Epilepsy module – evidence profile EPI5: Interventions to prevent epilepsy-related mortality including sudden unexpected death of someone with epilepsy (SUDEP)

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

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Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1 Background

As well as being a common condition, epilepsy is a disorder that associates with substantial risk. Seizures can result in injury, including head injury, burns and also mortality. The risk of mortality associated with epilepsy is known to be higher in LMICs than HICs owing to multiple inter-related reasons including lack of medications and more precarious living environments. (Levira et al., 2017; Watila et al., 2018,)
Mortality associated with epilepsy can be a direct result of a seizure, for example a seizure resulting in drowning; status epilepticus; or Sudden Unexpected Death in Epilepsy (SUDEP). (Mbizvo et al., 2019).
The rate of SUDEP is approximately 1 in 1000 people with epilepsy per year, (Kløvgaard et al., 2021) and this risk is increased in people with poorly controlled epilepsy and especially for those who experience generalized convulsive seizures, perhaps particularly if those convulsive seizures arise from sleep. The underlying cause of the epilepsy may reduce life expectancy and associated comorbidities, including the adverse impact on mental health that associates with epilepsy, can also result in premature death. (Puteikis et al., 2022) It can thus be difficult to disentangle direct and indirect effects of epilepsy on mortality.
Here we specifically evaluate modifiable risk factors and methods to reduce the direct risk from generalized convulsive seizures as this is the seizure type that most associates with mortality

2. Methodology

We summarized the evidence from recent meta-analyses and systematic reviews exploring how mortality associated with epilepsy may be modified.

2.1. PICO Question

EPI5: Which interventions are effective in preventing epilepsy related mortality including sudden unexpected death of someone with epilepsy (SUDEP)?

Population (P): All people with epilepsy
Intervention (I): Methods to reduce risk including checklists, monitoring of people with epilepsy (e.g. nocturnal supervision), access to specialist care, adherence to medication
Comparator (C): Care as usual
Outcomes (O):

- **Critical outcome 1:** Epilepsy related mortality
- **Critical outcome 2**: SUDEP

2.2. Search strategy

Existing systematic reviews were identified by conducting searches in the following bibliographic databases:

- PubMed
- Embase
- Cochrane reviews
- Global Index Medicus

All papers published from 1st January 2000 to June 2022 will be included in the search. Search strings will be structured to consider direct causes of mortality, either as MeSH terms or keywords, including the combination of the following:

(i) Epilepsy OR epileptic OR epilep* OR seizure OR seizures OR Status epilep*

(ii) Mortality OR Death OR Sudden Unexpected Death in Epilepsy OR SUDEP

This will result in papers that consider epilepsy related mortality. We limit the search further to capture methods being applied to reduce mortality without introducing bias. Additional search terms therefore include

(iii) Risk factors OR Interventions OR supervision OR checklist OR monitoring OR prevent*

(iv) Systematic review

It is thought that these terms will capture factors such as medication adherence, which will require monitoring

2.3. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases were assessed for eligibility by examining their titles and abstracts, based on the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant based on their titles and abstracts were retrieved and examined, considering the same inclusion criteria in the second stage of study selection. Data from eligible studies were extracted into pre-defined templates that include the general characteristics of the study, population, intervention, comparator, and outcomes.

All reviewers (AH, MR, AS) independently assessed the eligibility of the studies identified and extracted data from study reports. Discrepancies between the reviewers were resolved through discussions. The search strategy and results reporting the databases searched, the strategy used to search each database, the total number of citations retrieved from each database, and the reasons for excluding some publications after reviewing the full text have been carefully documented. The flow of articles throughout the search and up to the final cohort of included studies is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage.

2.4. Selection and coding of identified records

Endnote was used for the management of references. Data extraction was conducted in excel files with a predefined format which was designed by the involved reviewers. A wide range of study level data regarding date of searches, target population characteristics, type of intervention and control, average length of interventions, total number of participants, mean age, and risk of bias were extracted. All data were collected by two independent reviewers and discrepancies were resolved through discussions.

2.5. Quality assessment

The certainty of the evidence was assessed using **GRADE** (Grading of Recommendations, Assessment, Development and Evaluations). When available, we extracted the GRADE assessments from the meta-analysis. When the GRADE assessment was not available, we assessed it ourselves examining the following criteria:

- **Risk of bias (RoB):** We extracted the RoB ratings from the individual studies included in the meta-analyses (when available). We calculated the percentage of trials rated at low, high, and unclear risk of bias. Based on this information, and in order to take consistent decisions across the available evidence, we rated the RoB GRADE item using a decision tree. This decision tree can be accessed in the appendix.
- **Inconsistency:** We judged inconsistency by examining heterogeneity statistics: I2, which indicates the percentage of heterogeneity between effect sizes, and its 95% confidence interval (95% CI). When the 95% CI of the I^2 is not reported, we computed it and used it in our judgements. We judged inconsistency as serious when I^2 was over 75% and its 95% CI substantially overlaps with the category of considerable heterogeneity (above 75%). Substantial overlap was estimated with the median of the 95% CI. If the 95% CI was not available or could not be calculated, we rated it as

serious if heterogeneity was larger than 50% (category of substantial heterogeneity). If I^2 was not reported and could not be calculated, we rated it as serious.

- **Indirectness**: Direct evidence was derived from research that directly compares the interventions which we are interested in, delivered to the participants in which we are interested, and that measures the outcomes important to patients. We rated for each particular comparison how indirect the reviewed evidence was in terms of population, intervention, and outcomes.
- **Imprecision**: We rated this item based on a standard power calculation (α 0.05 and β 0.20) for detecting an effect size of 0.2, which requires a sample size of 400 participants in total. We judged as serious for all analyses that included less than 400 participants. Analyses including less than 100 participants was rated as very serious. A rating of serious was given when the number of participants included in the analyses was not available.
- **Other considerations**: For this item we explored publication bias. We rated it as serious if there was evidence for publication bias in the meta-analyses, based on statistical tests. However, we did not downgrade the evidence if a meta-analysis did not investigate it.

