National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

[O] Effectiveness of a nurse specialist in the management of epilepsy

NICE guideline number tbc

Evidence reviews underpinning recommendations 11.1.1-11.1.4 in the NICE guideline

November 2021

Draft for Consultation

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

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Effectiveness of a nurse specialist in the management of epilepsy

Review question

What is the effectiveness of a nurse specialist in the management of epilepsy?

Introduction

Clinical nurse specialists are invariably thought of as invaluable within any specialist service; potentially providing continuity between families and medical teams; they may be viewed as more easily accessible and more approachable, and may act as an active resource for education and training. Although their merits would seem self-apparent their role has not been systematically reviewed. Therefore, the aim of this review is to determine whether the involvement of nurse specialists improve outcomes for people with epilepsy.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• People with confirmed epilepsy
Intervention	• Any involvement by an epilepsy nurse specialist
Comparison	We will include any study which compared one nurse specialist strategy to another, these may include, for example: • Treatment as usual (as defined by investigators) • A study with an epilepsy nurse specialist undertaking a different role in the care team • No epilepsy nurse specialist input
Outcomes	**Critical** • Satisfaction, including patient, parents and carers (validated and non-validated scales will be included) • Attendances to emergency departments (self-reported and objective measures will be used) • Self-efficacy (validated and non-validated scales) • Health-related quality of life (only validated scales will be used) **Important** • Admission to hospital (inpatient) ○ Acute/ unplanned/ unscheduled ○ Planned • GP/ hospital visits (outpatient) • Depression and anxiety (validated tools only)

GP: general practitioner

For further details see the review protocol in appendix A.

Methods and process

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

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

Clinical evidence

Included studies

Four randomised controlled trials (RCTs), 2 cluster RCTs, 1 non-randomised controlled trial and 1 cohort study were identified for inclusion in this review (Davis 2004, Dorris 2017, Helde 2005, Hill 2017, Noble 2014, Pfaffin 2016, Ridsdale 2000, Ring 2018).

Two RCTs and 1 cluster RCT compared group nurse-led interventions with a control group (Davis 2004, Dorris 2017, Helde 2005); 1 cohort study (Hill 2017) compared care provided by a nurse-practitioner and a physician to care provided by a physician only and 1 non-randomised controlled trial, 2 RCTs and 1 cluster RCT compared individual nurse-led interventions with a control group (Noble 2014, Pfaffin 2016, Ridsdale 2000, Ring 2018).

The included studies are summarised in Table 2 to Table 4.

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

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 to Table 4.

Table 2: Summary of included studies. Comparison 1: group nurse-led intervention versus control group

Study	Population	Intervention	Comparison	Outcomes
Davis 2004 (TIGER trial) Cluster RCT UK	N (clusters) = 44 GP practices; n (cluster) = 22 practices were allocated to the intervention group and n (cluster) = 22 were allocated to the control group Age, years, mean (SD): Group nurse-	Group nurse-led intervention n= 399 Received a copy of a national guideline; attended workshops and summary protocols about the guideline; and received the services of a nurse specialist in epilepsy	Control group n= 370 Received a copy of a national guideline	• Mastery (proxy outcome for self-efficacy, Epilepsy-specific scale mastery scores) • Health-related quality of life (SF-36 general health profile scores)

Study	Population	Intervention	Comparison	Outcomes
	led intervention: 49.1 (16.8) Control group: 48.9 (16.6)			
Dorris 2017 RCT UK	N= 76 young people with epilepsy being treated in tertiary paediatric neuroscience centres in UK Age, years, mean (SD) in the intervention group 14.4 (1.5), in the control group 14.3 (1.4)	Group nurse-led intervention n=39 Psychosocial group intervention led by a nurse specialist and a psychologist	Wait list n=37	• Self-efficacy (SSEC scores) • Health-related quality of life (GEOS-YP and PedsQL scores) • Emotional distress (proxy outcome for depression and anxiety, PI-ED scores)
Helde 2005 RCT Norway	N= 111 adults with epilepsy Age, years, mean (range) in the intervention group 35.3 (16 to 69), in the control group 39.5 (16 to 37)	Group nurse-led intervention n=57 Educational group programme led by an epilepsy nurse specialist	Treatment as usual n=54 Included appointments with neurologists and telephone calls with nurses running the clinic, but not with the nurse running the intervention group	• Satisfaction (VAS scores) • Health-related quality of life (QOLIE-89 overall QOL scores) • Emotional wellbeing (proxy outcome for depression and anxiety, QOLIE-89 scores)

GEOS-YP: Glasgow Epilepsy Outcome Scale for Young Person; GPs: general practitioners; PedsQL: Paediatric Quality of Life Inventory PedsQL™; PI-ED: Paediatric Index of Emotional Distress; QOL: quality of life; QOLIE-89: Quality of Life in Epilepsy Inventory-89; RCT: randomised controlled trial; SD: standard deviation; SF-36: 36-item short form survey; SSEC: Seizure Self Efficacy Scale for Children; TIGER: Tayside Implementation of Guidelines in Epilepsy Randomized

Table 3: Summary of included studies. Comparison 2: nurse practitioner + physician versus physician only

Study	Population	Intervention	Comparison	Outcomes
Hill 2017 Observational study US	N=169 patients with epilepsy attending a hospital outpatient clinic. Age at new patient visit, years, median (IQR):	Nurse practitioner + physician n=65 Physician and nurse practitioner working together with both providers seeing each new patient.	Physician only n=104 Physician working alone.	• Presentation at emergency department • Admission to epilepsy monitoring unit

Study	Population	Intervention	Comparison	Outcomes
	Intervention group 37 (24-53); control group 40 (29-55), p = 0.05.			

IQR: interquartile range

Table 4. Summary of included studies. Comparison 3: individual nurse-led intervention versus control group

Study	Population	Intervention	Comparison	Outcomes
Noble 2014 Non-randomised controlled trial UK	N=85 adults with chronic epilepsy Participants were between 18 and 89 years old	Individual nurse-led intervention + treatment as usual n=44 One-to-one sessions tailored to the patient's needs, with a focus on day-to-day management and led by an epilepsy nurse specialist. People also had access to treatment as usual	Treatment as usual n=41 Usual care without restrictions.	• Satisfaction with medication information (Satisfaction with Information about Medicines Scale scores) • Emergency department visits (Client Services Receipt Inventory scores) • Mastery (proxy outcome for self-efficacy, Epilepsy Mastery Scale scores) • Health-related quality of life (Quality of life in Epilepsy Inventory-10 scores) • Depression (Hospital anxiety and Depression scale scores) • Anxiety (Hospital anxiety and Depression scale scores)
Pfafflin 2016 RCT Germany	N=143 people with epilepsy treated by neurologists in outpatient clinics Age, years, mean (SD) in the intervention group 42.6 (14.8), in the control group 44.9 (15)	Individual nurse-led intervention + treatment as usual n=67 People had sessions with the nurse specialist tailored to their needs	Treatment as usual n=76 Usual care without additional counselling	• Satisfaction with information and advice (Satisfaction with Epilepsy Care scores) • Satisfaction with patient-doctor relationship (Satisfaction with Epilepsy Care scores) • Satisfaction with organization of care (Satisfaction with Epilepsy Care scores)
Ridsdale 2000 RCT UK	N=90 people with newly diagnosed epilepsy Median age in the inter-	Individual nurse-led intervention n=43 Two one-to-one appointments with a nurse specialist at the local hospital,	Treatment as usual n=47 Usual care without additional counselling	• Number of people with anxiety (Hospital Anxiety Rating Scale scores) • Number of people with depression (Hospital Anxiety Rating

Study	Population	Intervention	Comparison	Outcomes
	vention group: 40.2, median age in the control group: 39.8	tailored to the person's needs		Scale scores)
Ring 2018 (EpAID trial) Cluster RCT UK	N (clusters) = 17 research sites; n (clusters) = 8 research sites were allocated to the intervention group and n (clusters) = 9 were allocated to the control group Age, years, mean (SD) in the intervention group 39.6 (13.3), in the control group 37.01 (12.5)	Individual nurse-led intervention n=184 Individual sessions led by a nurse specialist following a specific set of guidelines developed by the UK Epilepsy Specialist Nurse Association in association with the UK Royal College of Nursing	Treatment as usual n=128 Patients received the existing management approach at their clinics	• Health-related quality of life (ELDQoL-SSS32 and Epilepsy and Learning Disabilities Quality of Life scores) • Admission to hospital (any)

ELDQoL-SSS32: Epilepsy and Learning Disabilities Quality of Life seizure severity scale-32; EpAID: epilepsy and intellectual disability; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Overall, interventions led by epilepsy specialist nurses appeared to have an important benefit over treatment as usual in terms of outcome satisfaction and emotional wellbeing. This was most obvious when interventions were delivered in groups as opposed to individually. However, there was no important difference between the interventions for all other outcomes identified. In total, 7 studies were found relating to this review. The majority of the evidence was of low to very low quality, with most outcomes being seriously imprecise and at risk of bias due to lack of blinding.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

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

Two relevant studies were identified in the literature review of published economic evidence on this topic (Noble 2014, Ring 2018).

Excluded studies

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

Summary of studies included in the economic evidence review

Two relevant studies were identified in the literature review of published economic evidence on this topic (Noble 2014, Ring 2018).

One study considered the cost effectiveness of an epilepsy specialist nurse (ESN) led intervention in addition to the standard care compared to the standard care alone in people with epilepsy. This study considered a population of people with epilepsy attending an emergency department (ED), who were adults and had a diagnosis of epilepsy for more than 1 year (Noble 2014). The other study considered the cost effectiveness of a nurse-led intervention for epilepsy ('Learning Disability Epilepsy Specialist Nurse Competency Framework) compared to treatment as usual in people with an intellectual (learning) disability (ID) and epilepsy. This economic analysis was embedded in a cluster RCT, and included people with epilepsy with a developmental ID aged 18–65 years old (Ring 2018).

Both studies were a cost-utility analyses measuring effectiveness in terms of quality adjusted life years (QALYs). Both analyses adopted the perspective of the UK NHS and personal social services (PSS).

The base-case results of Noble 2014 suggest that the ESN led intervention in addition to the standard of care is less costly but with a small reduction in QALYs. The resulting base-case incremental cost-effectiveness ratio (ICER) suggests that there would be an additional cost of £26,445 per extra QALY if the ESN led intervention is not used. In probabilistic sensitivity analysis the ESN-led intervention was found to have 56% probability of being cost effective at a threshold of £20,000 per QALY gained, and 50% probability of being cost effective at a threshold of £30,000 per QALY gained; however, differences in costs or outcomes between interventions were not significant.

