease (2), Solid tumour without metastasis (2), Paraplegia and hemiplegia (2), Aspiration pneumonia (2), Dementia(2), Brain tumour (3), Anoxic brain injury (3), Moderate or severe liver disease (3), Metastatic cancer (6). Thresholds: low risk of death=0, low-medium=1, medium high=2, high>3

See Appendix D for full evidence tables

1.1.6 Summary of the predictive evidence

1.1.6.1 Adult/unclear follow up/SUDEP stratum

The evidence for this section was derived from two studies[4, 19] that did not directly present data on the predictive accuracy of the evaluated tools. However, both studies presented the scores of those who developed SUDEP during follow up, as well as the scores of those that did not develop SUDEP during follow up, which allowed the reviewer to calculate sensitivities and specificities at each threshold of the score. For each threshold of score (starting from ≥1 up to ≥ 9), 2x2 tables were created. 2x2 table cells for true positives (those who developed SUDEP with a score at or above the threshold), false negatives (those who developed SUDEP with a score below the threshold), false positives (those who did not develop SUDEP with a score at or above the threshold), and true negatives (those who did not develop SUDEP with a score below the threshold) were then populated. This permitted sensitivity and specificity data at each threshold to be calculated (albeit with high uncertainty for sensitivity because of the small sample sizes), but the ROC curves produced only permitted an estimation of the area under the curve (C statistics).

1.1.6.2 Discrimination

Table 4: Clinical evidence profile: Discriminative capacity (C statistic) of prediction tools featured in the studies (see Table 3).

Prediction tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve Individual study effects [point estimate (95% Cis)] Pooled effect/range /median	Quality
SUDEP – 7 inventory score	1	47	Very serious risk of bias[a]	NA	No serious indirectness	Very serious[b]	Likely to be between 0.9 and 0.95, based on the area under the ROC curve produced by reviewer (as extrapolation of data provided in paper). No 95% CIs were calculable, but uncertainty around this point estimate is likely to be very high, hence the allocation of 'very serious	VERY LOW

Prediction tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve Individual study effects [point estimate (95% Cis)] Pooled effect/range /median	Quality
							imprecision' to this outcome	
SUDEP – 7 inventory score REVISED	1	25	Very serious risk of bias[a]	NA	No serious indirectness	Very serious[b]	Likely to be between 0.7 and 0.8, based on the area under the ROC curve produced by reviewer (as extrapolation of data provided in paper). No 95% CIs were calculable, but uncertainty around this point estimate is likely to be very high, hence the allocation of 'very serious imprecision' to this outcome	VERY LOW

a) Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for all risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status.
b) The judgement of precision was based on the spread of confidence interval across two clinical thresholds: C statistics of 0.5 and 0.7. The threshold of 0.5 marked the boundary between no predictive value better than chance and a predictive value better than chance. The threshold of 0.7 marked the boundary above which the committee might consider recommendations. If the 95% Cis crossed one of these thresholds a rating of serious imprecision was given and if they crossed both of these thresholds a rating of very serious imprecision as given.

Table 5: Clinical evidence profile: sensitivity and specificity of prediction tools featured in the studies (see Table 3).

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SUDEP – 7 tool (threshold ≥1)	1	47	**1.0(0.025–1.0)**	**0.0(0.0–0.071)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool (threshold ≥2)	1	47	**1.0(0.025–1.0)**	**0.087(0.024–0.208)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW
SUDEP – 7	1	47	**1.0(0.025–1.0)**	**0.283(0.160–0.435)**	**Sensitivity**				

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
tool (threshold ≥3)					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious risk of imprecision	LOW
SUDEP – 7 tool (threshold ≥4)	1	47	**1.0(0.025–1.0)**	**0.457(0.309–0.610)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW
SUDEP – 7 tool (threshold ≥5)	1	47	**1.0(0.025–1.0)**	**0.630(0.476–0.768)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SUDEP – 7 tool (threshold ≥6)	1	47	**1.0(0.025–1.0)**	**0.826(0.686–0.922)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool (threshold ≥7)	1	47	**1.0(0.025–1.0)**	**0.913(0.792–0.976)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool (threshold ≥8)	1	47	**0.0(0.00–0.975)**	**0.957(0.852–0.995)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SUDEP – 7 tool (threshold ≥9)	1	47	**0.0(0.00–0.975)**	**0.978(0.885–0.999)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥1)	1	25	**1.0(0.158–1.0)**	**0.0(0.0–0.148)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SUDEP – 7 tool REVISED VERSION (threshold ≥2)	1	25	**1.0(0.158–1.0)**	**0.261(0.102–0.484)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥3)	1	25	**1.0(0.158–1.0)**	**0.348(0.164–0.573)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥4)	1	25	**1.0(0.158–1.0)**	**0.478(0.268-0.694)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				

Prediction tool	No of studies	n	Sensitivity	Specificity	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
					Very serious risk of bias[a]	NA	No serious indirectness	Serious risk of imprecision[b]	VERY LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥5)	1	25	**0.5(0.126-0.987)**	**0.826(0.612-0.951)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥6)	1	25	**0.5(0.126-0.987)**	**0.913(0.720-0.989)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥7)	1	25	**0.0(0.0-0.842)**	**0.957(0.781-0.999)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW

					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥8)	1	25	**0.0(0.0-0.842)**	**1.0(0.852-1.0)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW
SUDEP – 7 tool REVISED VERSION (threshold ≥9)	1	25	**0.0(0.0-0.842)**	**1.0(0.852-1.0)**	**Sensitivity**				
					Very serious risk of bias[a]	NA	No serious indirectness	Very serious risk of imprecision[b]	VERY LOW
					specificity				
					Very serious risk of bias[a]	NA	No serious indirectness	No serious imprecision	LOW

a) Risk of bias was assessed using the PROBAST checklist. Risk of bias was serious for all risk tools because none of the studies reported any blinding of assessors for risk tool data.
b) Imprecision was assessed based on inspection of the confidence region in the meta-analysis or, where meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the confidence interval around the point estimate crossed one of the clinical thresholds (0.90 or 0.60 for sensitivity and 0.5 and 0.1 for specificity), and downgraded by 2 increments when the confidence interval around the point estimate crossed both of the clinical thresholds. The upper clinical threshold marked the point above which recommendations would be possible, and the lower clinical threshold marked the point below which the tool would be regarded as of little clinical use.