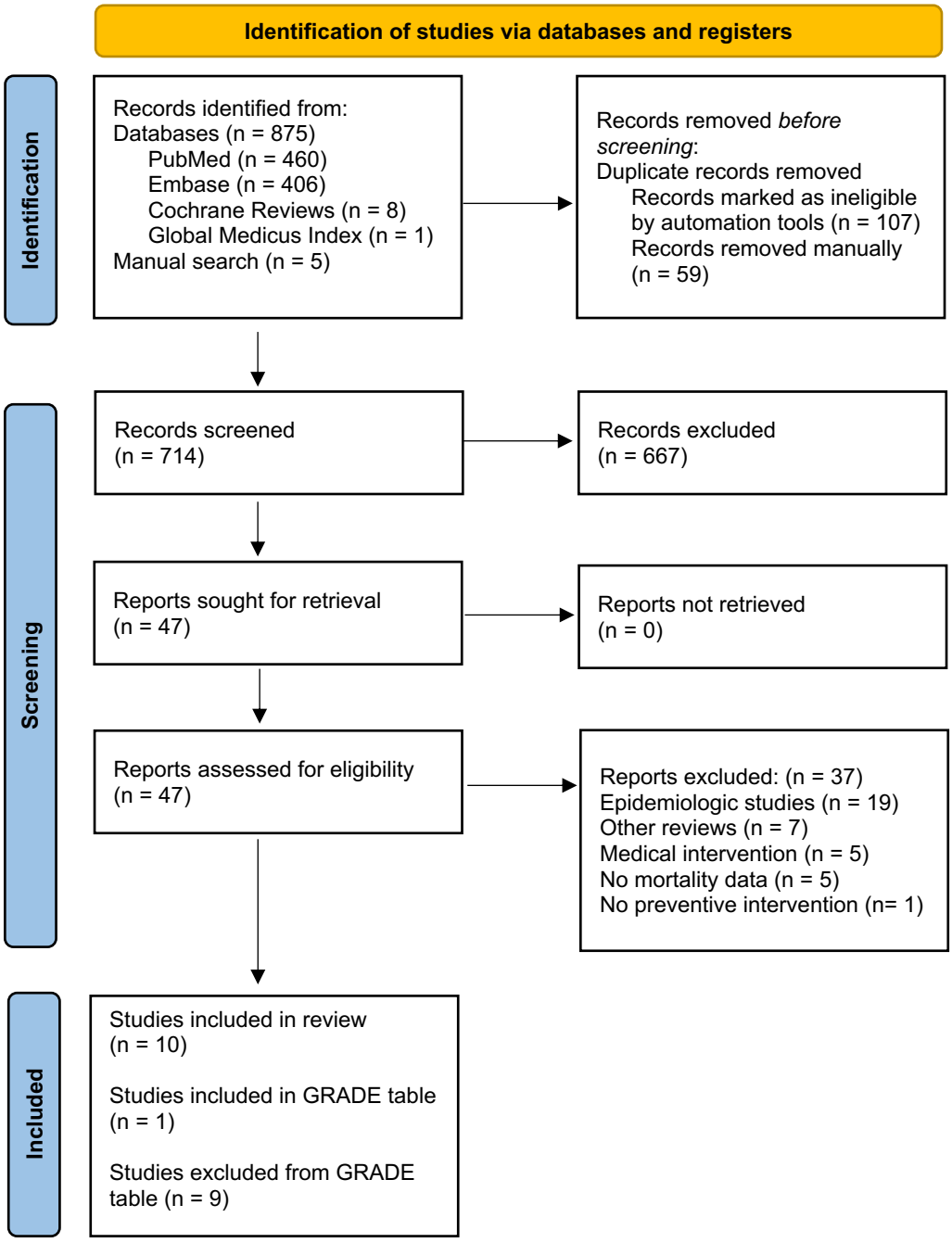
2.6. Analysis of subgroups or subsets

As mortality in epilepsy is seen across all ages and genders, subgroup analysis was not performed since it was thought reasonable that measures to reduce mortality would apply across all people with epilepsy.

3 Results

3.1. Systematic reviews and/or studies identified by the search process

Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



3.1.1. INCLUDED IN GRADE TABLES/FOOTNOTES

Maguire, M. J., Jackson, C. F., Marson, A. G., & Nevitt, S. J. (2020). Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). *The Cochrane database of systematic reviews*, *4*(4), CD011792. https://doi.org/10.1002/14651858.CD011792.pub3

3.1.2. EXCLUDED FROM GRADE TABLES/FOOTNOTES

Batson, S., Shankar, R., Conry, J., Boggs, J., Radtke, R., Mitchell, S., Barion, F., Murphy, J., & Danielson, V. (2022). Efficacy and safety of VNS therapy or continued medication management for treatment of adults with drug-resistant epilepsy: systematic review and meta-analysis. Journal of neurology, 269(6), 2874–2891. https://doi.org/10.1007/s00415-022-10967-6

Shum J, Friedman D. Commercially available seizure detection devices: A systematic review. J Neurol Sci. 2021 Sep 15;428:117611. doi: 10.1016/j.jns.2021.117611. Epub 2021 Aug 6. PMID: 34419933.

Al-Aqeel, S., Gershuni, O., Al-Sabhan, J., & Hiligsmann, M. (2020). Strategies for improving adherence to antiepileptic drug treatment in people with epilepsy. The Cochrane database of systematic reviews, 10(10), CD008312. https://doi.org/10.1002/14651858.CD008312.pub

Cooper, K., Kirkpatrick, P., Brand, C., Rolfe, A., & Florida-James, S. (2020). Discussing sudden unexpected death in epilepsy with children and young people with epilepsy and their parents/carers: A mixed methods systematic review. Seizure, 78, 159–167. https://doi.org/10.1016/j.seizure.2019.10.002

Mahr K, Bergmann MP, Kay L, Möller L, Reif PS, Willems LM, Menzler K, Schubert-Bast S, Klein KM, Knake S, Rosenow F, Zöllner JP, Strzelczyk A. Prone, lateral, or supine positioning at seizure onset determines the postictal body position: A multicenter video-EEG monitoring cohort study. Seizure. 2020 Feb 21;76:173-178. doi: 10.1016/j.seizure.2020.02.008. Epub ahead of print. PMID: 32109735.

Singh G, Sharma M, Krishnan A, Dua T, d'Aniello F, Manzoni S, Sander JW. Models of community-based primary care for epilepsy in low- and middle-income countries. Neurology. 2020 Jan 28;94(4):165-175. doi: 10.1212/WNL.0000000000008839. Epub 2020 Jan 9. PMID: 31919114.

Shankar R, Henley W, Boland C, Laugharne R, McLean BN, Newman C, Hanna J, Ashby S, Walker MC, Sander JW. Decreasing the risk of sudden unexpected death in epilepsy: structured communication of risk factors for premature mortality in people with epilepsy. Eur J Neurol. 2018 Sep;25(9):1121-1127. doi: 10.1111/ene.13651. Epub 2018 May 2. PMID: 29611888.