The base-case results of Ring 2018 suggest that nurse-led intervention for epilepsy (that is 'Learning Disability Epilepsy Specialist Nurse Competency Framework) is less effective and less costly than standard of care in adults with ID and epilepsy. Similarly to Noble 2014 the intervention led to cost savings but again with a small reduction in QALYs. The estimated base-case ICER estimated savings of £220,000 per QALY lost suggests that the intervention is likely to be cost effective compared to standard care. Uncertainty was assessed using probabilistic sensitivity analysis. Results were found to be sensitive to the perspective of the analysis, the level of ID of the person with epilepsy, and the exclusion of the accommodation costs. As stated in the paper, while results were sensitive to the perspective of the analysis and the exclusion of accommodation costs the results did not vary to an extent that their final interpretation would change. Results were very sensitive to the level of ID of the person with epilepsy (that is the intervention would increase its probability to be cost effective in patients with profound/severe learning disability rather than in patients with mild/moderate learning disability). In the probabilistic sensitivity analysis the nurse-led intervention was found to have 85% probability of being cost effective at a threshold of £20,000 per QALY, and 83% probability of being cost effective at a threshold of £30,000 per QALY; however, neither differences in costs or outcomes between interventions were statistically significant.

Although neither studies' population included children and young people, they were performed in the UK considering the NHS perspective; and therefore, they were deemed to be directly applicable (Noble 2014, Ring 2018). Both studies were assessed as having potentially serious methodological quality limitations (Noble 2014, and Ring 2018). In Noble 2014, the time horizon of the analysis did not cover a long enough period to include all relevant costs

and outcomes, and no deterministic sensitivity analysis was performed to explore all potential uncertainties in the economic evaluation, for example about the cost estimation. Furthermore, the estimates of interventions' relative effects were likely to be biased, because the study was statistically underpowered in terms of participants recruited. In Ring 2018, the time horizon of the analysis was again not long enough to include all relevant outcomes. Furthermore, as noted by the authors, although base-case and sensitivity analyses indicate a potential for the competency framework to reduce costs, it is possible that there are additional costs associated with the implementation of the competency framework that were not captured by the overall study although such costs are often not included in the base case for NICE economic evaluations.

See appendix H and appendix I for economic evidence tables and economic evidence profiles.

Economic model

Economic modelling was carried out, building on the results of Noble 2014, to evaluate the cost effectiveness of epilepsy nurse specialist (ESN)-led intervention(s) (vs treatment as usual, TAU) in children, young people and adults with confirmed epilepsy. See appendix J for full details.

The economic model built on the economic evaluation carried out by Noble 2014, i.e. by updating its cost estimates to 2019 prices, extending the time horizon to 20 years, modelling different subgroups, and epilepsy populations (seizure free versus not seizure free). The model was also adapted to children and young people (CYP).

The base-case results suggest that a ESN led intervention resulted in cost savings of £2,422 and a reduction in QALYs of 0.02 at 1 year. This leads to savings of greater than £100,000 per QALY lost. Results were unchanged at 20-year time horizon, for both CYP and adults. The results were robust to changes in intervention costs, cost estimates, approach to estimating long-term costs. The values were above conventionally held thresholds for interventions and suggests that ESN led interventions are cost saving and cost effective even if not health improving.

The results of this economic analysis also suggest that the ESN led intervention is more likely to be cost effective in people with a severe epilepsy (such as, people with epilepsy not seizure free or with ongoing seizures) than in people who are seizure free.

See appendix J for full details of the model.

Evidence statements

- One directly applicable cost-utility analysis from UK with potentially serious limitations compared the cost effectiveness of an epilepsy specialist nurse (ESN) led intervention in addition to the standard care compared to the standard care alone in adults with confirmed epilepsy attending an emergency department (ED). The ESN led intervention in addition to the standard care was found to be less costly but with a small reduction in QALYs, compared to standard care alone. The resulting base-case incremental cost-effectiveness ratio (ICER) suggests that there would be a cost saving of £26,445 per QALY if the ESN led intervention is added. In probabilistic sensitivity analysis the ESN-led intervention was found to have 56% probability of being cost effective at a threshold of £20,000 per QALY gained, and 50% probability of being cost effective at a threshold of £30,000 per QALY gained; however, differences in outcomes between interventions were not significant.
- One directly applicable cost-utility analysis from UK with potentially serious limitations compared the cost effectiveness of a nurse-led intervention for epilepsy ('Learning Disabil-

ity Epilepsy Specialist Nurse Competency Framework) compared to treatment as usual in people with an intellectual disability (ID) and epilepsy. The nurse-led intervention for epilepsy (that is 'Learning Disability Epilepsy Specialist Nurse Competency Framework) was found to be less effective and less costly than standard of care at 6 months follow-up: the incremental cost-effectiveness ratio (ICER) estimated savings of £220,000 per QALY lost. In the probabilistic sensitivity analysis the nurse-led intervention was found to have 85% probability of being cost effective at a threshold of £20,000 per QALY, and 83% probability of being cost effective at a threshold of £30,000 per QALY; however, neither differences in costs or outcomes between interventions were statistically significant.

- Evidence from the guideline economic analysis suggested that epilepsy nurse specialist (ESN)-led intervention(s) for CYP and adults with confirmed epilepsy could be cost saving from the perspective of the NHS and personal social services (PSS). The base-case results suggest that a ESN led intervention resulted in cost savings of £2,422 and a reduction in QALYs of 0.02 at 1 year equal to £117,514 saved per QALY lost. Results were robust to sensitivity analysis and differing time horizons.The economic analysis is directly applicable to the NICE decision-making context and is characterised by potentially serious limitations.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The following outcomes were identified as critical to evaluate nurse-led interventions: satisfaction, including patient, parents, and carers; attendance to emergency departments; self-efficacy and health-related quality of life. The committee agreed that these outcomes would provide a good balance between how effective a nurse-led intervention could be for the person's wellbeing while assessing whether it would reduce attendance to emergency departments.

Inpatient admission to hospital (planned and unplanned) and GP/ hospital visits were considered important outcomes because these can be distressing for people with epilepsy and their families or carers. Depression and anxiety were included as important outcomes because these are common conditions people with epilepsy experience and a reduction in these may increase their health and wellbeing.

The quality of the evidence

The quality of the evidence for this review was assessed using the GRADE methodology. The outcomes were considered to be of very low to high quality evidence, indicating uncertainty in the data. Some of the outcomes were downgraded due to indirectness because the outcomes reported by the studies were a proxy to the one listed in the protocol (for example, the outcome emotional wellbeing was used as a proxy for depression and anxiety). Outcomes were also downgraded for high to very high risk of bias, as assessed with the ROBINS-I checklist or Cochrane risk of bias 2 for cluster trials. The main sources of potential bias were: lack of blinding of study participants, investigators and outcome assessors; lack of information regarding drop-outs and because of unclear reporting bias, in cases where it was not clear whether the study protocol was registered prior the study started. Finally, some outcomes were downgraded due to imprecision as the studies had a small number of participants, therefore the confidence around the estimate for each of the outcomes was low.

Benefits and harms

The committee acknowledged that the clinical evidence for the effectiveness of ESNs was either weak or missing for a number of critical outcomes and therefore it was difficult, based solely on the clinical evidence, to strongly say that ESNs are effective. However, as there was moderate economic evidence of cost savings both long-term and with-in the first year, and evidence about ESNs improving satisfaction and emotional wellbeing, the committee agreed to recommend that children, young people and adults with epilepsy should have access to an ESN.

According to the committee's experience, ESNs play a key role in supporting other healthcare professionals across a range of settings, as well as in helping people living with epilepsy, their families or carers with help, advice and support to manage their condition.

In addition when discussing the evidence, the committee found that the results of the economic model though should be interpreted in light of some limitations; mainly they focused their discussion on the non-randomised nature of the study design on which was based heavily the economic analysis (Noble 2014). In this research, treatment allocation between intervention groups of people with epilepsy was not randomised. As such, potential baseline differences may have existed between treatment groups, and this might have reduced the accuracy of the study's results. However, they considered the recruitment strengths of this study, when judging the evidence.

The clinical evidence showed that nurse-led interventions improved satisfaction and emotional wellbeing, and that the role of the epilepsy specialist nurses in the included studies showing an important difference was mainly focused on information and advice provision. The committee noted that this was consistent with their experience and expertise, and that information and advice provision was one of the most important roles of epilepsy specialist nurses in clinical practice, particularly with regard to the social and clinical aspects of epilepsy. For this reason, the committee decided to recommend that children, young people and adults with epilepsy should be offered an information and care-planning session with an ESN that includes emotional wellbeing and self-management strategies.

The committee acknowledged that, in clinical practice, ESNs undertake a wide variety of roles, and that one of the main limitations of the clinical evidence was the gap between the limited tasks that ESNs were undertaking in the included studies compared with the varied tasks that ESNs assume in clinical practice. The committee noted that this may have underestimated the benefits that ESNs bring to epilepsy services. In the included studies, ESNs' main role was focused on information provision and education, which ESNs in current practice also do, in addition to other tasks, such as individualised risk assessment; monitoring; liaison linking services; medicines management and prescribing; seizure and risk of seizure management; service delivery, etc. ESNs are often part of a multidisciplinary team and a highly controlled study would be needed to study their contributions in isolation to the rest of the team or the health system where they work in. ESNs are highly valued by people with epilepsy and their families and carers, however the study design of the included studies did not allow to investigate their views and experiences of care.

ESNs also provide safety advice which, according to the committee's experience, leads to a potential reduction in risk of accidental injury or death (for example, falls from height or drowning in the bath) during seizures. ESNs also play a role in the provision of seizure management training and seizure management plans and emergency medication for parents, carers or educational staff. Finally, epilepsy specialist nurses have expertise in contraception and pregnancy in epilepsy and play a vital role in maximising the safety of the mother and baby, through provision of appropriate advice tailored to the individual.

People who continue to have seizures are at higher risk of injuries and other complications from seizures, including memory problems, reduced quality of life and a significant impair-

ment in activities of daily living, such as eating, bathing, dressing and work. The economic evidence suggested lower contact with health services in such groups following ESN-led intervention. Based on this and their experience and expertise, the committee agreed that, for people who continue to have seizures, information and care-planning session with an ESN should be offered at least twice per year and after emergency department visits in line with the intervention considered in the economic modelling and 1 previously published UK economic evaluation.

The committee, based on the clinical evidence which showed an important benefit over treatment as usual in terms of outcome satisfaction and emotional wellbeing with group nurse-led interventions, agreed that services should consider these type of sessions in young people and adults. Group sessions are an opportunity to discuss common issues and to share coping strategies and seek and obtain ongoing peer support.

The committee highlighted that ESNs would not be harmful in epilepsy care and, even though there was not strong evidence of clinical effectiveness, there was no logical explanation to how they could be harmful other than through wasted resources on ineffective interventions. The economic evidence highlighted that ESNs were likely to reduce resource use. It was hypothesised that this was likely through the person having better knowledge of epilepsy leading to better self-care (including first aid) and more confidence in their condition leading to less emergency admissions as a result of ESN interventions.

Cost effectiveness and resource use

The committee noted that two relevant papers had been identified in the literature review of published economic evidence on this topic (Noble 2014, and Ring 2018), and a bespoke economic analysis had been undertaken.