1.1.6.2.1 Mixed age, >5 yr. follow up, All-cause mortality stratum

Discrimination

Table 6: Clinical evidence profile: Discriminative capacity (C statistic) of prediction tools featured in the studies (see table 3).

Prediction tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve Individual study effects [point estimate (95% Cis)] Pooled effect/range /median	Quality
Charlson Index	1	558	No serious bias	NA	No serious indirectness	Unclear – assumed serious imprecision	Harrel's C[c]: 0.8703 (no uncertainty values given)	MODERATE
Elixhauser Index	1	558	No serious bias	NA	No serious indirectness	Unclear – assumed serious imprecision	Harrel's C: 0.8701 (no uncertainty values given)	MODERATE
Epilepsy-specific Index	1	558	No serious bias	NA	No serious indirectness	Unclear – assumed serious imprecision	Harrel's C: 0.8714 (no uncertainty values given)	MODERATE

a)Risk of bias was assessed using the PROBAST checklist (see Appendix F).Risk of bias was serious for all risk tools because none of the studies reported any blinding of assessors for risk tool data and outcome status.
b) *The judgement of precision was based on the spread of confidence interval across two clinical thresholds: C statistics of 0.5 and 0.7. The threshold of 0.5 marked the boundary between no predictive value better than chance and a predictive value better than chance. The threshold of 0.7 marked the boundary above which the committee might consider recommendations. If the 95% Cis crossed one of these thresholds a rating of serious imprecision was given and if they crossed both of these thresholds a rating of very serious imprecision as given.*
c) *Harrel's C index is analogous to the AUC or C score; in that it provides an overall measure of accuracy at all thresholds. However, it is designed for use with Cox proportional hazard models.*

Calibration

Table 7: Clinical evidence profile: Calibration (goodness of fit) (Schoenfeld p value) of prediction tools featured in the studies (see table 3).

Prediction tool	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Schoenfeld statistic p value [a] (<0.05 indicates proportionality assumption not met)	Quality
Charlson Index	1	558	No serious bias	NA	No serious indirectness	NA	0.1323	HIGH
Elixhauser Index	1	558	No serious bias	NA	No serious indirectness	NA	0.3672	HIGH
Epilepsy-specific Index	1	558	No serious bias	NA	No serious indirectness	NA	0.5597	HIGH

a)If the p value is <0.05 this indicates that linearity between predictor and the hazard of death (denoting calibration) is unlikely to be explained by sampling error.

See details of predictive evidence in Appendix D.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 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.

1.1.8 Economic model

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

1.1.9 Evidence statements

1.1.9.1 Clinical evidence statements

- None.

1.1.9.2 Economic

- No relevant economic evaluations were identified.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1 The outcomes that matter most

During protocol development, sensitivity and specificity of the prediction tool were agreed to be critical outcomes. Sensitivity is critical because it is vital to know how many people that go on to have SUDEP or die from other causes will be incorrectly labelled as low risk by the prediction tool (the higher the number of such false negatives, the lower the sensitivity). Specificity is also critical because it is important to know how many people who do not go on to have SUDEP or die from other causes will be mistakenly labelled as high risk by the prediction tool (the higher the number of such false positives, the lower the specificity). Knowledge of the likelihood of false negatives and false positives is essential so that clinicians can use tools where 1) patients at high risk will not be missed, and 2) patients at low risk will not be given inappropriately high levels of surveillance and anxiety. Sensitivity was deemed to be more important than specificity because the harms resulting from false negatives are worse than the harms resulting from false positives in the context of SUDEP/all-cause mortality prediction. This is because a false negative result could lead to patients who require preventative measures not receiving the care that they need, which may cause harm. In contrast, a false positive result may lead to increased costs and anxiety but is unlikely to lead to physically dangerous sequelae. However, specificity still needs to be high enough to correctly identify a reasonable proportion of those not requiring preventative measures as the use of a tool with 100% sensitivity with very poor specificity provides little advantage over not using a prediction tool at all because it will label most patients at high risk even when they are not.

C statistics were regarded as less important by the committee because they do not differentiate between sensitivity and specificity (from which they are derived) even though sensitivity may be more important in this context.

Calibration statistics were regarded as of equal status to sensitivity, as they allow an accurate evaluation of the agreement between the absolute risks yielded by the tools and the observed risks at all levels of risk; accurate risk evaluation may be of great importance when discussing results with the patient.

1.1.10.2 The quality of the evidence

The evidence examining SUDEP risk tool scores was graded low or very low. This was due to methodological limitations such as a lack of blinding and also the very high imprecision in sensitivity measures due to the small number of outcome events. The evidence looking at tools for all-cause mortality was moderate to high, as the methodology was more rigorous. However, measures of imprecision were not provided.

1.1.10.3 Benefits and harms

The data on the predictive accuracy of the SUDEP-7 and SUDEP-7 revised tools suggested a very high sensitivity (1.0) and specificity (0.91) at a threshold of $\geq$7 for SUDEP 7 and a high

sensitivity (1.0) and moderate specificity (0.48) at a threshold of ≥4 for the revised version. If sensitivities and specificities are above 0.9, a tool would normally be considered potentially useful. However, the very wide confidence intervals for sensitivity due to the small number of SUDEP events made these results largely meaningless, as they suggested that in the population, the sensitivity could plausibly lie anywhere between 0.025 to 1.0. The C statistics results showed a similarly encouraging point estimate, but again the confidence intervals (although not calculable) would have been too wide to enable any useful conclusions. Therefore, the committee concluded that there was inadequate evidence to recommend SUDEP prediction tools.

For all-cause mortality prediction, three tools were found with excellent Harrel's C statistics. No confidence intervals were provided, but given the large sample size of >500, it is highly likely that these estimates were precise. However, calibration evidence was poorly reported, with no clear measure of effect and only a p-value showing that the calibration was not entirely due to sampling error. Overall, the committee did not think that the evidence provided enough useful data to allow any recommendation for all-cause mortality tools.