Levira F, Thurman DJ, Sander JW, Hauser WA, Hesdorffer DC, Masanja H, Odermatt P, Logroscino G, Newton CR; Epidemiology Commission of the International League Against Epilepsy. Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia. 2017 Jan;58(1):6-16. doi: 10.1111/epi.13603. Epub 2016 Dec 18. PMID: 27988968; PMCID: PMC7012644.

Ferrer, P., Ballarín, E., Sabaté, M., Vidal, X., Rottenkolber, M., Amelio, J., Hasford, J., Schmiedl, S., & Ibáñez, L. (2014). Antiepileptic drugs and suicide: a systematic review of adverse effects. Neuroepidemiology, 42(2), 107–120. https://doi.org/10.1159/000356807

Table 1: PICO Table

Serial Number	Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
1	Methods to reduce risk including checklists.	Mortality	NR	NR
		SUDEP	NR	NR
2	Methods to reduce risk including monitoring of people with epilepsy (e.g. nocturnal supervision).	Mortality	NR	NR
		SUDEP	Maguire et al., 2020	The most recent systematic review and meta-analysis on SUDEP prevention.
3	Methods to reduce risk including access to specialist care.	Mortality	NR	NR
		SUDEP	NR	NR
4	Methods to reduce risk including adherence to medication.	Mortality	NR	NR
		SUDEP	NR	NR

NR: Not reported

3.2. Narrative description of studies that contributed to GRADE analysis

Maguire, M. J., Jackson, C. F., Marson, A. G., & Nevitt, S. J. (2020). Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). *The Cochrane database of systematic reviews*, *4*(4), CD011792. https://doi.org/10.1002/14651858.CD011792.pub3

Abstract:

Background: This is an updated version of the original Cochrane Review, published in 2016, Issue 7. Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus and in whom postmortem examination does not reveal a structural or toxicological cause for death. SUDEP has a reported incidence of 1 to 2 per 1000 patient-years and represents the most common epilepsy-related cause of death. The presence and frequency of generalised tonic-clonic seizures (GTCS), male sex, early age of seizure onset, duration of epilepsy, and polytherapy are all predictors of risk of SUDEP. The exact pathophysiology of SUDEP is currently unknown, although GTCS-induced cardiac, respiratory, and brainstem dysfunction appears likely. Appropriately chosen antiepileptic drug treatment can render around 70% of patients free of all seizures. However, around one-third will remain drug-resistant despite polytherapy. Continuing seizures place patients at risk of SUDEP, depression, and reduced quality of life. Preventative strategies for SUDEP include reducing the occurrence of GTCS by timely referral for presurgical evaluation in people with lesional epilepsy and advice on lifestyle measures; detecting cardiorespiratory distress through clinical observation and seizure, respiratory, and heart rate monitoring devices; preventing airway obstruction through nocturnal supervision and safety pillows; reducing central hypoventilation through physical stimulation and enhancing serotonergic mechanisms of respiratory regulation using selective serotonin reuptake inhibitors (SSRIs); and reducing adenosine and endogenous opioid-induced brain and brainstem depression.
Objectives: To assess the effectiveness of interventions in preventing SUDEP in people with epilepsy by synthesising evidence from randomised controlled trials of interventions and cohort and case-control non-randomised studies.
Search methods: For the latest update we searched the following databases without language restrictions: Cochrane Register of Studies (CRS Web, 4 February 2019); MEDLINE (Ovid, 1946 to 1 February 2019); SCOPUS (1823 to 4 February 2019); PsycINFO (EBSCOhost, 1887 to 4 January 2019); CINAHL Plus (EBSCOhost, 1937 to 4 February 2019); ClinicalTrials.gov (5 February 2019); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, 5 February 2019). We checked the reference lists of retrieved studies for additional reports of relevant studies and contacted lead study authors for any relevant unpublished material. We identified any grey literature studies published in the last five years by searching: Zetoc database; ISI Proceedings; International Bureau for Epilepsy (IBE) congress proceedings database; International League Against Epilepsy (ILAE) congress proceedings database; abstract books of symposia and congresses, meeting abstracts, and research reports.
Selection criteria: We aimed to include randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs; prospective non-randomised cohort controlled and uncontrolled studies; and case-control studies of adults and children with epilepsy receiving an intervention for the

prevention of SUDEP. Types of interventions included: early versus delayed pre-surgical evaluation for lesional epilepsy; educational programmes; seizure-monitoring devices; safety pillows; nocturnal supervision; selective serotonin reuptake inhibitors (SSRIs); opiate antagonists; and adenosine antagonists.

Data collection and analysis: We aimed to collect data on study design factors and participant demographics for included studies. The primary outcome of interest was the number of deaths from SUDEP. Secondary outcomes included: number of other deaths (unrelated to SUDEP); change in mean depression and anxiety scores (as defined within the study); clinically important change in quality of life, that is any change in quality of life score (average and endpoint) according to validated quality of life scales; and number of hospital attendances for seizures.

Main results: We identified 1277 records from the databases and search strategies. We found 10 further records by searching other resources (handsearching). We removed 469 duplicate records and screened 818 records (title and abstract) for inclusion in the review. We excluded 785 records based on the title and abstract and assessed 33 full-text articles. We excluded 29 studies: eight studies did not assess interventions to prevent SUDEP; eight studies were review articles, not clinical studies; five studies measured sensitivity of devices to detect GTCS but did not directly measure SUDEP; six studies assessed risk factors for SUDEP but not interventions for preventing SUDEP; and two studies did not have a control group. We included one cohort study and three case-control studies of serious to critical risk of bias. The 6-month prospective cohort study observed no significant effect of providing patients with SUDEP information on drug compliance and quality of life, anxiety and depression levels. The study was too short and with no deaths observed in either group to determine a protective effect. Two case control studies reported a protective effect for nocturnal supervision against SUDEP. However due to significant heterogeneity, the results could not be combined in meta-analysis. One study of 154 SUDEP cases and 616 controls reported an unadjusted odds ratio (OR) of 0.34 (95% CI 0.22 to 0.53; $P < 0.0001$). The same study demonstrated the protective effect was independent of seizure control, suggesting that nocturnal supervision is not just a surrogate marker of seizure control. The second case-control study of 48 SUDEP cases and 220 controls reported an unadjusted OR of 0.08 (95% CI 0.02 to 0.27; $P < 0.0001$). The third case-control study of residential care centre patients who were already receiving physical checks more than 15 minutes apart throughout the night did not report any protective effect for additional nocturnal supervision (physical checks < 15 minutes apart; use of listening devices; dormitory setting; and use of bed sensors). However the same study did ascertain a difference between centres: the residential centre with the lowest level of supervision had the highest incidence of SUDEP. The case-control studies did not report on quality of life or depression and anxiety scores.