Although neither studies population included children or young people, they were performed in the UK considering the NHS and PSS perspective; and therefore, the committee considered this economic evidence to be directly relevant to the guideline's decision-making. Noble 2014 study considered the cost effectiveness of an ESN led intervention in addition to TAU compared to TAU alone, in people with epilepsy attending an emergency department. Ring 2018 considered the cost effectiveness of an ESN-led intervention compared to standard care in people with epilepsy and an intellectual (learning) disability. The committee focused their discussion on Noble 2014, as it was highlighted that this study reflects the wider population of people with epilepsy, and its findings were believed more generalisable to the population of interest.

Based on the economic evidence review and economic model, the committee pointed out the vital role played by ESNs in epilepsy management, continuity of care and in fostering the coordination of the planning pathway of people with epilepsy across care services, which is likely to explain the cost savings identified in the economic evidence review and modelling. They observed that even if it was not possible to compare the cost effectiveness of TAU alone with the ESN led intervention in absence of TAU, only a small fraction of patients with epilepsy attending an ED are referred to neurology or primary care for a medical review; so they thought that the use of ESNs could be a very effectual way to save NHS resources. The committee acknowledged the small reductions in quality of life reported in the identified studies and model but highlighted that these were small and not significant. The view of the committee was that the population included in Ring 2018, that is people with an intellectual (learning) disability and epilepsy, was too narrow to reflect the whole spectrum of people with confirmed epilepsy. Therefore, the committee thought it was very unlikely that ESN led interventions would be harmful and that small differences in QALYs were most likely the result of statistical variance and insensitive measures of quality of life.

Based on Noble 2014 and the economic model, the committee agreed that people with epilepsy should have access to an ESN who they could contact between scheduled reviews and after emergency department visits. Even if the evidence for the effectiveness of ESN led interventions was weak there was moderate UK evidence that they would lead to cost savings with no harm to people with epilepsy. The evidence supported the committee´s experience that people with epilepsy and their families valued the approachable nature of epilepsy specialist nurses, so the recommendations reflect the need to offer information in a timely manner. The committee also acknowledged in the recommendations made, that people´s information needs may vary from time to time and more contact may be needed soon after diagnosis, when seizures are ongoing or after an emergency department visit. This was supported by the findings of the sensitivity analysis of the economic model, which suggested that the ESN intervention added to standard care was cost effective either for children and young people or adults with epilepsy regardless of the intensity or frequency of the intervention delivery, and not only for people with ongoing seizures.

The recommendations will lead to an increase in the number of appointments with an ESN for a large patient group. This may lead to a significant resource impact in the immediate term although the economic evidence suggests this will be more than recouped within the first year. Although the exact role and interventions undertaken may vary, most epilepsy centres will already have ESNs connected to the service. Scheduled sessions with an ESN may also replace ad-hoc appointments with ESNs or other health care professionals therefore the number of additional appointments may not be large.

Other factors the committee took into account

In order to have a full picture of the experiences of the participants included in the studies, the committee considered the qualitative findings reported by two of the studies included in the systematic review (Noble 2014 and Ring 2018). Noble 2014 did two different semi-structured interviews. In the first one, they explored the views, experiences and reasons for visiting the emergency department from the participant’s perspective. Overall, participants felt visiting the emergency department varied between being at home with a significant other who knew how to manage seizures and being in a public space, in the presence of someone less familiar with their condition. Some of the interviewed participants felt that attending the emergency department was the right decision because they were living by themselves and therefore felt more isolated and vulnerable, or in order to avoid the seizure’s consequences, such as lesions related to falls. The second semi-structured interview conducted by Noble 2014 assessed whether the nurse specialist intervention met the participant’s needs 1 year after its completion. Participants felt that the nurse-led intervention helped, particularly because they perceived nurses to be more approachable than other specialists. Ring 2018 assessed the views of family carers, paid support workers and nurses. The interviews with family carers revealed that services varied significantly depending on the place where they received care. For example, some accessed epilepsy treatments through the nurse prescribers, whereas others had appointments just with the neurologist or psychiatrist, seeing nurses with specific training in epilepsy less often. Families valued that nurses where available when needed and also their approachable nature. They appreciated that nurses were able to communicate effectively with other healthcare professionals, particularly with respect to writing care plans and securing social care funding for specialist equipment.

Recommendations supported by this evidence review

This evidence review supports recommendations 11.1.1-11.1.4.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

Table 5: Review protocol for effectiveness of a nurse specialist in the management of epilepsy

Field	Content
PROSPERO registration number	CRD42019152151
Review title	Effectiveness of epilepsy nurse specialist
Review question	What is the effectiveness of a nurse specialist in the management of epilepsy?
Objective	The objective of this review is to determine whether having an epilepsy nurse specialist as part of the epilepsy care management strategy is effective in improving the outcomes of people with epilepsy. The review will investigate how the nurse specialist may undergo different roles within the care management team and how this influences care. Information gathered may also be relevant for, and help inform recommendations for the review question on "What information and support is needed by people, parents or carers in relation to epilepsy, and when should this be provided?"
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare • CINAHL

Field	Content
	Searches will be restricted by: • Date: no date limits • English language studies • Human studies
Condition or domain being studied	Epilepsy
Population	Inclusion: people with confirmed epilepsy Exclusion: newborn babies (under 28 days) with acute symptomatic seizures
Intervention	Any involvement by an epilepsy nurse specialist Note: We cannot predetermine what role the nurse specialist may play within a care team; therefore, studies will be categorised according to their individual intervention design. We aim to group studies with similar level of nurse involvement (for example if studies list the activities of the nurse specialist we will group those which share at least 50% of activities); however this may not be possible if all identified studies are highly heterogeneous.
Comparator	We will include any study which compares one nurse specialist strategy to another, these may include, for example: • Treatment as usual (as defined by investigators) • A study with an epilepsy nurse specialist undertaking a different role in the care team • No epilepsy nurse specialist input
Types of study to be included	• Systematic review/meta-analyses of RCT or cohort studies • RCT • Non-randomised or quasi-randomised studies • Prospective/retrospective cohort studies (comparative only) Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	Studies with a mixed population (this is, including people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported.

Field	Content
	Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary, and tertiary care)
Primary outcomes (critical outcomes)	• Satisfaction, including patient, parents and carers (validated and non-validated scales will be included) • Attendances to emergency departments (self-reported and objective measures will be used) • Self-efficacy (validated and non-validated scales) • Health-related quality of life (only validated scales will be included) Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/details/118?result=true http://www.cometinitiative.org/studies/searchresults (https://onlinelibrary.wiley.com/doi/full/10.1111/epi.14735)
Secondary outcomes (important outcomes)	• Admission to hospital (inpatient): ○ Acute/ unplanned/ unscheduled ○ Planned • GP/ hospital visits (outpatient) • Depression and anxiety (validated tools only)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria outlined in the review protocol. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies (see Developing NICE guideline: the manual section 6.4) and will include: study setting; study design; study aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of intervention and control groups; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias.

Field	Content
	All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic advisor and Chair. Duplicate screening will not be undertaken for this question.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. <u>Data synthesis</u> Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm and <1% events in the other. Risk difference will be used for outcomes with zero events in both arms. Mean differences or standardised mean differences will be presented for continuous outcomes. We will collate data on the different roles that the nurse specialist has across and within the identified studies to aid interpretation of data. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • study location Exact sub-group analysis may vary depending on differences identified within included studies.

Field	Content
	If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis; reviewers will consider if meta-analysis is appropriate given characteristics of included studies. Minimal important differences (MIDs): Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes For risk ratios: 0.8 and 1.25. For continuous outcomes: For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm. For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used. For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
Analysis of sub-groups	Stratification If data is available, results will be presented separately by: • Age group: • Infants and children (0 to 11 years old) • Young people (> 11 to 25 years old) • Adults (> 25 to 65 years old) • Older people (> 65 years old) • Those with and without a developmental delay (includes learning disabilities)

Field	Content			
	• Infants, children and young people versus parents and carers			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	20th December 2019			
Anticipated completion date	7th April 2021			
Stage of review at time of this sub-mission	Review stage	Started	Completed	
	Preliminary searches	☑	☑	
	Piloting of the study selection process	☑	☑	
	Formal screening of search results against eligibility criteria	☑	☑	
	Data extraction	☑	☑	
	Risk of bias (quality) assessment	☑	☑	
	Data analysis	☑	☑	
Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail epilepsies@nice.org.uk 5c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance			
Review team members	NGA technical team			
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which is funded by NICE and			

Field	Content	
	hosted by the Royal College of Obstetricians and Gynaecologists. NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112	
Other registration details	Not applicable	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019152151	
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.	
Keywords	Epilepsy, nurse specialist	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	

Field	Content
Details of final publication	www.nice.org.uk

GP: general practitioner; RCT: randomised controlled trial, RoB: risk of bias

Appendix B – Literature search strategies

Literature search strategies for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

Clinical

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

EMCare 1995 to 2021 March 03; Embase Classic+Embase 1947 to 2021 March 03; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 March 03, 2021
EMCare 1995 to March 03, 2021
Date of last search: 03 March 2021

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

#	searches
1	exp epilepsy/ or landau kleffner syndrome/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd, emcr
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(convulsion* or dravet syndrome or epilep* or continous spike wave of slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6	or/2,4-5
7	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
8	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
9	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
10	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or smei or lennox gastaut or lgs or (landau adj2 kleffner)).ti,ab.
11	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or (dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
12	or/6-11
13	exp advanced practice nurse/ or nurse/ or exp nurse specialist/

#	searches
14	13 use emczd, emcr
15	advanced practice nursing/ or exp nurse practitioners/ or exp nurse specialists/ or nurses/
16	15 use ppez
17	(aprn* or ((advanced or expert) adj3 nurs*) or (epilep* adj3 nurs*) or (epileps* adj5 nurs* adj5 educat*) or (nurs* adj3 ((care adj3 coord*) or (case adj3 manag*) or clinician* or practitioner* or specialist*)) or nurs* educat*).ti,ab.
18	(epilep* adj3 nurs*).ti,ab.
19	or/14,16-18
20	12 and 19
21	limit 20 to english language
22	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
23	22 use emez
24	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)
25	24 use mesz
26	23 or 25
27	21 not 26

Database(s): CINAHL - ProQuest

Date of last search: 03 March 2021

#	searches
s22	s15 and s21 narrow by language: - english
s21	s16 or s17 or s18 or s19 or s20
s20	tx ((aprn* or ((advanced or expert) n3 nurs*) or (epilep* n3 nurs*) or (epileps* n5 nurs* n5 educat*) or (nurs* n3 ((care n3 coord*) or (case n3 manag*) or clinician* or practitioner* or specialist*)) or “nurs* educat*”)) or tx (epilep* n3 nurs*)
s19	(mh "nurses")
s18	(mh "nurse specialist service (saba ccc)")
s17	(mh "advanced practice nurses+")
s16	(mh "advanced nursing practice+")
s15	s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14
s14	tx (dravet*1 or (“intractable childhood epilepsy” n2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe n2 (myoclonic or polymorphic) n2 epilepsy n2 infancy) or smeb or smei)
s13	(mh "epilepsies, myoclonic+")
s12	tx (dravet or smei or “lennox gastaut” or lgs or (landau n2 kleffner))