The committee, therefore, agreed that a recommendation was not possible for the use of any particular SUDEP or all-cause mortality prediction tools. The committee discussed whether it is appropriate to have risk prediction tools for SUDEP or all-cause death. The committee considered that a tool, even if accurate on a population level, may give erroneous results for some individuals, with the attendant harms. The determination of a high risk is frightening to the patient and may cause significant adverse psychological effects. The committee agreed that medical care should focus on assuming that all people are at risk of death and that the main attention should be on identifying and modifying risk factors, stopping all seizures and discussing this with the individual with epilepsy and their family and carers. Nevertheless, risk tools were acknowledged to have a potential important role, as there is often a need to prioritise those people at highest risk and ensure they get urgent and proactive care. There are insufficient resources to assume all people are at high risk and it may be important to yield higher scores to prompt more urgent action. The example was given of a patient who might intuitively be regarded as of low risk by a non-epilepsy clinician but who might yield a high score demonstrating a real risk. This might precipitate preventative action that might not otherwise be taken.

When developing a research recommendation, the committee agreed that a tool should not focus entirely on SUDEP and should look at all causes of mortality, because there are other causes of death in epilepsy such as suicide, injury, or drowning.

The committee agreed any new tools would require development from very large databases. Large national or international registries, recording SUDEP, all causes of death and a wide range of plausible risk factors would be necessary in order to produce data of sufficient detail to inform a useful tool. These would ideally need to collect data over a long period in order to collect useful numbers of outcomes. These developmental databases could then be used to create new algorithms, which could be validated in large external datasets.

In addition, the committee was aware that the SUDEP-7 tool showed some promise, despite the uncertainties in the data, and also agreed that further larger-scale validation studies of SUDEP-7 should be conducted in the shorter term.

1.1.11 Cost effectiveness and resource use

No economic evidence was identified for this review.

The committee concluded they were unable to make a recommendation based on the clinical evidence presented. Subsequently, the committee made a research recommendation for a risk prediction tool to be developed.

1.1.12 Other factors the committee took into account

None.

1.1.13 Recommendations supported by this evidence review

This evidence review supports the research recommendations on:

- identifying and mitigating SUDEP risk factors,
- developing a risk prediction tool to detect all-cause mortality (including SUDEP)
- creating a validation of a risk prediction tool to detect the probability of epilepsy-related death in people with epilepsy.

No recommendations were made from this evidence review.

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Appendices

Appendix A Review protocols

A.1 Review protocol for prediction of death/SUDEP

ID	Field	Content
1.	Review title	Prediction of a death, including SUDEP, in people with epilepsy
2.	Review question	What are the most accurate tools to predicting death, including SUDEP, in people with epilepsy?
3.	Objective	To evaluate the best risk prediction tools for predicting death, including SUDEP, in people with epilepsy.
4.	Searches	The following databases (from inception) 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 Other searches: • None

		The searches may be re-run 6 weeks before 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
6.	Population	Inclusion: People with a diagnosis of epilepsy. Exclusion: New-born babies with acute symptomatic seizures
7.	Predictor	Any risk prediction tools for death, including SUDEP, used clinically
9.	Types of study to be included	Internal or external validation studies of the prediction tools. External validation studies (tested on a very different sample to the derivation sample) are preferred, although internal derivation studies (where the validation sample are different, but still drawn from the identical population to the derivation sample) will still be included with a downgrade for indirectness. These validation studies will almost certainly be prospective cohort studies, but retrospective cohorts will also be used if available
10.	Other exclusion criteria	Case-control studies, cross-sectional studies Non-English language studies.
11.	Context	There is evidence that epilepsy-related death (including SUDEP) may be preventable in some people, and it is therefore important to be able to predict who is likely to die for reasons related to epilepsy so that preventative actions (such as risk modification and earlier onset of management) can be affected.
12.	Primary outcomes (critical outcomes)	Discrimination: sensitivity, specificity, C statistic. These measures assess how accurately the tool can predict those who will and will not, die. Calibration: tests how well the tool results predict the absolute risk of death.

		Net classification Improvement: a sensitive method for evaluating the different levels of predictive accuracy accruing from a change in the prediction tool. Follow up times: any available but stratify as <1 yr., 1-5 yrs., >5 yrs.
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 these potentially eligible studies will be retrieved and assessed in line with the criteria outlined above. A standardised form will be used to extract data from the included studies (see Developing NICE guidelines: the manual section 6.4). 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.

15.	Risk of bias (quality) assessment	Risk of bias quality assessment will be assessed using PROBAST. 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	Where possible suitably adjusted data will be meta-analysed where appropriate. Sensitivity and specificity data will be meta-analysed using a Bayesian approach (using WinBugs software) if 3 or more data points are found. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. C statistics, Net Reclassification Improvement (NRI) and calibration statistics will be meta-analysed using the generic inverse variance function on RevMan. Heterogeneity between the studies in C statistics effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 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. 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/
17.	Analysis of sub-groups	*Non-conditional stratification* children vs adult (18 years or over) Follow up time: <1 yr., 1-5 yrs., >5 yrs. *Conditional stratification* If heterogeneity is identified, where data is available, subgroup analysis will be carried out for the following subgroups: Young stratum: <2, 2-11, 11-18) v older stratum (18-55, >55) Learning disability vs none Head injury vs none Types of seizure gender
18.	Type and method of	☐ Intervention

	review	☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	**Review stage**	**Started**	
		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** NGCEpilepsies@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: •
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/documents.
29.	Other registration details	N/A
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	Epilepsies, risk factors, seizure
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

A.2 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).[17] **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.