Authors' conclusions: We found limited, very low-certainty evidence that supervision at night reduces the incidence of SUDEP. Further research is required to identify the effectiveness of other current interventions - for example seizure detection devices, safety pillows, SSRIs, early surgical evaluation, educational programmes, and opiate and adenosine antagonists - in preventing SUDEP in people with epilepsy.

3.3. Grading the Evidence

Table 2: Intervention to prevent premature mortality and SUDEP in people with epilepsy

Author(s): Asma Hallab, Michele Romoli, Arjune Sen
Question: Intervention to prevent premature mortality and SUDEP in people with epilepsy
Population: People with epilepsy in general [a]
Reference List: Maguire et al., 2020

Certainty assessment							№ of patients		Effect		Certainty[1]	Importance[2]
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions	Control	Relative (95% CI)	Absolute (95% CI)		
Monitoring of people with epilepsy (e.g. nocturnal supervision) [b]- Maguire et al., 2020												
1	Case-control	Very serious[c]	Not relevant [d]	Not serious	serious	-	34/190 (17.9%)	109/278 (39.2%)	OR 0.34 (0.22 to 0.53)		⊕◯◯◯ VERY LOW	CRITICAL
Checklists – Not reported												
Access to specialist care – Not reported												
Adherence to medication – Not reported												

a- 154 SUDEP cases aged between 16 and 50 years at death. The cases included 97 men and 57 women with a mean age of 32 years.
b- Supervision at night was defined as "the presence of an individual of normal intelligence and at least 10 years old in the bedroom or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device". Control group had no nocturnal supervision.
c- Only one study included
d- Risk of bias was reported as unclear in most of aspects

3.4. Additional evidence not mentioned in GRADE tables

Batson et al., 2022:

Vagus nerve stimulation (VNS) Therapy® is an adjunctive neurostimulation treatment for people with drug-resistant epilepsy (DRE) who are unwilling to undergo resective surgery, have had unsuccessful surgery or are unsuitable for surgery. A systematic review and meta-analysis were conducted to determine the treatment effects of VNS Therapy as an adjunct to anti-seizure medications (ASMs) for the management of adults with DRE. A literature search was performed in August 2020 of the Medline®, Medline® Epub Ahead of Print, Embase, and the Cochrane library databases. Outcomes examined included reduction in seizure frequency, seizure freedom, ASM load, discontinuations, and serious adverse events (SAEs). Comparators included best medical practice, ASMs, low-stimulation or sham VNS Therapy. Four RCTs and six comparative observational studies were identified for inclusion. Against comparators, individuals treated with VNS had a significantly better odds of experiencing a ≥ 50% reduction in seizure frequency (OR: 2.27 [95% CI 1.47, 3.51]; p = 0.0002), a ≥ 75% reduction in seizure frequency (OR: 3.56 [95% CI 1.59, 7.98]; p = 0.002) and a reduced risk for increased ASM load (risk ratio: 0.36 [95% CI 0.21, 0.62]; p = 0.0002). There was no difference in the odds of discontinuation or the rate of SAEs between VNS versus comparators. This meta-analysis demonstrated the benefits of VNS Therapy in people with DRE, which included improvement in seizure frequency without an increase in the rate of SAEs or discontinuations, thereby supporting the consideration of VNS Therapy for people who are not responding to ASMs and those unsuitable or unwilling to undergo surgery.

Shum et al., 2021

Importance: Epilepsy can be associated with significant morbidity and mortality. Seizure detection devices could be invaluable tools for both people with epilepsy, their caregivers, and clinicians as they could alert caretakers about seizures, reduce the risk of sudden unexpected death in epilepsy, and provide objective and more reliable seizure tracking to guide treatment decisions or monitor outcomes in clinical trials.
Objective: To synthesize the characteristics of commercial seizure detection tools/devices currently available.
Methods: We performed a systematic search utilizing a diverse set of resources to identify commercially available seizure detection products for consumer use. Performance data was obtained through a systematic review on commercially available products.
Observations: We identified 23 products marketed for seizure detection/alerting. Devices utilize a variety of mechanisms to detect seizures, including movement detectors, autonomic change detectors, electroencephalogram (EEG) based detectors, and other mechanisms (audio). The optimal device for a person with epilepsy depends on a variety of factors including the main purpose of the device, their age, seizure type and personal preferences. Only 8 devices have published peer-reviewed performance data and the majority for tonic-clonic seizures. An informed conversation between the clinician and the patient can help guide if a seizure detection device is appropriate.
Conclusions and relevance: Seizure detection devices have a potential to reduce morbidity and mortality for certain people with epilepsy. Clinicians should be familiar with the characteristics of commercially available devices to best counsel their patients on whether a seizure detection device may be beneficial and what the optimal devices may be.

Al-Aqeel et al., 2020

Background: Poor adherence to antiepileptic medication is associated with increased mortality, morbidity and healthcare costs. In this review, we focus on interventions designed and tested in randomised controlled trials (RCTs) and quasi-RCTs to assist people with adherence to antiepileptic medication. This is an update of a Cochrane review first published in 2011, and last updated in 2017.
Objectives: To determine the effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy.
Search methods: For the latest update, we searched the following databases on 18 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE, CINAHL Plus and PsycINFO. CRS Web includes RCTs or quasi-RCTs from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), CENTRAL, and the Specialized Registers of Cochrane Review Groups including Epilepsy. We also searched the reference lists of relevant articles.
Selection criteria: RCTs and quasi-RCTs of adherence-enhancing interventions aimed at people with a clinical diagnosis of epilepsy (as defined in individual studies), of any age and treated with antiepileptic drugs in a primary care, outpatient or other community setting.
Data collection and analysis: All review authors independently assessed lists of potentially relevant citations and abstracts. At least two review authors independently extracted data and performed a quality assessment of each study according to the Cochrane tool for assessing risk of bias. We graded the level of evidence for each outcome according to GRADE. The studies differed widely according to the type of intervention and measures of adherence; therefore combining data was not appropriate.
Main results: We included 20 studies reporting data on 2832 participants. Thirteen studies targeted adults with epilepsy, one study included participants of all ages, one study included participants older than two years, one recruited pediatric patients aged between 1 month to 15 years, one study targeted caregivers of children with epilepsy, one targeted adolescents and caregivers, and two studies targeted families of children with epilepsy. We identified three ongoing studies. Follow-up time was generally short in most studies, ranging from 1 to 12 months. The studies examined three main types of interventions: educational interventions, behavioural interventions and mixed interventions. All but three studies compared treatment with usual care or 'no intervention'. Due to heterogeneity between studies in terms of interventions, methods used to measure adherence and the way the studies were reported, we did not pool the results and these findings were inappropriate to be included in a meta-analysis. Education and counselling of participants with epilepsy had mixed success (moderate-certainty evidence). Behavioural interventions such as the use of intensive reminders provided more favourable effects on adherence (moderate-certainty evidence). The effect on adherence to antiepileptic drugs described by studies of mixed interventions showed improved adherence in the intervention groups compared to the control groups (high-certainty evidence). Eleven studies described seizure frequency or seizure severity or both, with four of them, reporting improved adherence and decreased seizure frequency in the intervention groups (moderate-certainty evidence). Findings related to self-efficacy and quality of life were mixed, with no clear pattern across types of intervention.
Authors' conclusions: Behavioural interventions such as intensive reminders and the use of mixed interventions demonstrate some positive results, however, we need more reliable evidence on their efficacy, derived from carefully-designed RCTs before we can draw a firm conclusion. None of the newly included studies have provided additional information that would lead to significant changes in our conclusions.