#	searches
s11	tx (bcects or bects or brec or “benign epilepsy” or (benign n2 (childhood or neonatal or pediatric or paediatric) n2 epileps*) or (benign n2 (childhood or neonatal or pediatric or paediatric) n2 (convulsion* or epileps* or seizure* or spasm*)) or (benign n3 (convulsion* or epileps*) n2 centrotemporal n2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) n1 (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) n2 (convulsion* or epileps* or seizure* or spasm*)))
s10	(mh "epilepsy, rolandic")
s9	tx ((myoclonic n2 (astatic or atonic)) or (myoclonic n3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generalized idiopathic epilepsy” or “generalised idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) n2 (seizure* or spasm*))
s8	(mh "epilepsies, myoclonic+")
s7	tx (((early or infantile) n2 myoclonic n2 encephalopath*) or ((early or infantile) n2 epileptic n2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) n2 (seizure* or spasm*)) or “generalised flexion epileps*” or “generalized flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) n1 (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)
s6	(mh "spasms, infantile")
s5	tx (convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”)
s4	(mh "status epilepticus+")
s3	(mh "convulsions, febrile")
s2	(mh "seizures")
s1	(mh "epilepsy+")

1
2

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 03 of 12, March 2021;
Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2021
Date of last search: 03 March 2021

#	searches
#1	mesh descriptor: [epilepsy] explode all trees
#2	mesh descriptor: [seizures] this term only
#3	mesh descriptor: [spasms, infantile] this term only
#4	mesh descriptor: [status epilepticus] explode all trees
#5	((convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”)):ti,ab,kw
#6	mesh descriptor: [spasms, infantile] this term only
#7	((((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near/2 (seizure* or spasm*)) or “generalised flexion epileps*” or “generalized flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) near/1 (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)):ti,ab,kw
#8	mesh descriptor: [epilepsies, myoclonic] explode all trees
#9	(((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generalized idiopathic epilepsy” or “generalised idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) near/2 (seizure* or spasm*))):ti,ab,kw
#10	mesh descriptor: [epilepsy, rolandic] this term only
#11	((bcects or bects or brec or “benign epilepsy” or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near/1 (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab,kw
#12	((dravet or smei or “lennox gastaut” or lgs or (landau near/2 kleffner))):ti,ab,kw
#13	mesh descriptor: [epilepsies, myoclonic] explode all trees
#14	((dravet*1 or (“intractable childhood epilepsy” near/2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe near/2 (myoclonic or polymorphic) near/2 epilepsy near/2 infancy) or smeb or smei)):ti,ab,kw
#15	{or #1-#14}
#16	mesh descriptor: [advanced practice nursing] this term only
#17	mesh descriptor: [nurse practitioners] explode all trees
#18	mesh descriptor: [nurse specialists] explode all trees
#19	mesh descriptor: [nurse specialists] this term only
#20	((aprn* or ((advanced or expert) near/3 nurs*) or (epilep* near/3 nurs*) or (epileps* near/5 nurs* near/5 educat*) or (nurs* near/3 ((care near/3 coord*) or (case near/3 manag*) or clinician* or practitioner* or specialist*)) or “nurs* educat*”)):ti,ab,kw
#21	((epilep* near/3 nurs*)):ti,ab,kw

#	searches
#22	{or #16-#21}
#23	#15 and #22

Database(s): DARE; HTA database - CRD
Date of last search: 03 March 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures, febrile this term only
3	mesh descriptor seizures this term only
4	mesh descriptor status epilepticus explode all trees
5	mesh descriptor spasms, infantile this term only
6	mesh descriptor epilepsies, myoclonic explode all trees
7	mesh descriptor epilepsy, rolandic this term only
8	mesh descriptor epilepsies, myoclonic explode all trees
9	((convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”))
10	((((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) near1 (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”))
11	(((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) near2 (seizure* or spasm*)))
12	((bcects or bects or brec or “benign epilepsy” or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near1 (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*))))
13	((dravet or smei or “lennox gastaut” or lgs or (landau near2 kleffner)))
14	((dravet* or (“intractable childhood epilepsy” near2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei))
15	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

Economic

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

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

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continous spike wave of slow sleep or infant* spasm*).ti,ab.
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)).ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)).ti,ab.

#	searches
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*))).ti,ab.
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jacknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or smei).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*)).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or smeb or smei).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to engish language

Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD

Date of last search: 31 March 2021

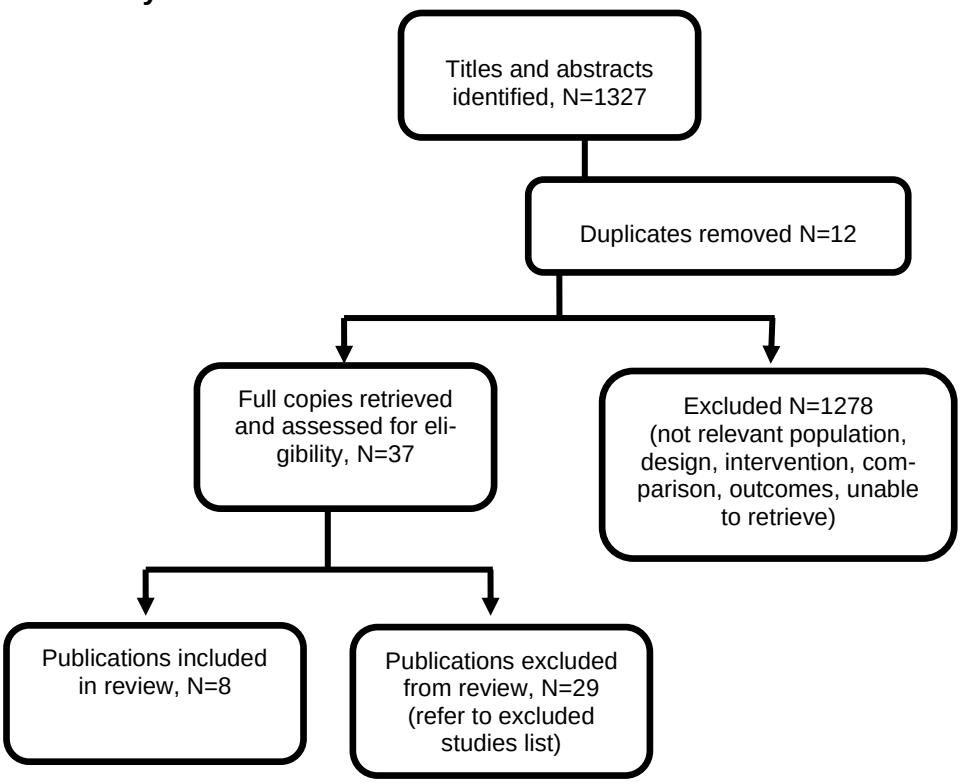
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”)
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or “petit mal*” or pyknolepsy or “typical absence*”)
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or “brief seizure” or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only
10	(bcects or bects or brec or “benign epilepsy” or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or ((“childhood absence” or “juvenile absence” or myoclonic or myoclonia or “myoclonic astatic” or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 “eyelid myoclonia”) or (ige near2 phantom absenc*) or “impulsive petit mal” or (janz near3 (epilep* or “petit mal”)) or “jeavons syndrome*” or ((janz or lafora or “lafora body” or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epilep*) or “perioral myoclon*”)
13	mesh descriptor spasms, infantile this term only
14	(((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epilepsy” or “propulsive petit mal“or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or “lennox gastaut” or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	(“child* epileptic encephalopath*” or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or “progressive familial epilep*” or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or “muscle jerk”)
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) or ((absence or astatic or atonic or tonic or “tonic clonic”) near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or “focal onset” or local or partial or “simple partial”) near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or (“intractable childhood epilepsy” near2 (“generalised tonic clonic” or gtc)) or icegtc* or (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	(((clonic or “grand mal” or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

1
2

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the effectiveness of a nurse specialist in the management of epilepsy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

Table 6: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Davis, J., Roberts, R., Davidson, L. W., Norman, A., Ogston, S., Grimshaw, J. M., Davey, P., Grant, J., Ruta, D., Implementation Strategies for a Scottish National Epilepsy Guideline in Primary Care: Results of the Tayside Implementation of Guidelines in Epilepsy Randomized (TIGER) Trial, Epilepsia, 45, 28-34, 2004 **Ref Id**	**Sample size** N (clusters) = 44 GP practices; n (cluster) = 22 practices (399 participants) were allocated to the intervention group and n (cluster) = 22 (370 participants) were allocated to the control group **Characteristics** Age, years, mean (SD) Group nurse-led intervention: 49.1 (16.8) Control group: 48.9 (16.6) Males, n (%) High intervention group: 178 (44.7)	**Interventions** Group nurse-led intervention: Received a copy of a national guideline; attended workshops and summary protocols about the guideline; and received the services of a nurse specialist in epilepsy (the main remit of the nurse specialist was to "offer advice and training to practices in establishing epilepsy review programs, to promote the use of the guideline in epilepsy management, and to provide information on epilepsy for both prac-	**Details** Locations (clusters) were randomised with a computer generated random sequence. Data was collected from the general practice notes. Analysis was conducted by intention to treat. Follow-up: 12 months (no measure	**Results** *Primary outcomes* Mastery (proxy outcome for self-efficacy, Epilepsy-specific scale mastery scores), mean (range) Before the intervention Group nurse-led intervention: 19.9 (19.2 to 20.7), n= 399 Control group: 20.1 (19.4 to 20.8), SD = 6.8, n=370 After the intervention Group nurse-led intervention: 19.7 (19.1 to 20.4), n=399 Control group: 20.3 (19.7 to 20.8), n=370 Mean difference (95% CI) between baseline and post-intervention = 0.40 (-0.90 to 1.70)	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0 for cluster randomized, parallel group trials)** **Domain 1a: Bias arising from the randomization process: Some concerns** 1a.1 Was the allocation sequence random? yes, computer generated random numbers 1a.2: Is it likely that the allocation sequence was subverted? no information 1a.3: Were baseline imbalances that suggest a problem with the randomization process? no, no imbalances are apparent **Domain 1b: Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomization: Low risk** 1b.1 Were all the individual participants identified before randomization of clusters (and if the trial specifically recruited patients were they all recruited before randomization of clusters)? yes, part of the inclusion criteria of the trial is that patients should be receiving