Appendix B Literature search strategies

This literature search strategy was used for the following reviews:

- What are the most accurate tools for predicting a further seizure, in people who have had a single seizure?
- What are the most accurate tools to predicting death, including 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.[17]

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 risk factor terms

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 August 2020	Exclusions
Embase (OVID)	1974 – 13 August 2020	Exclusions

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.	(risk* adj2 assess*).ti,ab.
28.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
29.	((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
30.	("ERA scale" or "ERA checklist" or "ERAC" or "Epilepsy risk awareness scale" or "SUDEP and seizure safety checklist" or "Epilepsy self-management scale" or "ESMS" or "Chalfont Seizure Severity Scale").ti,ab.
31.	((risk or predict*) and "EpSMon").ti,ab.
32.	or/27-31
33.	26 and 32

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.	(risk* adj2 assess*).ti,ab.
26.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
27.	((risk* or predict* or prognos*) adj4 (tool* or rule* or index* or indices or score* or scoring or scale* or model* or system* or algorithm* or stratif* or criteria or calculat*)).ti,ab.
28.	("ERA scale" or "ERA checklist" or "ERAC" or "Epilepsy risk awareness scale" or "SUDEP and seizure safety checklist" or "Epilepsy self-management scale" or "ESMS"

	or "Chalfont Seizure Severity Scale").ti,ab.
29.	((risk or predict*) and "EpSMon").ti,ab.
30.	or/25-29
31.	24 and 30

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 9: 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)

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.

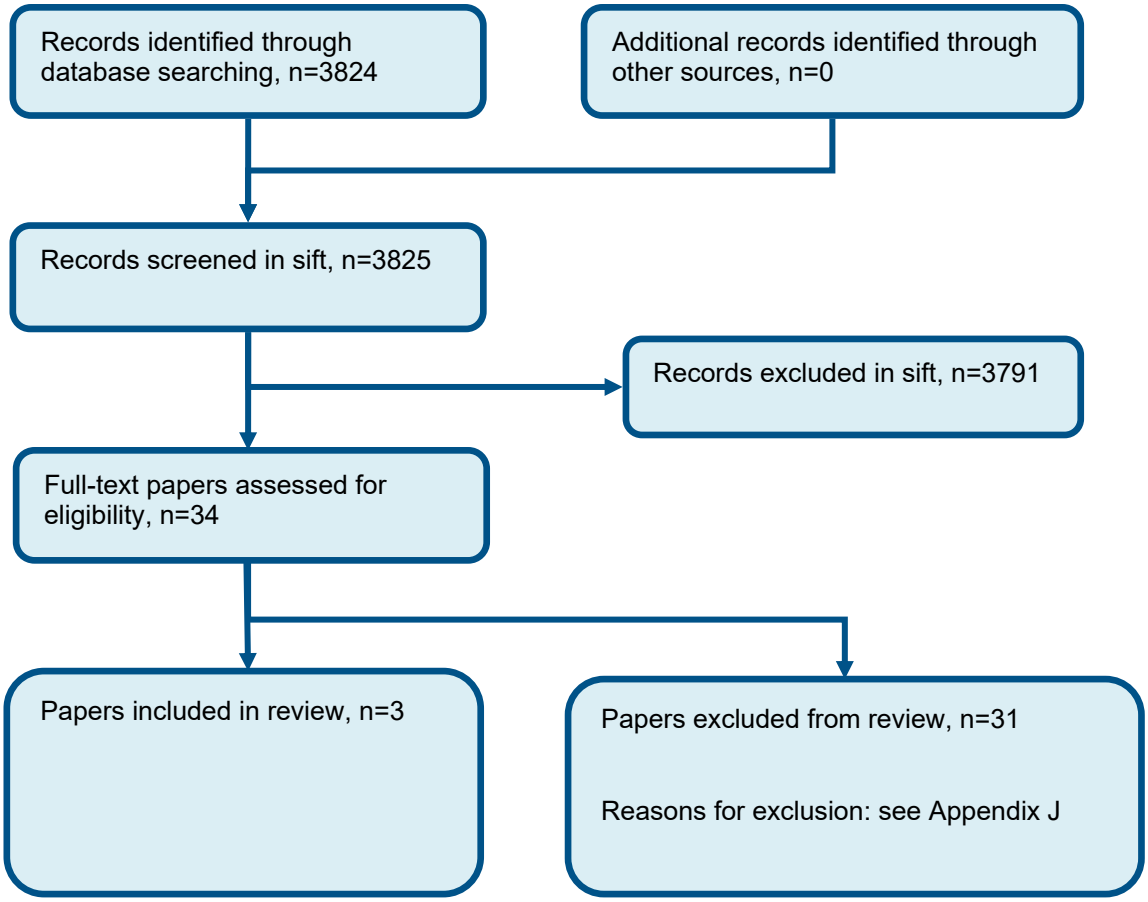
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
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)

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

Appendix C Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of prediction of SUDEP/death from any cause



Appendix D Predictive evidence

Reference	**Baysal-Kirac, 2017[4]**
Study type	Largely cross-sectional study evaluating the association between SUDEP-7 score and heart rate variability; however, there was data on the subsequent death of one patient with SUDEP, which was a longitudinal element
Study methodology	Data source: Secondary care centre Recruitment: Consecutive patients
Number of patients	n = 47
Patient characteristics	Age, mean (sd): 34.6 (11.3) Gender (male to female ratio): 21:26 Ethnicity: unclear Setting: Faculty of medicine Epilepsy centre (likely to be secondary care) in Istanbul Country: Turkey Learning disability: 23.4% with IQ<70 Head Injury: unclear Type of Epilepsy: TLE (n=20), extratemporal or multifocal epilepsy (n=27) Inclusion criteria: Antiepileptic drug -resistant epilepsy (failure of 2 tolerated and appropriately chosen AEDs) Exclusion criteria: Signs or symptoms of diseased other than epilepsy that could influence cardiac autonomic functions
Target condition(s)	Epilepsy – death or SUDEP
Index test(s) and reference standard	Index predictive test

Reference	Baysal-Kirac, 2017[4]
	SUDEP – 7 inventory score from 1 to 10 (details in Table 3) Reference standard (and follow up) Autopsy confirmed SUDEP (follow up unclear)
Results	**Number of SUDEP events: 1** **Discrimination:** This paper did not present C statistics or even sensitivity/specificity at each SUDEP-7 threshold. However, the paper contained a graph that gave information about the SUDEP 7 scores and death from SUDEP for the 47 people with epilepsy (just one participant, with a SUDEP-7 score of 7, died). The data on the scores for each participant is given here. The numbers may not be entirely accurate because they were estimated from a graph, but are broadly correct:

SUDEP7 score	Number with no SUDEP	Number with SUDEP
1	4	0
2	9	0
3	8	0
4	8	0
5	9	0
6	4	0
7	3	1
8	1	0
9	1	0

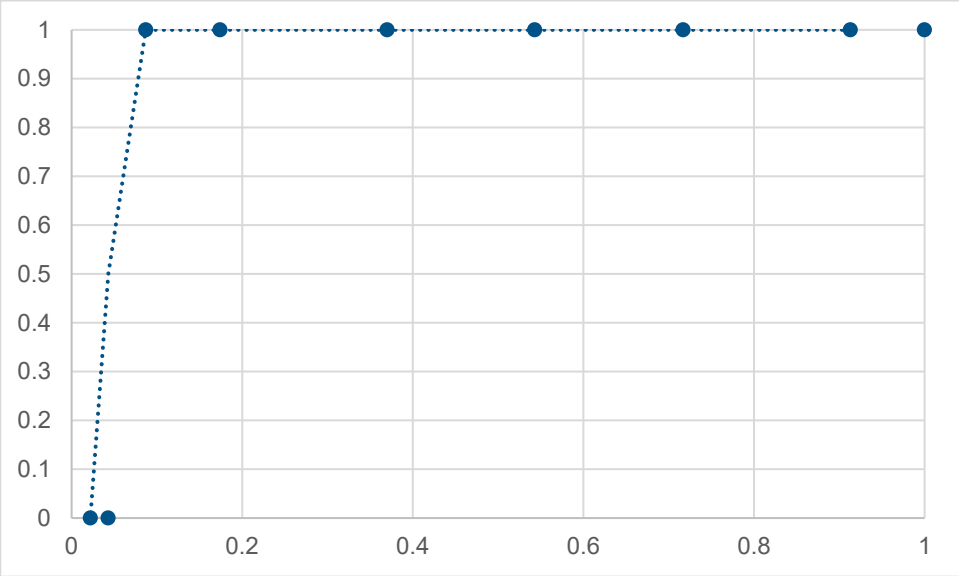
This made it possible to calculate sensitivities and specificities for each threshold.

Threshold score	1-spec	sen	spec
≥1	1	1	0
≥2	0.913	1	0.087
≥3	0.717	1	0.283
≥4	0.543	1	0.457
≥5	0.37	1	0.63

Reference	**Baysal-Kirac, 2017[4]**

≥6	0.174	1	0.826
≥7	0.087	1	0.913
≥8	0.043	0	0.957
≥9	0.022	0	0.978

A ROC curve was then produced in excel, using these data. It was not possible to calculate the C statistic, using online ROC curve calculators, presumably because of the single person with SUDEP. However, the ROC curve below shows an undoubtedly high C statistic, which could be estimated as between 0.90 and 0.95. Care is needed in interpretation though, as it is likely the 95% CIs would be extremely wide because of the single datapoint for SUDEP.



Source of funding	Funding not reported. No conflicts of interest stated.
Limitations	Risk of bias: Very serious; unclear if those adjudicating the tool score were aware of outcome; unclear follow up; very small number of outcomes (n=1) Indirectness: No serious indirectness

Reference	**Baysal-Kirac, 2017[4]**
Comments	

Reference	**Keezer, 2015[12]**
Study type	External validation study
Study methodology	Data source: National General practice Study of Epilepsy, a community-based prospective cohort of 558 people with incident epilepsy followed for a median 23.3 years. Recruitment: External database, compiled from 275 UK GPs who had been asked to report any patient with newly suspected epileptic seizures
Number of patients	n = 558
Patient characteristics	Age, median (IQR) at index seizure: 24.4 (13.8 – 56.1) Gender (male to female ratio): 291:267 Ethnicity: unclear Setting: primary care (275 GP practices across UK) Country: UK Learning disability: unclear Head Injury: unclear Type of Epilepsy: idiopathic/cryptogenic: 76.3%; remote symptomatic 23.7% Inclusion criteria: People with newly suspected recurrent unprovoked epileptic seizures. Exclusion criteria: Single recorded seizure after 12 months of follow up; acute symptomatic seizures occurring within 90 days of the precipitating event
Target condition(s)	Epilepsy – death or SUDEP
Index test(s) and reference standard	Index predictive test **The Charlson index:** 19 comorbidities. Thresholds: low risk of death=0, low-medium=1, medium high=2, high≥3

Reference	Keezer, 2015[12]
	The Elixhauser index: 21 comorbid conditions. Thresholds: low risk of death<0, low-medium=0, medium high=1-4, high≥5 **The Epilepsy-specific index:** 14 comorbid conditions. Thresholds: low risk of death=0, low-medium=1, medium high=2, high≥3 Further details of the tools in Table 3. Reference standard (and follow up) Death (might include SUDEP but not confined to it). Confirmed by death certificate. Follow up 23.3 years
Results	**Number of events: not clearly reported** **Discrimination (multivariable Harrell's C statistic):** Charlson Index: =0.8703 Elixhauser Index: =0.8701 Epilepsy-specific Index: =0.8714 **Calibration (Multivariable Schoenfeld statistic p value, where a value<0.05 indicates the proportionality assumption is not met):** Charlson Index: =0.1323 Elixhauser Index: =0.3672 Epilepsy-specific Index: =0.5597
Source of funding	This work received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.
Limitations	Risk of bias: No serious risk of bias