Cooper et al., 2020:

Purpose: To synthesise the quantitative and qualitative evidence on the views and experiences of children and young people with epilepsy (CYPwE), their family members/caregivers and healthcare professionals on conversations between healthcare professionals and CYPwE/caregivers about the possibility of sudden unexplained death in epilepsy (SUDEP).
Methods: Mixed methods systematic review in accordance with Joanna Briggs Institute methodology, PRISMA guidelines and guided by an a-priori protocol.
Results: 656 potentially relevant studies were identified, 11 of which fulfilled the inclusion criteria for the review: 6 quantitative studies, 4 qualitative studies and 1 opinion/text article. Data synthesis resulted in the following 2 integrated findings: (i) Caregivers, and where appropriate CYPwE, should be provided with information on SUDEP and how it relates to them; (ii) Information on SUDEP should be delivered face-to-face, with supporting written information, by a suitably knowledgeable healthcare professional whom the caregiver/CYPwE feels comfortable with, at an appropriate time at or close to diagnosis.
Conclusion: This review confirms that healthcare professionals should discus SUDEP with CYPwE and/or their caregivers at or around the time of diagnosis and that the discussion should include prevalence of SUDEP, risk factors and risk reduction methods relative to the individual concerned. Apart from delivering SUDEP information face-to-face, with written or online information provided to reinforce messages, there is a lack of evidence on "how" to impart this sensitive information. Further research exploring the most acceptable and effective methods of discussing SUDEP with CYPwE and their caregivers is therefore indicated.

Mahr et al., 2020

Purpose: Most patients who die from sudden unexpected death in epilepsy (SUDEP) are found in the prone position. We evaluated whether changes in body position occur during generalized convulsive seizures (GCSs).
Method: GCSs in patients undergoing video-EEG-monitoring between 2007 and 2017 at epilepsy centers in Frankfurt and Marburg were analyzed in relation to changes in body position.
Results: A total of 494 GCSs were analyzed among 327 patients. At seizure onset, positions included supine (48.2 %), right lateral (19.0 %), left lateral (15.6 %), sitting or standing (14.0 %), and prone (3.2 %). Between seizure onset and the start of generalization, 57.5 % of participants altered body positions. During four seizures, patients adopted a prone position, while, in five seizures, patients moved from a prone position. Patients who experienced GCS onset while in a nonprone position had a 2.1 % risk of entering the prone position by the end of their seizure. In contrast, 56.2 % of those in an initial prone position remained so at the end of the GCS, with an odds ratio for maintaining that position of 60.2 (95 % confidence interval: 29.1-124.3; $p < 0.001$). The likelihood of ending up in the prone position post-GCS did not vary among patients with different nonprone starting positions ($p = 0.147$).
Conclusions: Seizures in prone position occur during sleep and the highest risk for postictal prone positioning appears to be being in the prone position at GCS onset. Epilepsy patients should therefore be advised to go to sleep in a supine or lateral position to reduce their SUDEP risk.

Singh et al., 2020

Objective: To review systematically community-based primary care interventions for epilepsy in low- and middle-income countries to rationalize approaches and outcome measures in relation to epilepsy care in these countries.
Methods: A systematic search of PubMed, EMBASE, Global Index Medicus, CINAHL, and Web of Science was undertaken to identify trials and implementation of provision of antiseizure medications, adherence reinforcement, and/or health care provider or community education in community-based samples of epilepsy. Data on populations addressed, interventions, and outcomes were extracted from eligible articles.

Results: The 24 reports identified comprise mostly care programs addressing active convulsive epilepsy. Phenobarbital has been used most frequently, although other conventional antiseizure medications (ASMs) have also been used, but none of the newer. Tolerability rates in these studies are high, but overall attrition is considerable. Other approaches include updating primary health care providers, reinforcing treatment adherence in clinics, and raising community awareness. In these programs, the coverage of existing treatment gap in the community, epilepsy-related mortality, and comorbidity burden are only fleetingly addressed. None, however, explicitly describe sustainability plans.
Conclusions: Cost-free provision, mostly of phenobarbital, has resulted in short-term seizure freedom in roughly half of the people with epilepsy in low- and middle-income countries. Future programs should include a range of ASMs. These should cover apart from seizure control and treatment adherence, primary health care provider education, community awareness, and referral protocols for specialist care. Programs should incorporate impact assessment at the local level. Sustainability in the long term as much as resilience and scalability should be addressed in future initiatives.

Shankar et al., 2018

Background and purpose: Good practice guidelines highlight the importance of making people with epilepsy aware of the risk of premature mortality in epilepsy particularly due to sudden unexpected death in epilepsy (SUDEP). The SUDEP and Seizure Safety Checklist ('Checklist') is a structured risk communication tool used in UK clinics. It is not known if sharing structured information on risk factors allows individuals to reduce SUDEP and premature mortality risks. The aim of this study was to ascertain if the introduction of the Checklist in epilepsy clinics led to individual risk reduction.
Methods: The Checklist was administered to 130 consecutive people with epilepsy attending a specialized epilepsy neurology clinic and 129 attending an epilepsy intellectual disability (ID) clinic within a 4-month period. At baseline, no attendees at the neurology clinic had received formal risk advice, whereas all those attending the ID clinic had received formal risk advice on multiple occasions for 6 years. The Checklist was readministered 1 year later to each group and scores were compared with baseline and between groups.
Results: Of 12 risk factors considered, there was an overall reduction in mean risk score for the general ($P = 0.0049$) but not for the ID ($P = 0.322$) population. Subanalysis of the 25% of people at most risk in both populations showed that both sets had a significant reduction in risk scores ($P < 0.001$).
Conclusion: Structured discussion results in behavioural change that reduces individual risk factors. This impact seems to be higher in those who are at current higher risk. It is important that clinicians share risk information with individuals as a matter of public health and health promotion.