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1146025 **Country/ies where the study was carried out** UK **Study type** Cluster randomised controlled trial. **Aim of the study** To assess the effectiveness of 2 dissemination and implementation strategies in people with epilepsy in a primary care setting **Study dates** 1998 **Source of funding** Glaxo-Wellcome, Janssen-Cilag, Novartis, Parke-Davis, Sanofi, and UCB-	Control group: 178 (49) <u>Type of seizures, n (%)</u> Not reported **Inclusion criteria** • Those who were attending the relevant GP practices and receiving antiseizure medications for epilepsy • > 16 years old **Exclusion criteria** • Those receiving antiseizure medications for other condition which was not epilepsy	titioners and patients" <u>Control group:</u> Received a copy of a national guideline	of variability was reported)	<u>Health-related quality of life (General Health profile SF-36 scores), mean (range)</u> <u>Before the intervention</u> Group nurse-led intervention: 62.1 (59.1 to 65.1), n= 399 Control group: 63.7 (58.3 to 69.2), SD = 52.8, n=370 <u>After the intervention</u> Group nurse-led intervention: 62.0 (57.9 to 66.0), n=399 Control group: 63.4 (58.3 to 68.5), n=370 Mean difference (95% CI) between baseline and post-intervention = -0.20 (-8.92 to 8.52)	medication for epilepsy in their GP practices 1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention? no information 1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between arms? no **Domain 2: Bias due to deviations from intended interventions: Low risk** 2.1a: Were participants aware that they were in a trial? yes 2.1b: If Y/PY/NI to 2.1a: Were participants aware of their assigned intervention during the trial? yes 2.2: Were carers and trial personnel aware of participants' assigned intervention during the trial? yes 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice? probably no 2.5a Were any clusters analysed in a group different from the one to which they were assigned? no 2.5b Were any participants analysed in a group different from the one to which their original cluster was randomized? no **Domain 3: Bias due to missing outcome data: Low risk** 3.1a: Were outcome data available for all, or nearly all, clusters randomized? no. The attendance to the workshops was very low, and of all the staff invited to participate in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pharma (allowed the provision of hospitality at the workshop sessions)					workshop, 9.6% attended 3.1b Were outcome data available for all, or nearly all, participants within clusters? no, low response rate (56% of all participants approached completed the survey) 3.2 If N/PN/NI to 3.1a or 3.1b: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups? yes, the numbers of patients declining or ineligible was similar in the arms of the study 3.3 If N/PN/NI to 3.1a or 3.1b: Is there evidence that results were robust to the presence of missing outcome data? no information **Domain 4: Bias in measurement of the outcome: some concerns** 4.1a: Were outcome assessors aware that a trial was taking place? no information 4.1b: If Y/PY/NI to 4.1: Were outcome assessors aware of the intervention received by study participants? no information 4.2: Was the assessment of the outcome likely to be influenced by knowledge of intervention received? no information **Domain 5: Bias in the selection of the reported result: some concerns** Are the reported outcome data likely to have been selected, on the basis of the results, from... 5.1: ... multiple outcome measurements (for example, scales, definitions, time points) within the outcome domain? no information 5.2: multiple analyses of the data? no infor-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					mation **Domain 6: Overall judgement of bias:** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the results **Other information** The study also had an "intermediate intervention group" but results have not been included in this review as only 1 control group was needed. Analyses done for calculating the effective sample size of the intervention and control group were as follows: Average cluster size = (399+370)/(22+24)= 16.75 <u>Mastery outcome:</u> ICC= 0.019, obtained from https://www.abdn.ac.uk/hsru/what-we-do/tools/#panel177 database of ICCs TIGER dataset Liverpool epilepsy score - Mastery of epilepsy score Design effect= 1 + (16.75-1) x 0.019= 1.299 Effective sample size in group nurse-led intervention = 399/1.299=307 Control group = 370/1.299= 284 <u>Health-related quality of life</u> ICC= 0.00, obtained from https://www.abdn.ac.uk/hsru/what-we-do/tools/#panel177 database of ICCs TIGER dataset SF36 - general health perception Design effect= 1 + (16.75-1) x 0.00 = 1 Effective sample size in group nurse-led in-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					tervention = 399/1=399 Effective sample size in control group = 364/1= 364
Full citation Dorris, L., Broome, H., Wilson, M., Grant, C., Young, D., Baker, G., Balloo, S., Bruce, S., Campbell, J., Concannon, B., Conway, N., Cook, L., Davis, C., Downey, B., Evans, J., Flower, D., Garlovsky, J., Kearney, S., Lewis, S., Stephens, V., Turton, S., Wright, I., A randomized controlled trial of a manual-based psychosocial group intervention for young people with epilepsy [PIE], Epilepsy and Behavior, 72, 89-98, 2017 **Ref Id**	**Sample size** N=76 young people with epilepsy, n=39 allocated to the group nurse-led intervention group and n=37 allocated to the wait list group **Characteristics** Age, years, mean (SD) Intervention group: 14.4 (1.5) Control group: 14.3 (1.4) Females, n (%) Intervention group: 26 (65.4) Control group: 24 (66.7) Type of seizures, n (%) Generalized clonic/ tonic-clonic Intervention group: 25 (43.1) Control group: 29 (40.8)	**Interventions** Intervention group: group nurse-led intervention, which consisted on a manual-based psychosocial group intervention for young people with epilepsy. The intervention was facilitated by an ESN and a clinical psychologist and consisted of 6 weekly 2-hour sessions using guided discussion, group exercises and role-plays. Specifically, sessions 1-3 focused on sharing experiences of having epilepsy, increasing epilepsy knowledge, and improving self-management of the condition; whilst sessions 4–6 focused on increasing resilience and developing coping	**Details** Participants were randomised in blocks based on age, gender, and type of mental health support. Study participants and those delivering the intervention were not blinded to the type of intervention, however the second author inputted the data remained blinded until study completion. Results reported by intention to treat.	**Results** *Critical outcomes* Self-efficacy (SSEC scores), mean (SD) Baseline Intervention group: 57.15 (14.72), n=39 Control group: 59.26 (12.80), n=37 3 months follow-up Intervention group: 60.69 (8.23), n=39 Control group: 60.55 (10.45), n=37 Mean difference (95% CI) between baseline and 3 month follow-up: -2.25, 95% CI -9.42 to 4.92 Health-related quality of life PedsQL scores, mean (SD) Baseline Intervention group: 70.93 (15.41), n=39 Control group: 69.36 (19.42), n=37 3 months follow-up Intervention group: 67.79 (11.74), n=39 Control group: 69.19 (17.79), n=37	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Randomisation method was not reported 1.2: Whether the allocation sequence was concealed was not reported 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, people delivering the intervention were aware of participant's assigned intervention during trial 2.3: No information, trialists do not report whether deviations arose from the experimental context 2.6: Yes, ITT analysis **Domain 3: Missing outcome data: Low risk** 3.1: No, data was lost for >95% of the participants 3.2: No, no evidence that the result was not biased by missing outcome data 3.3: No, authors explain that data is likely to be missing because control participants were enrolled into the study 5 months in advance to the other group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
711906 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** To assess the efficacy of a psychosocial group intervention focused on improving epilepsy knowledge, self-management skills and quality of life in people with epilepsy **Study dates** April to July 2015 **Source of funding** UCB Pharma and Yorkhill Children's Foundation	<u>Focal</u> Intervention group: 12 (20.7) Control group: 19 (26.8) <u>Absences</u> Intervention group: 16 (27.6) Control group: 16 (22.5) <u>Myoclonic</u> Intervention group: 4 (6.9) Control group: 5 (7.1) <u>Status epilepticus</u> Intervention group: 1 (1.7) Control group: 1 (1.4) <u>Tonic</u> Intervention group: 0 (0) Control group: 1 (1.4) **Inclusion criteria** • Those with a diagnosis of controlled or refractory epilepsy for at least 6	strategies for anxiety or low mood through strategies such as problem solving, using strategies as CBT and mindfulness. <u>Control group:</u> Wait-list control.	Follow-up: 6 weeks (no measure of variability was reported)	Mean difference (95% CI) between baseline and 3 month follow-up: 2.97 (-7.13 to 13.08) <u>GEOS-YP scores, mean (SD)</u> <u>Baseline</u> Intervention group: 62.61 (14.85), n=39 Control group: 66.20 (13.95), n=37 <u>3 months follow-up</u> Intervention group: 65.83 (11.62), n=39 Control group: 66.16 (12.13), n=37 Mean difference (95% CI) from baseline to 3 months follow-up: -3.92 (-12.14 to 4.30) *Important outcomes* **Emotional distress (proxy outcome for depression and anxiety, PI-ED scores)** <u>Baseline</u> Intervention group: 14.49 (6.61), n=39 Control group: 12.76 (7.84), n=37 <u>3 months follow-up</u> Intervention group: 13.72 (5.86), n=39 Control group: 13.95 (7.76), n=37	**Domain 4: Measurement of the outcome: Low risk** 4.1: No, outcomes were measured with objective and validated measures 4.2: No, measurement or ascertainment could not have differed between intervention groups 4.3: No, outcome assessors were not aware of the intervention received **Domain 5: Selection of the reported result: High risk** 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements 5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6: Overall judgement of bias: High risk** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	months before the start of the trial • Ability to provide written consent • Aged between 12 and 17 years old • Level of expressive and receptive English language and attending mainstream schooling **Exclusion criteria** • Formal diagnosis of learning disability • Those who reported suicidal ideation or scores ≥40 in the Beck Depression/Anxiety Inventory for Youth • Diagnosis of non-epileptic seizures in the absence of epileptic seizures			Mean difference (95% CI) from baseline to 3 months follow-up: 1.96 (-2.20 to 6.12)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Those with epilepsies occurring in the context of postnatally acquired lesions, immune mediated disorders, or metabolic disorders				
Full citation Helde, G., Bovim, G., Brathen, G., Brodtkorb, E., A structured, nurse-led intervention program improves quality of life in patients with epilepsy: A randomized, controlled trial, Epilepsy and Behavior, 7, 451-457, 2005 **Ref Id** 1146194 **Country/ies where the study was carried out** Norway **Study type**	**Sample size** N=111 adults with uncontrolled epilepsy, n= 57 allocated to the educational intervention and n= 54 allocated to treatment as usual **Characteristics** <u>Age, years, mean (range)</u> Intervention group: 35.3 (16 to 69) Control group: 39.5 (16 to 37) <u>Females, n (%)</u> Intervention group: 32 (56) Control group: 32 (59) <u>Type of seizures,</u>	**Interventions** <u>Intervention group:</u> group nurse-led intervention, which consisted of a group education programme plus follow-up teaching and support from an epilepsy nurse, in close collaboration with a neurologist. The group educational session served as a starting point for further contact and individual counselling during follow- up, which was delivered within the first 3 months from the inclusion in the trial, and were aimed to provide general	**Details** Computer generated randomisation was performed in blocks. The design was open label. Analysis was intent to treat. Results are reported at 2 years follow-up, after the completion of the study. Follow-up: 2 years (no measure of variability was reported)	**Results** *Critical outcomes* <u>Satisfaction (VAS scores), mean (SD)</u> Intervention group: 95.1 (8.7), n=57 Control group: 72.0 (27.9), n=54 <u>Health-related quality of life (QOLIE-89 overall QOL scores), mean (SD)</u> Intervention group: 51.3 (0.9), n=57 Control group: 51.7 (1.4), n=54 *Important outcomes* <u>Emotional wellbeing (proxy outcome for depression and anxiety, QOLIE-89 scores), mean (SD)</u> Intervention group: 52.8 (1.1), n=57 Control group: 49.5 (1.5), n=54	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Randomisation method was not reported 1.2: Whether the allocation sequence was concealed was not reported 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, people delivering the intervention were aware of participant's assigned intervention during trial 2.3: No information, trialists do not report whether deviations arose from the experimental context 2.6: Yes, ITT analysis **Domain 3: Missing outcome data: High risk** 3.1: No information about the extent of missing data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To assess whether an epilepsy nurse led intervention improves quality of life in adults with epilepsy **Study dates** February 2001 to March 2002 **Source of funding** Glaxo-SmithKline	n Secondarily generalized clonic/ tonic-clonic Intervention group: 34 Control group: 30 Primarily generalized clonic/ tonic-clonic Intervention group: 13 Control group: 13 Absences Intervention group: 3 Control group: 5 Myoclonic Intervention group: 4 Control group: 5 Simple partial Intervention group: 18 Control group: 18 Complex partial Intervention group: 32 Control group: 34 Unclassified	information about daily management of epilepsy. Follow-up teaching and support was delivered by telephone, and the nurse called the patients at least every 3 months to ensure availability and continuity of care. Control group: treatment as usual, defined as 'conventional treatment according to individual needs'. This consisted of appointments with the caring neurologists and telephone contact with nurses working in the outpatient clinic of attendance.			3.2: No, no evidence that the result was not biased by missing outcome data 3.3: No information 3.4: No information **Domain 4: Measurement of the outcome: High risk** 4.1: No, outcomes were measured with objective and validated measures 4.2: No, measurement or ascertainment could not have differed between intervention groups 4.3: No information 4.4: Yes, as outcomes such as health-related quality of life and emotional well-being were measured 4.5: Yes, as above **Domain 5: Selection of the reported result: High risk** 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements 5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6: Overall judgement of bias: High risk** The study is judged to have some concerns