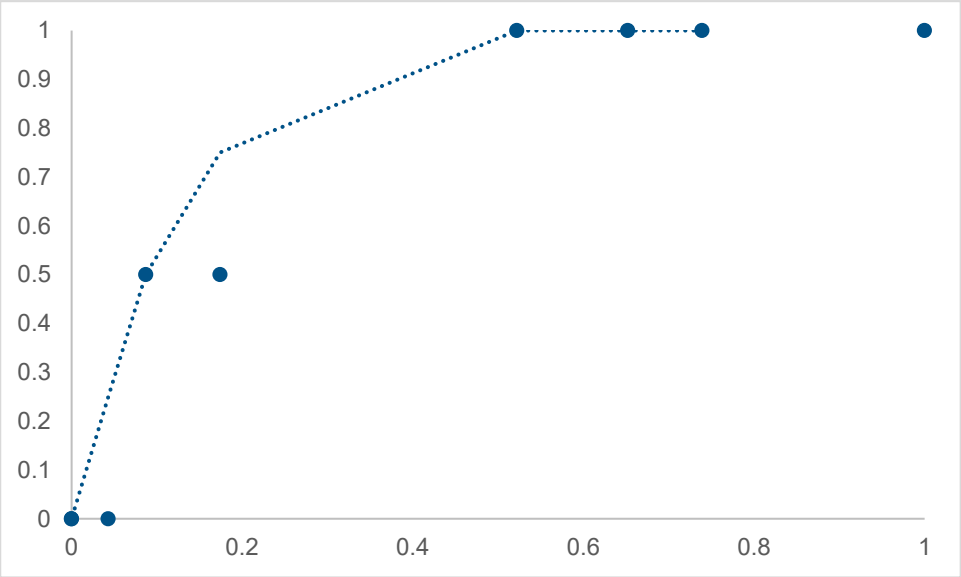
Reference	**Keezer, 2015[12]**
	Indirectness: No serious indirectness
Comments	

Reference	**Novak, 2015[19]**
Study type	Largely cross-sectional study evaluating the association between SUDEP-7 score and heart rate variability; however, there was data on the subsequent death of 2 patients with SUDEP, which was a longitudinal element
Study methodology	Data source: unclear Recruitment: unclear
Number of patients	n = 25
Patient characteristics	Age, mean (sd): 33 (10.3) Gender (male to female ratio): 10:15 Ethnicity: unclear Setting: unclear Country: USA Learning disability: unclear Head Injury: unclear Type of Epilepsy: Drug resistant; type not specified Inclusion criteria: ages 18–70; a history of localized, partial epilepsy; a history of generalizes tonic–clonic or tonic seizures with loss of consciousness; DRE with three or more simple partial, complex partial, or tonic–clonic seizures per month (1981 ILAE classification, partial onset seizures with or without loss of consciousness); prior exposure to at least one or more antiepileptic drugs at therapeutic doses alone or in combination; an EEG and/or an MRI consistent with a localization related epilepsy; and at least three seizures per month for at least

Reference	**Novak, 2015[19]**
	2months prior to the study. Exclusion criteria: progressive medical, cardiac, or other illness; allergy to fish products or fish oil; history of coagulation disorder; history of non-epileptic seizures; consumption of fish oil 30 days or less prior to enrolment; any change in antiepileptic drugs 30 days or less prior to enrolment; warfarin treatment 30 days or less prior to enrolment; history of poor compliance with therapy; drug or alcohol abuse; uncountable seizures as a result of seizure clustering; and pregnancy.
Target condition(s)	Epilepsy – death or SUDEP
Index test(s) and reference standard	Index predictive test SUDEP-7 risk inventory (revised version) Reference standard (and follow up) Autopsy-determined SUDEP (follow up unclear)
Results	**Number of SUDEP events: 2** **Discrimination:**

SUDEP7 score	Number with no SUDEP	Number with SUDEP
1	6	0
2	2	0
3	3	0
4	8	1
5	2	0
6	1	1
7	1	0
8	0	0
9	0	0

Threshold score	1-spec	sen	spec

Reference	**Novak, 2015[19]**			
	≥1	1	1	0
	≥2	0.739	1	0.261
	≥3	0.652	1	0.348
	≥4	0.522	1	0.478
	≥5	0.174	0.5	0.826
	≥6	0.087	0.5	0.913
	≥7	0.043	0	0.957
	≥8	0	0	1.0
	≥9	0	0	1.0
				
	Calibration			
Source of funding	NIH/NCCAM grant (non-commercial)			

Reference	**Novak, 2015[19]**
Limitations	Risk of bias: Very serious; unclear if those adjudicating the tool score were aware of outcome; unclear follow up time; low number of events Indirectness: No serious indirectness
Comments	

Reference	
Study type	External validation study
Study methodology	Data source: Recruitment:
Number of patients	n =
Patient characteristics	Age, median (IQR): Gender (male to female ratio): Ethnicity: Setting: Country: Learning disability: unclear Head Injury: unclear Type of Epilepsy: Inclusion criteria: Exclusion criteria:

Reference	
Target condition(s)	Epilepsy – death or SUDEP
Index test(s) and reference standard	Index predictive test Reference standard (and follow up)
Results	**Discrimination:** **Calibration**
Source of funding	
Limitations	Risk of bias: Very serious; unclear if those adjudicating the tool score were aware of outcome; unclear follow up; very small number of outcomes (n=1) Indirectness: No serious indirectness
Comments	