Levira et al., 2017

To determine the magnitude of risk factors and causes of premature mortality associated with epilepsy in low- and middle-income countries (LMICs). We conducted a systematic search of the literature reporting mortality and epilepsy in the World Bank-defined LMICs. We assessed the quality of the studies based on representativeness; ascertainment of cases, diagnosis, and mortality; and extracted data on standardized mortality ratios (SMRs) and mortality rates in people with epilepsy. We examined risk factors and causes of death. The annual mortality rate was estimated at 19.8 (range 9.7-45.1) deaths per 1,000 people with epilepsy with a weighted median SMR of 2.6 (range 1.3-7.2) among higher-quality population-based studies. Clinical cohort studies yielded 7.1 (range 1.6-25.1) deaths per 1,000 people. The weighted median SMRs were

5.0 in male and 4.5 in female patients; relatively higher SMRs within studies were measured in children and adolescents, those with symptomatic epilepsies, and those reporting less adherence to treatment. The main causes of death in people with epilepsy living in LMICs include those directly attributable to epilepsy, which yield a mean proportional mortality ratio (PMR) of 27.3% (range 5-75.5%) derived from population-based studies. These direct causes comprise status epilepticus, with reported PMRs ranging from 5 to 56.6%, and sudden unexpected death in epilepsy (SUDEP), with reported PMRs ranging from 1 to 18.9%. Important causes of mortality indirectly related to epilepsy include drowning, head injury, and burns. Epilepsy in LMICs has a significantly greater premature mortality, as in high-income countries, but in LMICs the excess mortality is more likely to be associated with causes attributable to lack of access to medical facilities such as status epilepticus, and preventable causes such as drowning, head injuries, and burns. This excess premature mortality could be substantially reduced with education about the risk of death and improved access to treatments, including AEDs.

Ferrer et al., 2014

Background: Since the FDA (Food and Drug Administration) report on antiepileptic drugs (AEDs) and suicide risk was released (2008), several studies have been published on this controversial relationship. This systematic review (SR) gives an updated approach to this health issue.
Summary: We searched 6 databases. We ultimately included 11 publications: 4 cohort studies, 1 case-crossover study, 2 community case-control studies, and 4 SRs. Overall, 1 SR described studies already included; 3 studies reported a 2- to 4-fold overall increase in risk; 1 study reported an increased risk of suicide among epilepsy patients on AEDs with high risk of depression; 1study showed a protective effect among epilepsy patients; 2 studies were conducted with patients with bipolar disorder (1 showed a protective effect, whereas the other showed a 3-fold increase in risk of suicide), and the other 3 studies reported results for single AEDs. Several biases affected the published results.
Key messages: There is no clear evidence of an association between the use of AEDs and an increased risk of suicide because of the heterogeneity in the studies at the clinical and methodological level. A future study should cover all indications for use, retrieve information from a healthcare database, and include a defined set of covariates to avoid bias.

4. From Evidence to Recommendations

4.1. Summary of findings

Table 3: Summary of findings table

GRADE Table	Source	Intervention	Number of Studies	Effects	Certainty of Evidence
GRADE Table 1 Methods to reduce mortality and SUDEP risk in people with epilepsy.	Maguire et al., 2020	Monitoring of people with epilepsy (e.g. nocturnal supervision)	1	OR 0.34 (0.22 to 0.53)	⊕◯◯◯ VERY LOW
		Checklists	NR	-	-
		Access to specialist care	NR	-	-
		Adherence to medication.	NR	-	-

NR: Not reported

4.2. Evidence to decision

Table 4: Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognised priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of a seizure. SUDEP represents the most common epilepsy-related cause of death, and prevention strategies are still uncertain.	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	We found limited and very low-certainty evidence that supervision at night reduces the incidence of SUDEP (OR 0.34, 95%CI 0.22 to 0.53). However, if the estimate is confirmed in large real-world studies, it would mean that SUDEP risk can be	The committee should additionally consider the practicality of nocturnal supervision for all, for example those who live alone; older children who may wish greater privacy