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Intervention group: 0 Control group: 1 **Inclusion criteria** • Those patients with diagnosis of epilepsy • Those receiving antiseizure medication for more than 1 year • Those patients who registered one or more seizures during the previous year • Those patients aged 16–70 years old • Those patients attending the neurology outpatient clinic in Trondheim, Norway who were able to cooperate and understand written and oral information and who gave written informed consent				for multiple domains in a way that substantially lowers confidence in the result

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria • Those patients with any other condition requiring comprehensive care • Patients attending regularly the Health and Home Service System due to epilepsy • Patients who participated in other clinical trials and were not able to take part in the study as a whole.				
Full citation Hill CE, Thomas B, Sansalone K, et al., Improved availability and quality of care with epilepsy nurse practitioners, Neurology. Clinical practice, 7, 109-117, 2017 **Ref Id**	**Sample size** N=169. Intervention group n=65. Control group n=104. **Characteristics** Patients with epilepsy attending an hospital outpatient clinic. Identified	**Interventions** Intervention: Physician and nurse practitioner working together with both providers seeing each new patient. Control: Physician working alone. Allocation to care model dependent on nurse practi-	**Details** As the final diagnosis was not known at the time of the new patient appointment, patients eventually diagnosed in the follow-up period with	**Results** *Critical outcomes* Presentation to emergency department: intervention group n=14/65; control group n=16/104. *Important outcomes* Admission to epilepsy monitoring unit: intervention group n=14/65; control group n=25/104.	**Limitations** **Risk of bias assessed with the ROBINS-I assessment tool** **1. Bias due to confounding: serious risk** 1.1: Yes. Potential for confounding. 1.2: No. 1.4: No. Analysis did not control for variables. 1.6: No. 1.7: Analysis did not adjust for all important confounding domains or for time-varying confounding. 1.8: No. No adjustment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1310743 **Country/ies where the study was carried out** United States **Source of funding** Study type Retrospective observational cohort study. **Aim of the study** To "… investigate the quality of care delivered to patients with epilepsy by a multidisciplinary care model that includes an NP compared to a more traditional physician-only care model." p 110 **Study dates** January 2014 - December 2014.	from electronic hospital record database. Age at new patient visit, years, median (IQR): Intervention group 37 (24-53); control group 40 (29-55), p = 0.05. Female, n (%): intervention group n=77 (46); control group 32 (49) , p = 0.45. Race, non-white, n (%): n=52/157 (33); control group n=15/62 (24). Data not available for all patients, p = 0.06. Etiology, suspected, n (%): Partial - intervention group n=119 (70); control group n=50 (77). Generalised - intervention group n=18 (11); control group n=6 (9). Unknown - intervention group	tioner availability and patient preferences regarding time and date. All physicians and nurse practitioners are reported to be epilepsy specialists, who had undergone specialised training and learning within epilepsy clinics and either exclusively or primarily saw epilepsy patients. Reporting of group allocation made on basis of documentation in electronic records. If the record for a new patient visit only included documentation from a physician, the patient was considered to be assigned to the physician only model of care. If the record included documentation by a physician and a	psychogenic nonepileptic seizures (PNES) were included in the study population. I The only difference observed between the patients in the 2 care models with regard to demographic characteristics was in age (table 2). Follow-up: 1 year (no measure of variability was reported)		**2. Bias in selection of participants into the study: moderate risk** 2.1: Yes 2.4: No **3. Bias in classification of interventions: moderate risk** 3.1: Yes 3.2: No 3.3: Yes **4. Bias due to deviations from intended interventions: low risk** 4.1: No **5. Bias due to missing data: low risk** 5.1: Yes 5.2: No 5.3: No **6. Bias in measurement of outcomes: low risk** 6.1: No 6.2: Yes 6.3: Yes 6.4: No **7. Bias in selection of the reported result: low risk** 7.1: No 7.2: No 7.3: No **Domain 6: Overall judgement of bias. Serious risk. The study is judged to be at serious risk of bias in at least one domain.**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Epilepsy Foundation Clinical Research Training Fellowship; and the National Institute of Neurologic Disorders and Stroke T32 Award in Neurologic Clinical Epidemiology.	n=32 (19); control group n=9 (14). Convulsive seizures, n (%): intervention group n=122 (72); control group n=44 (68), p = 0.30. Drug-resistant, n (%): intervention group n=67 (40); control group n=21 (32), p = 0.12. Duration of epilepsy, years, median (IQR): intervention group 10 (2-22); control group 11 (1-24)., p = 0.86. Neurologic and psychiatric comorbidities, median (IQR): - intervention group 1 (0-2); control group 1 (0-2), p = 0.63. Psychogenic non-epileptic seizures diagnosed n= during study, n (%): intervention group 9 (5); control group n=4 (6), p =	nurse practitioner then the patient was considered to be assigned to the nurse practitioner/physician model of care. 6/9 physicians saw patients under both models of care.			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	0.73. Length of time from initial visit to final follow-up visit, days, median (IQR): intervention group 255 (159-336); control group n=267 (162-349), p = 0.26. **Inclusion criteria** • a new patient visit at the Penn Epilepsy Center at the Hospital of the University of Pennsylvania during 2014 • > 17 years • diagnosis of seizure assigned to the initial visit defined by ICD-9 345.xx or 780.39 • at least one follow-up appointment within 12 months. **Exclusion criteria** • Patients without				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	'active epilepsy' (defined as experiencing ≥1 seizure in the last year) • Currently taking an antiepileptic medication.				
Full citation Noble, A. J., McCrone, P., Seed, P. T., Goldstein, L. H., Ridsdale, L., Clinical- and cost effectiveness of a nurse led self-management intervention to reduce emergency visits by people with epilepsy, PLoS ONE [Electronic Resource], 9, e90789, 2014 **Ref Id** 1060283 **Country/ies where the study was carried out** UK **Study type**	**Sample size** N=85 adults with epilepsy, n=44 allocated to the epilepsy nurse specialist group and n=41 allocated to the treatment as usual group **Characteristics** Age 18–24 years, n (%) Control = 6(14.6); Intervention = 8(18.2) 25–34, n (%) Control = 8(19.5); Intervention = 12(27.3) 35–45, n (%) Control = 7(17.1); Intervention =	**Interventions** Intervention group: Nurse led self-management intervention plus treatment as usual (TAU): it was designed to be responsive to be tailored to individual patient's needs, it was delivered by an ESN, and consisted of two 1-to-1 sessions delivered on an outpatient basis to people with epilepsy (PWE) attending ED (lasting 45–60 and 30 minutes, respectively). Its goal was to improve PWE's self-care for their epilepsy's day-to-day management; therefore; the ESN	**Details** Adults attending the emergency department were prospectively recruited. One group attending a hospital were offered the intervention group in combination with treatment as usual, and the participants attending a different hospital were offered treatment as usual alone.	**Results** *Critical outcomes* Satisfaction with medication information (Satisfaction with Information about Medicines Scale scores) at 6 months post-recruitment* (higher= more satisfied) IRR (95% CI) ¶ : -0.16 (-2.40 to 2.08) Emergency department visits (Client Services Receipt Inventory) at 6 months post-recruitment IRR (95% CI) 1.07 (0.45 to 2.54) Mastery (proxy outcome for self-efficacy, Epilepsy Mastery Scale scores)* (higher scores indicate greater confidence) IRR (95% CI) §: -0.80 (-2.23 to 0.62) Health-related quality of life (Quality of life in Epilepsy Inventory-10 scores)* (higher = poorer quality) IRR (95% CI) ß: 0.98 (-1.40 to	**Limitations** **Risk of bias assessed with the ROBINS-I assessment tool** **1. Bias due to confounding: low risk** 1.1: no **2. Bias in selection of participants into the study: low risk** 2.1: no 2.4: yes **3. Bias in classification of interventions: low risk** 3.1: yes 3.2: yes 3.3: no **4. Bias due to deviations from intended interventions: low risk** 4.1: no **5. Bias due to missing data: low risk** 5.1: yes 5.2: no 5.3: no **6. Bias in measurement of outcomes:**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Non-randomised controlled trial **Aim of the study** To assess the effectiveness of a nurse-led self-management intervention on adults with chronic epilepsy **Study dates** May 2009 to March 2011 **Source of funding** NIHR, HR&R	7(15.9) <u>46–53, n (%)</u> Control = 12(29.3); Intervention = 8(18.2) <u>54–89, n (%)</u> Control = 8(19.5); Intervention = 9(20.5) <u>Females, n (%)</u> Intervention group: 20 (45.5) Control group: 19 (46.3) <u>Type of seizures, n (%)</u> <u>Generalized or unknown</u> Intervention group: 17 (38.6) Control group: 19 (46.3) <u>Focal</u> Intervention group: 27 (61.4) Control group: 22 (53.7) **Inclusion criteria** • Those patients with a docu-	role was to provide PWE with the knowledge, support and skills to mitigate disability and improve outcome <u>Control group:</u> TAU alone, defined as 'standard medical review': this consisted of a medical review of epilepsy at least yearly delivered by a generalist or specialist; with referral of PWE to secondary or tertiary services when seizures are not controlled and/or treatment fails.	Analyses were intention to treat. Follow-up: 1 year (no measure of variability was reported)	3.36) *Important outcomes* <u>Depression (Hospital anxiety and Depression scale scores)* (higher= more symptoms)</u> IRR (95% CI) ¥: -0.67 (-1.94 to 0.59) <u>Anxiety (Hospital anxiety and Depression scale scores)* (higher= more symptoms)</u> IRR (95% CI) Δ: -1.01 (-2.56 to 0.55) *Positive coefficients indicate an increase in the score on the outcome variable associated with receiving the ESN led self-management intervention, whilst a negative coefficient the opposite. Adjustments were made for baseline variables related to outcome at P<0.10 ¶ Adjusted for: baseline Primary care QOF 8 score, Deprivation, ED visits, Depression, Anxiety, QoL, Felt stigma, Satisfaction with medication information, Medical knowledge, Mastery. § Adjusted for: Baseline Seizure frequency, gender, ED visits, sei-	**moderate risk** 6.1: yes, as outcomes such as quality of life or emotional well-being were reported 6.2: yes, open trial 6.3: yes 6.4: no **7. Bias in selection of the reported result: low risk** 7.1: no 7.2: no 7.3: no Overall bias: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	mented diagnosis of epilepsy for more than 1 year • Those patients older than 18 years when fully able to complete questionnaires • With no life-threatening or serious co-morbidities • Those patients who had not attended an ESN in the prior year and who had not been referred by ED to Neurology for outpatient care • Residents within Lambeth, Southwark, or Lewisham - London. **Exclusion criteria** • None reported [see 'inclusion criteria']			zure severity, AED number, depression, anxiety, QoL, felt stigma, satisfaction medication information, mastery ß Adjusted for: Baseline Seizure frequency, ED visits, AED number, depression, anxiety, QoL, stigma, mastery ¥ Adjusted for: ED visits, depression, anxiety, quality of life, felt stigma, satisfaction with medication information, mastery Δ Adjusted for: ED visits, AED number, depression, anxiety, QOL, felt stigma, mastery.	
Full citation Pfafflin, M.,	**Sample size** N=143 people	**Interventions** Intervention group:	**Details** Participants	**Results** *Primary outcomes*	**Limitations** **Methodological limitations assessed using**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Schmitz, B., May, T. W., Efficacy of the epilepsy nurse: Results of a randomized controlled study, Epilepsia, 57, 1190-1198, 2016 **Ref Id** 1146491. **Country/ies where the study was carried out** Germany. **Study type** RCT. **Aim of the study** To assess the effectiveness of an epilepsy nurse specialist intervention on satisfaction scores in people with epilepsy **Study dates** Not reported, study published	with epilepsy. n=67 allocated to the epilepsy nurse specialist group and n=76 allocate d to the treatment as usual group **Characteristics** Age, years, mean (SD) Intervention group: 42.6 (14.8) Control group: 44.9 (15) Females, n (%) Intervention group: 34 (50.7) Control group: 45 (59.2) Type of seizures, n (%) Generalized clonic/ tonic-clonic Intervention group: 16 (23.9) Control group: 10 (13.3) Focal Intervention group: 46 (68.7) Control group: 58 (77.3)	Individual nurse-led intervention in addition to usual care. This consisted of counselling on daily management of epilepsy according to PWE individual's needs and it was delivered by an epilepsy nurse (EN). The EN addressed the following topics by means of a questionnaire: 'epilepsy, therapeutic issues, risks and adverse effects of medication and other therapies, pregnancy, problems in daily life with seizures, consequences of seizures for driving—for the employment or the job of the patient and for school and families, social issues, and an open question for topics not listed'. The nurses provided leaflets and other written information	were randomised with a computer generated block randomization list. Patients were assessed with a questionnaire to assess their needs. It involved areas such as epilepsy, therapeutic issues, risks and adverse effects of medication and other therapies, pregnancy. Results were collected at the end of the study period, 6 months after baseline.	Satisfaction with information and advice (Satisfaction with Epilepsy Care scores) at 6 months, mean (SD) Intervention group: 77.9 (2.06), n=67 Control group: 72.4 (2.03), SD= 17.6, n=76 Satisfaction with patient-doctor relationship (Satisfaction with Epilepsy Care scores) at 6 months, mean (SD) Intervention group: 82.2 (2.16), n=67 Control group: 79.2 (2.03), SD = 17.6, n=76 Satisfaction with organization of care (Satisfaction with Epilepsy Care scores) at 6 months, mean (SD) Intervention group: 81.4 (1.85), n=67 Control group: 77.5 (1.78), SD = 15.5, n=76	**the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Yes, randomisation was performed with a computer generated list 1.2: Whether the allocation sequence was concealed was not reported 1.3: Yes, characteristics were different between treatment groups for etiology **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, people delivering the intervention were aware of participant's assigned intervention during trial 2.3: Yes, n=5 in the intervention group did not received counselling because the did not want it 2.4: no 2.6: Yes, ITT analysis **Domain 3: Missing outcome data: Low risk** 3.1: No, data was lost for >95% of the participants 3.2: No, no evidence that the result was not biased by missing outcome data 3.3: No **Domain 4: Measurement of the outcome: High risk** 4.1: No, outcomes were measured with objective and validated measures 4.2: No, measurement or ascertainment could not have differed between intervention groups