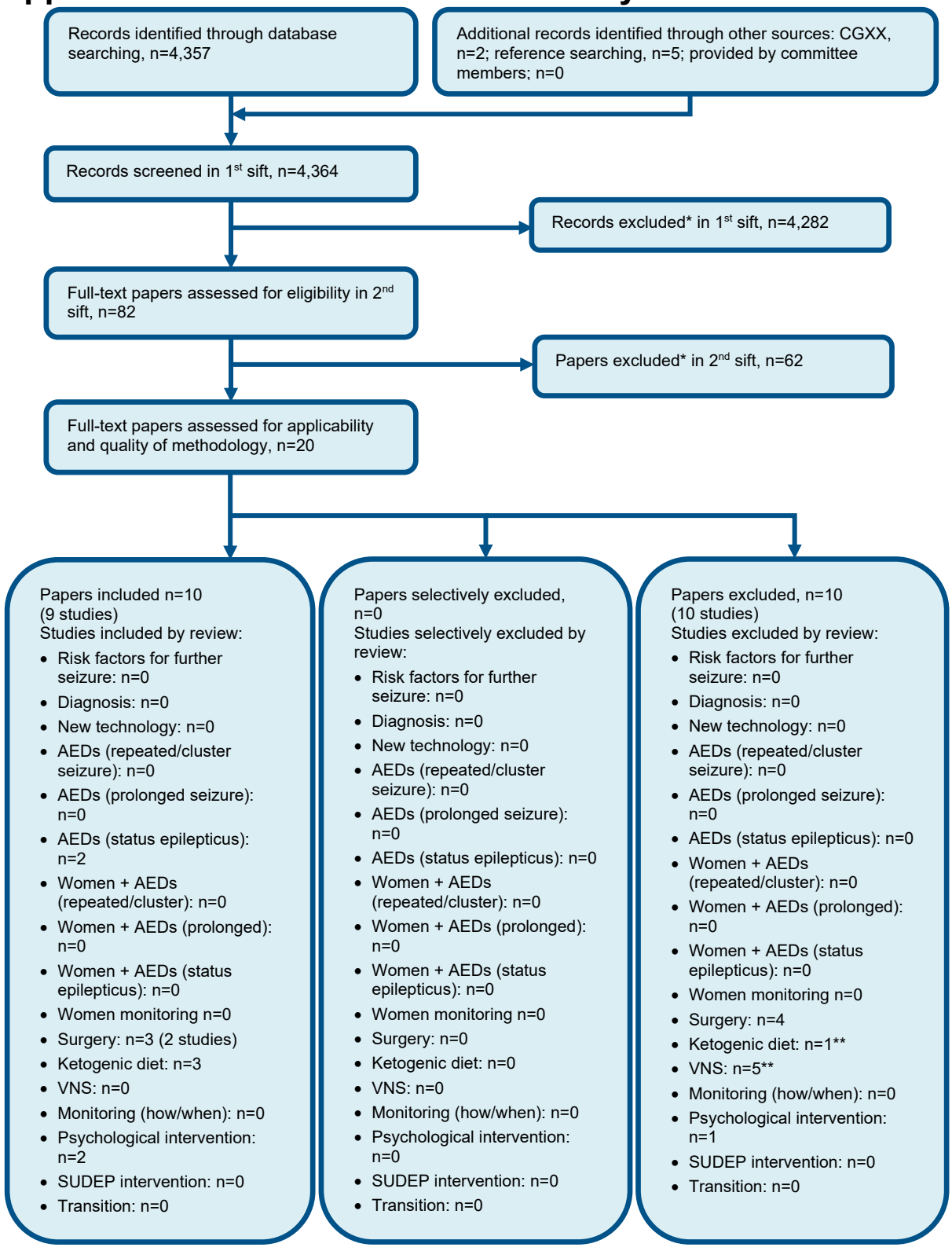
Appendix E Risk of bias (PROBAST)

Study	Appropriate data sources?	Appropriate inclusion and exclusion?	Similar health across participants?	Predictors defined/assessed same for all?	Predictor assessments made without knowledge of outcome data?	Predictors all available at time model meant to be used?	All relevant predictors analysed?	Pre-specified outcome used?	Predictors excluded from outcome definition?	Outcome defined in same way for all?	Outcome determined without knowledge of predictor information?	Reasonable number of outcome events? (100)	Time interval between baseline and outcome appropriate? (≥1 years)	All enrolled included in analysis?	Missing data handled appropriately?	Nonbinary predictors handled appropriately?	Complexities in data accounted for?	Relevant performance measures?	Model recalibrated or likely that calibration not needed?	Overall rating
Baysal-Kirac, 2017[4]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	U	N	U	Y	Y	Y	Y	Y	Y	Very serious risk of bias
Keezer, 2015[12]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	No serious risk of bias
Novak, 2015[19]	Y	Y	Y	Y	U	Y	Y	N	Y	Y	U	N	U	Y	Y	Y	Y	Y	Y	Very serious risk of bias

Appendix F Forest plots

Not applicable

Appendix G Economic evidence study 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.

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 10: Studies excluded from the clinical review

Study	Reason for exclusion
Wandschneider, 2015[32]	No useable outcomes
Hughes, 2009[11]	The group without SUDEP were recruited by the study author, but the group with SUDEP was taken from another study. This does not accord with the protocol design.
Monte, 2007[16]	systematic review - references checked
Shankar, 2015[25]	conference abstract
Shankar, 2018[26]	no useable outcomes
Shankar, 2018[27]	review article - references checked
Watkins, 2018[33]	review article - references checked
Arora, 2015[3]	conference abstract only
Brown, 2013[5]	review article - references checked
Chen, 2005[6]	no useable outcomes
DeGiorgio, 2010[7]	HRV correlated with SUDEP-7 scores; no associations of any measures with actual SUDEP or death outcome were evaluated.
Hirdes, 2014[9]	no useable outcomes - mostly HR data. Does give some data (table 6) that would yield sensitivity/specificity BUT not specifically for people with epilepsy. Similar situation with C statistics (Table 5) as well.
Shankar, 2016[28]	did not evaluate prediction tool; no useable outcomes
Watkins, 2018[34]	review article - references checked
Zhang, 2016[35]	did not evaluate prediction tool; no useable outcomes
Annegers, 2000[1]	did not evaluate prediction tool
Antoniuk, 2001[2]	did not evaluate prediction tool
Langan, 2005[13]	did not evaluate prediction tool
Langan, 1998[14]	did not evaluate prediction tool
Nilsson, 1999[18]	did not evaluate prediction tool
Ridsdale, 2011[21]	did not evaluate prediction tool
Shankar, 2013[24]	Review - references checked
Shankar, 2020[23]	did not evaluate prediction tool
Sun, 2020[29]	did not evaluate prediction tool
Hitiris, 2007[10]	did not evaluate prediction tool
Odom, 2018[20]	No useable outcomes
Ficker, 1998[8]	did not evaluate prediction tool
Lear-Kaul, 2005[15]	did not evaluate prediction tool
Salmo, 2002[22]	did not evaluate prediction tool
Tennis, 1995[30]	did not evaluate prediction tool
Walczak, 2001[31]	did not evaluate prediction tool

J.2 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 11: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix K Research recommendations

K.1 Development of a risk prediction tool for all-cause epilepsy-related death

Why this is important

The currently available risk tools for predicting epilepsy-related mortality (including SUDEP) have inadequate levels of predictive accuracy to allow reliable and safe prediction of epilepsy-related mortality. It is therefore critical for a new risk tool to be developed, ideally based on a large-scale cohort study.