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			substantially cut through the implementation of a relatively simple lifestyle action in most cases. Therefore, the desirable anticipated effect would at least be rated as moderate.	Nocturnal supervision may be particularly indicated for people who have convulsive seizures from sleep Further risk reduction strategies include sleeping on back and not prone to reduce risk.
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☒ **Trivial** ☐ Varies ☐ Don't know	We found no data regarding potential undesirable effect of night supervision, and we expect to find no major reasonable undesirable effect regarding this intervention.	
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects	☒ **Very low** ☐ Low ☐ Moderate ☐ High ☐ No included studies	We found no available meta-analysis, with only cohort or case-control studies being retrieved from systematic review.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called 'utility values'.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ **No important uncertainty or variability**	• SUDEP prevention is critical to both patients and clinicians. • A qualitative systematic review (Gronholm et al., 2023) was conducted to assess values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. • Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and wellbeing. The utility value could be limited by certain factors and barriers present in the health systems. For instance, low awareness, poor funding	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			and poor political buy-in, or other social barriers. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgments regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☒ **Probably favors the intervention** ☐ Favors the intervention ☐ Varies ☐ Don't know	The balance of benefits versus harms is in favour of the intervention given the low anticipated risk of harm and potential to reduce mortality	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☒ **Varies** ☐ Don't know	We found no data regarding costs, but it might be reasonable to expect that, depending on the type of intervention, the costs will vary. For example, a monitor placed in a child's room that is linked to a monitor in a parent's room will be of far less cost, than if awake carers are required in a supported living accommodation	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	We found no data regarding costs, but it might be reasonable to expect that, at least in a consistent part of the population, the intervention can be applied with low costs.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	• Is there important variability in the cost of the items of resource use that differ between the options being considered?			
Cost effectiveness	Does the cost-effectiveness of the intervention favor the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgments regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☐ Varies ☒ **No included studies**	We found no data regarding costs, but it might be reasonable to expect that, at least in a consistent part of the population, the intervention can be applied with low costs.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favor of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☒ **Probably increased** ☐ Increased ☐ Varies ☐ Don't know	We found no studies addressing this point. The qualitative review (Gronholm et al., 2023) noted considerations for ensuring MNS interventions are equitable, equally available and non-discriminatory: • Accessibility, physical/practical considerations • time & travel constraints. • Accessibility, informational barriers • Affordability - medication and treatment costs These factors may be exacerbated for certain groups: • People with low education/literacy (e.g., written instructions, psychoeducation materials) • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities • Low resource settings - affordability/cost considerations exacerbated.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	We found no feasibility study. However, the intervention has been tested in cohort studies, and seems overall to have reasonable sustainability and few barriers for implementation. To this regard, night supervision might find barriers depending on spouse, carers or parents' habits, workplace, age and gender in all countries (low, middle and high income). • The qualitative review (Gronholm et al., 2023) also considered feasibility, and how this can be enhanced in the following areas: • Acceptability of interventions for stakeholders - requires increased engagement with specialist staff, increased visibility of the task-sharing workforce within health facilities, perception of usefulness by providers and service users (e.g., via positive feedback), context-specific interventions, standardised implementation steps for simpler decision-making and delivery	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			• Health worker workload, competency - requires training, refreshers, supervision; networking with others in same role. • Availability of a task-sharing workforce; • Availability of caregivers; • Participant education and literacy requires verbal explanations/tasks; • Logistical issues - such as e.g., mobile populations, affordability of travel to receive care, lack of private space; • Limited resources/mental health budget. • Sustainability considerations identified were: • Training and supervision; • Integrating into routine clinical practice.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socio-culturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favor of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socio-culturally acceptable to patients/beneficiaries as well as to those implementing	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes	We found no studies regarding this point. However, preventing death with night-time supervision seems aligned with human rights principles and	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socio-culturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socio-economic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?	☐ Varies ☐ Don't know	acceptable at socio-cultural levels Consideration must, though, be given to the privacy of the individual with epilepsy and the practicality of such supervision in those who live alone. • The qualitative review (Gronholm et al., 2023) noted several considerations which would impact the right to health and access to healthcare. (e.g., stigma and discrimination and lack of confidentiality could affect the help-seeking among service users). • The importance of socio-cultural acceptability of MNS interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects improve the acceptability of implemented interventions. • When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers Also, considerations of age, sex and language have been highlighted as	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			important to acceptability and accessibility. • Mitigating steps to improve sociocultural acceptability include: • To train health workers in non-judgmental care • Integrate preventative mental health awareness messages to reduce the stigma • Train acceptable counsellors for the local settings and target groups • Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility and fidelity.	

4.3. Summary of judgements

Table 5: Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	✓ **Moderate**	- Large
Undesirable effects	- Don't know	- Varies		- Large	- Moderate	- Small	✓ **Trivial**
Certainty of the evidence	- No included studies			✓ **Very low**	- Low	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	- Probably no important uncertainty or variability	✓ **No important uncertainty or variability**
Balance of effects	- Don't know	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	✓ **Probably favours intervention**	- Favours intervention
Resources required	- Don't know	✓ **Varies**	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **Don't know**	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Equity, equality and non-discrimination	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	✓ **Probably increased**	- Increased
Feasibility	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes
Human rights and socio-cultural acceptability	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes

✓ Indicates category selected, - Indicates category not selected

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Appendix I: mhGAP process note

mhGAP Guideline Update: Notes on process for identifying level of evidence review required v2_0 (13/12/2021)

This document is intended to provide guidance to focal points on the level of evidence review required as part of the evidence retrieval process for the mhGAP guideline update process. As a general rule, the update process should be informed by existing high quality systematic reviews.
The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development https://apps.who.int/iris/handle/10665/145714.

Three main categories of evidence review are proposed in this document:

1) Existing relevant, up to date, high quality systematic review(s) provide the evidence required. **An existing systematic review is sufficient to prepare the evidence summaries**. It may be possible to include more than one systematic review for the same PICO, as different reviews may match different outcomes of a PICO. However, if more than one systematic review is available for the same PICO outcome, one review should be selected, based on quality, relevance, search comprehensiveness and date of last update. The selection process should be transparently reported, with justification of choices.
2) Existing high quality systematic reviews are either out of date or do not fully address the PICO, though it is considered that the review can be updated to meet these requirements. **An update of an existing systematic review is required before the evidence summaries can be prepared**. The update process may require addition of new studies published after the review, or inclusion of outcomes not covered by the existing reviews.
3) Existing systematic reviews are either not of sufficiently high quality or cannot be updated to fully address the PICO. **A new systematic review is required before the evidence summaries can be prepared**