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in 2016. **Source of funding** UCB Pharma	<u>Unclear</u> Intervention group: 4 (6.0) Control group: 4 (5.3) <u>No data available</u> Intervention group: 1 (1.5) Control group: 3 (4.0) **Inclusion criteria** • Those patients older than 16 years of age with epileptic seizures who were referred to an epilepsy outpatient clinic • Those patients who gave written consent to participate in the study **Exclusion criteria** • Patients with language or learning difficulties if not capable of respond-	about driving regulations, pregnancy, social support, and self-support groups. <u>Control group:</u> Usual care only, defined as routine care without additional counselling.	Follow-up: 6 months (no measure of variability was reported)		4.3: No information 4.4: Yes, as outcomes such as health-related quality of life and emotional well-being were measured 4.5: Yes, as above **Domain 5: Selection of the reported result: High risk** 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements 5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6: Overall judgement of bias: High risk** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ing to the questionnaire • Those patients who had non-epileptic seizures				
Full citation Ridsdale, L., Kwan, I., Cryer, C., Robins, D., Ramkoleea, P., Dellaportas, C. D., Hart, Y., McKeran, R., Modarres, M., Mueller, J., Schon, F., Wren, D., Newly diagnosed epilepsy: Can nurse specialists help? A randomized controlled trial, Epilepsia, 41, 1014-1019, 2000. **Ref Id** 1146523. **Country/ies where the study was carried out** UK. **Study type**	**Sample size** N=90 adults with epilepsy, n=43 allocated to the nurse led intervention and n=47 allocated to the treatment as usual group **Characteristics** Age, years, median Intervention group: 40.2 Control group: 39.8 Females, n (%) Intervention group: 25 (53) Control group: 20 (46) Type of seizures, n (%) Not reported **Inclusion criteria** • Those patients	**Interventions** Intervention group: two 1-to 1 appointments with an epilepsy nurse specialist (ESN) in secondary care -hospital (lasting 45-50 and 15-20 minutes, respectively): This consisted of advice on driving, self-help groups, epilepsy types and causes, side effects and interactions of ASMs, risk avoidance, besides how to manage a new diagnosis of epilepsy, and was tailored to patients' individual needs. Control group: Treatment as usual, defined as usual medical	**Details** Participants were randomised in blocks. Those from one hospital were offered an appointment with a nurse specialist and the participants recruited from the other hospital, were usually seen by their specialist. Follow-up: 3 months (no measure of variability was reported)	**Results** *Important outcomes* Number of people with anxiety post-intervention (score ≥ 8 in the Hospital Anxiety Rating Scale scores) Intervention group: 15/47 Control group: 18/43 Number of people with depression post-intervention (score ≥ 8 in the Hospital Anxiety Rating Scale scores) Intervention group: 9/47 Control group: 8/43	**Limitations** **Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)** **Domain 1: Randomisation: Some concerns** 1.1: Randomisation method was not reported 1.2: Whether the allocation sequence was concealed was not reported 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Some concerns** 2.1: Yes, participants were aware of their assigned intervention during the trial 2.2: Yes, people delivering the intervention were aware of participant's assigned intervention during trial 2.3: No information, trialists do not report whether deviations arose from the experimental context 2.6: No, 'as treated' analyses 2.7: No **Domain 3: Missing outcome data: High risk** 3.1: No information about the extent of missing data 3.2: No, no evidence that the result was not biased by missing outcome data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT. **Aim of the study** To assess the effect of a nurse led intervention on depression and anxiety scores in people with epilepsy **Study dates** 1996 to 1998. **Source of funding** NHS R&D London.	older than 17 years of age who had newly diagnosed with epilepsy (involving two or more attacks at initial treatment with ASMs) **Exclusion criteria** • Those patients with a learning or language difficulty who were not able complete a questionnaire	care.			3.3: No information 3.4: No information **Domain 4: Measurement of the outcome: High risk** 4.1: No, outcomes were measured with objective and validated measures 4.2: No, measurement or ascertainment could not have differed between intervention groups 4.3: No information 4.4: Yes, as outcomes such as emotional well-being were measured 4.5: Yes, as above **Domain 5: Selection of the reported result: High risk** 5.1: No, there was no reference to a study protocol, therefore is not possible to know whether data was produced in accordance with a pre-specified plan 5.2: No, there was no reference to a study protocol, therefore is not possible to know whether the numerical results were selected on the basis of multiple eligible outcome measurements 5.3: No, there was no reference to a study protocol, therefore is not possible to know whether the results were selected on the basis of multiple eligible analyses of the data **Domain 6: Overall judgement of bias: High risk** The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ring, H., Howlett, J., Pennington, M., Smith, C., Redley, M., Murphy, C., Hook, R., Platt, A., Gilbert, N., Jones, E., Kelly, J., Pullen, A., Mander, A., Donaldson, C., Rowe, S., Wason, J., Irvine, F., Training nurses in a competency framework to support adults with epilepsy and intellectual disability: The EpAID cluster RCT, Health Technology Assessment, 22, 2018 **Ref Id** 955848 **Country/ies where the study was carried out** UK **Study type** Two-arm cluster	N (clusters) = 17 research sites; n (clusters) = 8 research sites (n=184 adults with LDs) were allocated to the intervention group and n (clusters) = 9 (n=128 adults with LDs) were allocated to the control group **Characteristics** Age, years, mean (range) Intervention group: 39.6 (18.1 to 65.5) Control group: 37.0 (18.4 to 63.5) **Females, n (%)** Intervention group: 85 (46.2) Control group: 67 (52.3) **Type of seizures, n** Generalized clonic/ tonic-clonic Intervention group: 11	Intervention group: Learning Disability ESN competency Framework. This provides guidelines (were developed by the UK Epilepsy Nurses Association and the UK Royal College of Nursing) to support the delivery of epilepsy care and management. It consisted of a series of interventions that can be taken in clinical, educational and professional domains relevant to the optimal delivery of epilepsy management in adults with an ID and epilepsy, it addresses nine skills domains, and it is tailored to the competency level of the nurse delivering the interventions: 1) Clinical diagnosis and management of epilepsy; 2) Assessing and man-	Participant recruitment was completed before randomisation. Randomisation was done by an independent company and used block randomisation with fixed block sizes and it took place close to the start of the intervention phase to avoid participants withdrawing before the start of the intervention. In order to maintain allocation concealment, a minimum of 2	*Critical outcomes* Health-related quality of life (ELDQoL-SSS32 and Epilepsy and Learning Disabilities Quality of Life scores), mean (SD) Change from baseline Intervention group: –0.75 (9.83), n=160 Control group: –1.21 (8.62), n=109 *Important outcomes* Admission to hospital (any) Intervention group: 30/184 Control group: 20/128	**Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0 for cluster randomized, parallel group trials)** **Domain 1a: Bias arising from the randomization process** 1a.1 Was the allocation sequence random? Yes, randomisation was done by an independent organism using block randomisation with fixed block sizes 1a.2: Is it likely that the allocation sequence was subverted? no 1a.3: Were baseline imbalances that suggest a problem with the randomization process? No **Domain 1b: Bias arising from the randomization process** 1b.1 Were all the individual participants identified before randomization of clusters (and if the trial specifically recruited patients were they all recruited before randomization of clusters)? yes 1b.2 If N/PN/NI to 1b.1: Is it likely that selection of individual participants was affected by knowledge of the intervention? 1b.3 Were there baseline imbalances that suggest differential identification or recruitment of individual participants between arms? No **Domain 2: Bias due to deviations from intended interventions** 2.1a: Were participants aware that they were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To assess the efficacy and the economic efficiency of the introduction of nurse-led care intervention (that is Learning Disability Epilepsy Specialist Nurse Competency Framework) focused on optimising nurse management of epilepsy in people with an intellectual (learning) disability (ID) and epilepsy. **Study dates** November 2014 to November 2015. **Source of funding** NIHR (National Institute for Health Research)	Control group: 7 <u>Focal</u> Intervention group: 69 Control group: 33 <u>Focal and generalised</u> Intervention group: 93 Control group: 45 **Inclusion criteria** • Those patients aged 18–65 years old • Those patients with a developmental ID with an IQ of ≤ 70 and with a diagnosis of epilepsy (with a history of at least one seizure in the 6 months preceding recruitment into the trial) **Exclusion criteria** • Those patients reporting the	aging risk; 3) Impact of epilepsy; 4) Capacity and consent to treatment; 5) Personal planning and organisation; 6) Multidisciplinary team working; 7) Personal and professional development; 8) Evidence-based practice; and 9) Development of educational programmes. Core element of the competency framework is that it is a list of what management a nurse should be able to deliver at their given level of competence. The nurses delivered their interventions at a frequency determined by PWE individual's needs, through home visits, telephone clinics and visits to the local primary care or ID team base as appropriate.	sites were randomised at a time. The study was not blinded, but authors undertook appropriate measures to minimise the risk of bias being introduced. Analysis was intention to treat and controlled for baseline individual level and cluster level variables. Follow-up: 6 months (no measure of variability was reported)		in a trial? yes 2.1b: If Y/PY/NI to 2.1a: Were participants aware of their assigned intervention during the trial? no 2.2: Were carers and trial personnel aware of participants' assigned intervention during the trial? yes 2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention beyond what would be expected in usual practice? no 2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? no 2.5a Were any clusters analysed in a group different from the one to which they were assigned? no 2.5b Were any participants analysed in a group different from the one to which their original cluster was randomized? no 2.6 If Y/PY/NI to 2.5: Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group? **Domain 3: Bias due to missing outcome data:** 3.1a: Were outcome data available for all, or nearly all, clusters randomized? yes 3.1b Were outcome data available for all, or nearly all, participants within clusters? yes 3.2 If N/PN/NI to 3.1a or 3.1b: Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Health Technology Assessment programme.	presence of a rapidly progressive physical or neurological illness • Those patients reporting alcohol or drug dependence.	<u>Control group:</u> Treatment as usual, defined as 'existing management approach for each participant'			3.3 If N/PN/NI to 3.1a or 3.1b: Is there evidence that results were robust to the presence of missing outcome data? **Domain 4: Bias in measurement of the outcome:** 4.1a: Were outcome assessors aware that a trial was taking place? yes 4.1b: If Y/PY/NI to 4.1: Were outcome assessors aware of the intervention received by study participants? yes 4.2: Was the assessment of the outcome likely to be influenced by knowledge of intervention received? No **Domain 5: Bias in the selection of the reported result:** Are the reported outcome data likely to have been selected, on the basis of the results, from... 5.1: ... multiple outcome measurements (for example, scales, definitions, time points) within the outcome domain? no 5.2: multiple analyses of the data? no **Domain 6: Overall judgement of bias: low risk of bias** **Other information** Analyses done for calculating the effective sample size of the intervention and control group were as follows: Average cluster size = (177+126)/17= 17.8 <u>Health-related quality of life outcome:</u> ICC= 0.00, obtained