Rationale for research recommendation

Importance to 'patients' or the population	There are currently no tools to provide patients with a sufficiently accurate risk assessment of the risk of epilepsy-related mortality. The development of such a tool would allow more rapid attention to high-risk patients.
Relevance to NICE guidance	Prediction of death has been considered in this guideline, but we did not find any tools with adequate predictive accuracy. The development of such a tool is therefore essential.
Relevance to the NHS	The development of an accurate tool would allow better targeting of early treatment decisions. There is often a need to prioritise those people at highest risk and ensure they get urgent and proactive care. There are insufficient resources to assume all people are at high risk.
National priorities	High. A tool that might accurately reduce mortality in an already vulnerable population is of high priority. In particular multiple reports have highlighted that epilepsy is a risk for mortality in maternal deaths (MBRRACE) and in people with learning disabilities (LeDeR). Please also see the rationale relating to the research recommendation entitled: To identify and mitigate SUDEP risk factors.
Current evidence base	The data on the predictive accuracy of the SUDEP-7 and SUDEP-7 revised tools suggested a very high sensitivity (1.0) and specificity (0.91) at a threshold of >7 for SUDEP 7 and a high sensitivity (1.0) and moderate specificity (0.48) at a threshold of >4 for the revised version. If sensitivities and specificities are above 0.9 a tool would normally be considered potentially useful. However, the very wide confidence intervals for sensitivity due to the small number of SUDEP events made these results largely meaningless, as they suggested

	that in the population the sensitivity could plausibly lie anywhere between 0.025 to 1.0. The C statistics results showed a similarly encouraging point estimate, but again the confidence intervals (although not calculable) would have been too wide to enable any useful conclusions. Therefore, the committee concluded that there was no useful evidence upon which to recommend SUDEP prediction tools. For all-cause mortality prediction, three tools were found with excellent Harrel's C statistics. No confidence intervals were provided, but given the large sample size of >500, it is highly likely that these estimates were precise. However, calibration evidence was poorly reported, with no clear measure of effect, and only a p value showing that the calibration was not entirely due to sampling error. Overall, the committee did not think that the evidence provided enough useful data to allow any recommendation for all-cause mortality tools.
Equality considerations	It would be essential that any developed tool to be applicable across all ethnicities, age groups, genders and be designed with particular attention to those most vulnerable to epilepsy-related mortality, for example those with learning disabilities.

Modified PICO table

Population	People with epilepsy. The types of epilepsy will be heterogeneous, and the numbers of people with each type will be large enough to permit sufficient validity in the subsequent regression analyses.
Baseline variables to be included in logistic regression	The researchers will, pre-hoc, select a range of biologically plausible risk factors for epilepsy-related death and measure these in all participants at baseline. Pre-hoc selection is important to avoid a 'fishing expedition'; that is, to increase the probability that any detected associations are not spurious.
Outcomes	SUDEP Other epilepsy-related death After an adequate follow-up period of at least 5-years the associations between the baseline risk factors and these outcomes will be analysed in a logistic regression analysis.
Study design	Large scale prospective cohort study.
Timeframe	Minimum 5-year follow up.
Additional information	Factors found to be significant predictors for epilepsy-related death and SUDEP after multivariable adjustment for other factors will be included in the prediction model, with score weighting based on the strength of effects. An analysis will be stratified appropriately so that the tool can be made to fit different sub-groups of patients. The resultant model will be a new risk prediction tool for second seizures.

K.2 External validation of a risk prediction tool to detect the probability of epilepsy-related death in people with epilepsy.

Why this is important

After a prediction tool has been developed using a specific cohort of patients it needs to be externally validated to demonstrate that it can accurately predict the outcome in other cohorts.

Rationale for research recommendation

Importance to 'patients' or the population	There are currently no tools to provide patients with a sufficiently accurate risk assessment of epilepsy-related death. Validation of a thoroughly developed tool should allow more rapid and pro-active attention to high-risk patients.
Relevance to NICE guidance	Prediction of death has been considered in this guideline, but we did not find any tools with adequate predictive accuracy. Validation of an adequately developed tool is therefore essential.
Relevance to the NHS	Validation of a tool based on a rigorous developmental process would allow better targeting of early treatment decisions. There is often a need to prioritise those people at highest risk and ensure they get urgent and proactive care. There are insufficient resources to assume all people are at high risk.
National priorities	None known
Current evidence base	The data on the predictive accuracy of the SUDEP-7 and SUDEP-7 revised tools suggested a very high sensitivity (1.0) and specificity (0.91) at a threshold of >7 for SUDEP 7 and a high sensitivity (1.0) and moderate specificity (0.48) at a threshold of >4 for the revised version. If sensitivities and specificities are above 0.9 a tool would normally be considered potentially useful. However, the very wide confidence intervals for sensitivity due to the small number of SUDEP events made these results largely meaningless, as they suggested that in the population the sensitivity could plausibly lie anywhere between 0.025 to 1.0. The C statistics results showed a similarly encouraging point estimate, but again the confidence intervals (although not calculable) would have been too wide to enable any useful conclusions. Therefore, the committee concluded that there was no useful evidence upon which to recommend SUDEP prediction tools. For all-cause mortality prediction, three tools were found with excellent Harrel's C statistics. No confidence intervals were provided, but given the large sample size of >500, it is highly likely that these estimates were precise. However, calibration evidence was poorly reported, with no clear measure of effect, and only a p value showing that the calibration was not entirely due to sampling error. Overall, the committee did not think that the evidence provided enough useful data to allow any recommendation for all-cause mortality tools.

Equality considerations	None known

Modified PICO table

Population	A sample of people with epilepsy that are external to those used in the developmental study, and may cover several sub-populations (each of which will be analysed separately)
Prediction tool	The tool developed by the previous research recommendation
Outcome	Epilepsy-related death SUDEP
Study design	Prospective cohort
Timeframe	Minimum follow up of 5 years, though preferably longer
Additional information	The predictive accuracy of the tool will be examined by discrimination and calibration methods at the discretion of the reviewers