Figure 1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

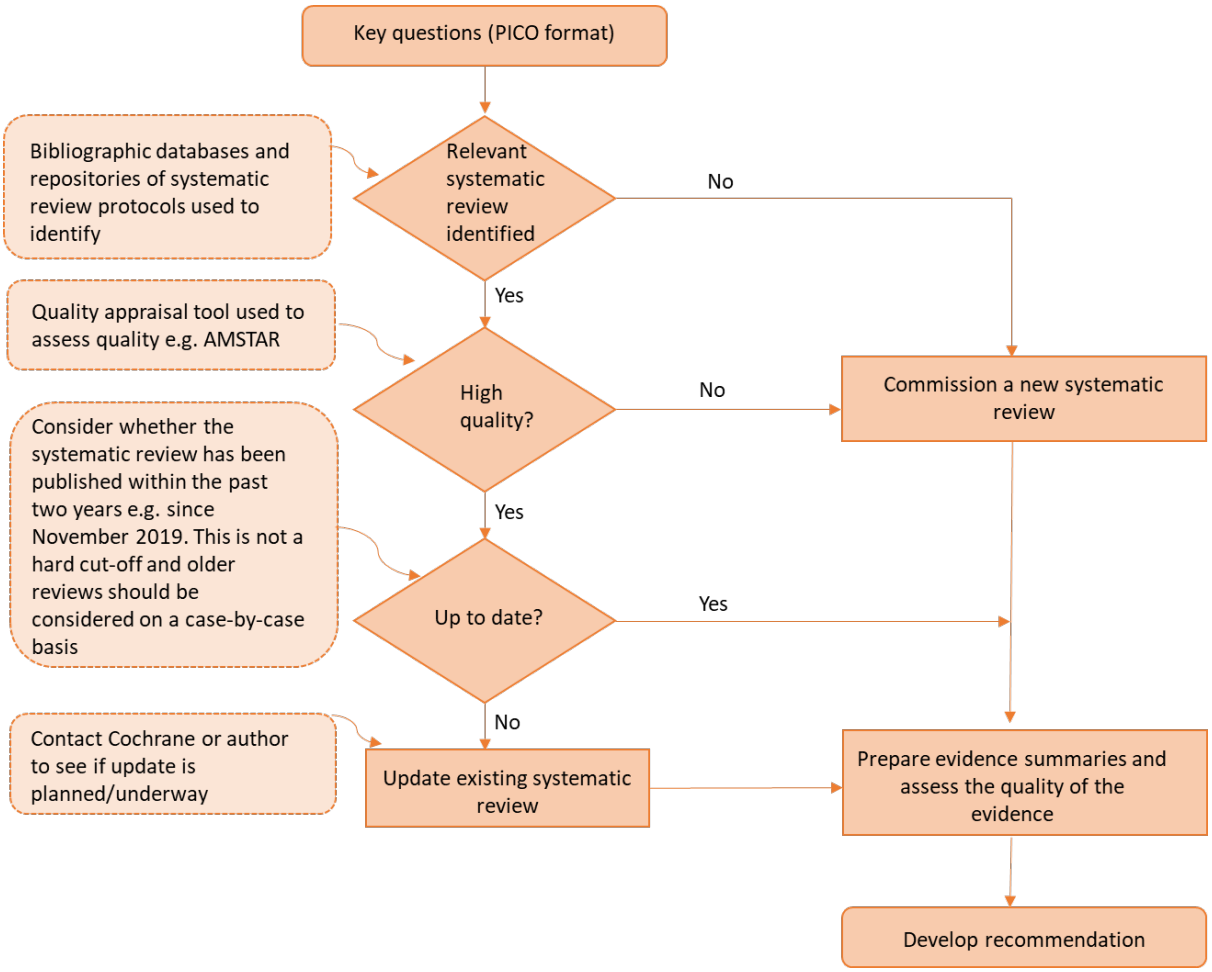

Figure 1: Is a new systematic review needed

All key questions are currently in PICO format as presented in the Appendix of the planning proposal PICOs. Subsequent steps include the following:

1. **Identify and evaluate existing systematic reviews**: Identify one or more systematic review(s) to address each PICO question. Existing systematic reviews will inform the guideline development process, whether or not a new systematic review or an update of an existing review is required, and the evidence review team will detail existing systematic reviews in each case. The method for identifying existing systematic reviews should be fully detailed in the evidence summary and include the following sources:
    a. Search of bibliographic databases, such as PubMed/Medline, EMBASE, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHIL, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus.
    b. Search of repositories of systematic reviews protocols, including PROSPERO, Open Science Framework (OSF), and Cochrane.
2. **Assess if systematic review is up to date:** It is preferred that identified systematic reviews have been published within the past two years e.g. since

November 2019. This is not a hard cut-off and older reviews should be considered on a case-by-case basis, particularly those covering the time period since the last update of the mhGAP guideline in 2015. It is acknowledged that COVID has led to a pausing of many mental health research activities over the past two years, and this may also impact the availability of systematic reviews within the preferred two year period. For any reviews that fall outside the two year period, the guideline methodologist will advise on suitability.

3. **Appraise quality of systematic review:** Use the AMSTAR-2 quality appraisal tool to assess the quality of the identified systematic review(s) https://amstar.ca/docs/AMSTAR-2.pdf . This includes consideration of the extent to which the PICO is fully addressed by the systematic review(s) identified.

By following the process outlined in figure 1, and steps 1-3 above, the FP and evidence review team will have sufficient evidence to assess which of the three main categories of evidence review apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

Appendix II: Search terms used to identify systematic reviews

Search terms on PubMed:

("epilepsie"[All Fields] OR "epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epilepsies"[All Fields] OR "epilepsy s"[All Fields] OR ("epilepsy"[MeSH Terms] OR "epilepsy"[All Fields] OR "epileptic"[All Fields] OR "epileptics"[All Fields] OR "epileptic s"[All Fields] OR "epileptical"[All Fields] OR "epileptization"[All Fields]) OR "epilep*"[All Fields] OR ("seizural"[All Fields] OR "seizure s"[All Fields] OR "seizured"[All Fields] OR "seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields] OR "seizuring"[All Fields]) OR ("seizural"[All Fields] OR "seizure s"[All Fields] OR "seizured"[All Fields] OR "seizures"[MeSH Terms] OR "seizures"[All Fields] OR "seizure"[All Fields] OR "seizuring"[All Fields]) OR ("Status"[All Fields] AND "epilep*"[All Fields])) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ("death"[MeSH Terms] OR "death"[All Fields] OR "deaths"[All Fields]) OR ("sudden unexpected death in epilepsy"[MeSH Terms] OR ("sudden"[All Fields] AND "unexpected"[All Fields] AND "death"[All Fields] AND "epilepsy"[All Fields]) OR "sudden unexpected death in epilepsy"[All Fields]) OR ("sudden unexpected death in epilepsy"[MeSH Terms] OR ("sudden"[All Fields] AND "unexpected"[All Fields] AND "death"[All Fields] AND "epilepsy"[All Fields]) OR "sudden unexpected death in epilepsy"[All Fields] OR "sudep"[All Fields] OR "sudeps"[All Fields])) AND ("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("intervention s"[All Fields] OR "interventions"[All Fields] OR "interventive"[All Fields] OR "methods"[MeSH Terms] OR "methods"[All Fields] OR "intervention"[All Fields] OR "interventional"[All Fields]) OR ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "supervision"[All Fields] OR "supervise"[All Fields] OR "supervised"[All Fields] OR "supervises"[All Fields] OR "supervising"[All Fields] OR "supervisions"[All Fields]) OR ("checklist"[MeSH Terms] OR "checklist"[All Fields] OR "checklists"[All Fields] OR "checklist s"[All Fields]) OR ("monitor s"[All Fields] OR "monitorable"[All Fields] OR "monitored"[All Fields] OR "monitoring"[All Fields] OR "monitoring s"[All Fields] OR "monitoring, physiologic"[MeSH Terms] OR ("monitoring"[All Fields] AND "physiologic"[All Fields]) OR "physiologic monitoring"[All Fields] OR "monitor"[All Fields] OR "monitorings"[All Fields] OR "monitorization"[All Fields] OR "monitorize"[All Fields] OR "monitorized"[All Fields] OR "monitors"[All Fields]) OR "prevent*"[All Fields]) AND ("systematic review"[Publication Type] OR "systematic reviews as topic"[MeSH Terms] OR "systematic review"[All Fields])