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					from https://www.abdn.ac.uk/hsru/what-we-do/tools/#panel177 database of ICCs TIGER dataset SF36 - general health perception Design effect= 1 + (17.8-1) x 0.00 = 1 Effective sample size in group nurse-led intervention = 160/1=160 Effective sample size in control group = 109/1= 109 Admission to hospital outcome ICC= 0.02, no relevant ICC found in database of ICCs, therefore 0.02 was chosen, as described in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1466680/ Design effect= 1 + (17.8-1) x 0.02 = 1.35 Effective sample size in group nurse-led intervention = 184/1.35=135 Effective sample size in control group = 128/1.35= 94.

1 *CI: confidence interval; ICC: intraclass correlation coefficient; IRR: incidence rate ratio; SD: standard deviation;*

Appendix E – Forest plots

Forest plots for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

No meta-analysis was conducted, the quality assessment for these outcomes is provided in the GRADE profiles in appendix F.

1

2 Appendix F – GRADE tables

3 GRADE tables for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

4 Table 7: Clinical evidence profile. Comparison 1: group nurse-led intervention versus control group - general population

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group nurse-led intervention	Control group	Relative (95% CI)	Absolute	Quality	Importance
Satisfaction (measured with: VAS; Better indicated by higher values)												
1 (Helde 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57	54	-	MD 23.1 higher (15.32 to 30.88 higher)	⊕⊕OO LOW	CRITICAL
Mastery (proxy outcome for self-efficacy) (measured with: Epilepsy-specific scale mastery scores; Better indicated by higher values)												
1 (Davis 2004)	Cluster RCT[a]	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	307	284	-	MD 0.4 higher (0.9 lower to 1.7 higher)	⊕⊕OO LOW	CRITICAL
Health-related quality of life (general health profile scores) (measured with: SF-36 ; Better indicated by higher values)												
1 (Davis 2004)	Cluster RCT[a]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	399	364	-	MD 0.2 lower (8.92 lower to 8.52 higher)	⊕⊕⊕O MODERATE	CRITICAL
Health-related quality of life (overall QOL scores) (measured with: QOLIE-89 ; Better indicated by higher values)												
1 (Helde 2005)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	57	54	-	MD 0.4 lower (0.84 lower to 0.04 higher)	⊕OOO VERY LOW	CRITICAL
Emotional wellbeing (proxy outcome for depression and anxiety) (measured with: QOLIE-89 ; Better indicated by higher values)												
1 (Helde 2005)	RCT	very serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	57	54	-	MD 3.3 higher (2.81 to 3.79 higher)	⊕OOO VERY LOW	IMPORTANT

[a] *Intraclass correlation coefficients (ICCs) were not available from the study, therefore external estimates were used to reduce the size of each trial to its "effective sample size", thus total Ns reported in the evidence table may differ from the ones reported in the clinical evidence profiles. For further information, please see "other information" section in appendix D – Clinical evidence tables*

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

2 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

3 Outcome is indirect

4 95% CI crosses 1 MID (+/-0.5 control group SD x 1.4 for HRQoL [QOLIE-89 scores] = +/-0.7)

Table 8: Clinical evidence profile. Comparison 1: group nurse-led intervention versus control group - stratified analyses for young people (> 11 to 25 years old)

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group nurse-led intervention	Control group	Relative (95% CI)	Absolute	Quality	Importance
Self-efficacy (measured with: SSEC ; Better indicated by higher values); young people (> 11 to 25 years old)												
1 (Dorris 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39	37	-	MD 2.25 lower (9.42 lower to 4.92 higher)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life (measured with: GEOS-YP scores; Better indicated by higher values); young people (> 11 to 25 years old)												
1 (Dorris 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	37	-	MD 3.92 lower (12.14 lower to 4.3 higher)	⊕⊕OO LOW	CRITICAL
Health-related quality of life (measured with: PedsQL scores; Better indicated by higher values) ; young people (> 11 to 25 years old)												
1 (Dorris 2017)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39	37	-	MD 2.97 higher (7.13 lower to 13.08 higher)	⊕⊕OO LOW	CRITICAL
Emotional distress (proxy outcome for depression and anxiety) (measured with: PI-ED; Better indicated by lower values); young people (> 11 to 25 years old)												
1 (Dorris 2017)	RCT	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	39	37	-	MD 1.96 higher (2.2 lower to 6.12 higher)	⊕OOO VERY LOW	IMPORTANT

1 Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

2 95% CI crosses 1 MID (+/-0.5 control group SD at baseline x 12.8 for self-efficacy [SSEC scores] =+/- 6.4; x 19.42 for health-related quality of life [PedsQL scores]= +/- 9.71; x 7.84

for emotional distress [PI-ED scores] = +/- 3.92)
2 Outcome is indirect

Table 9. Comparison 2: Nurse practitioner and physician led intervention versus physician only led intervention

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nurse practitioner and physician led intervention	Physician only	Relative (95% CI)	Absolute	Quality	Importance
Presentation to emergency department												
1 (Hill 2017)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/65 (21.5%)	16/104 (15.4%)	RR 1.4 (0.73 to 2.67)	62 more per 1000 (from 42 fewer to 257 more)	⊕OOO VERY LOW	CRITICAL
Admission to epilepsy monitoring unit												
1 (Hill 2017)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/65 (21.5%)	25/104 (24%)	RR 0.9 (0.5 to 1.59)	24 fewer per 1000 (from 120 fewer to 142 more)	⊕OOO VERY LOW	IMPORTANT

1 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
2 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 10: Clinical evidence profile. Comparison 3: individual nurse-led intervention versus control group - general population

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual nurse-led intervention	Control group	Relative (95% CI)	Absolute		
Satisfaction with medication information; (assessed with: Satisfaction with Information about Medicines Scale; Better indicated by higher values)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	IRR -0.16 (-2.40 to 2.08)	-	⊕⊕⊕O MODERATE	CRITICAL
Emergency department visits (assessed with: Client Services Receipt Inventory)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	IRR 1.07 (0.45 to 2.54)	-	⊕⊕⊕O MODERATE	CRITICAL
Mastery (proxy outcome for self-efficacy) (assessed with: Epilepsy Mastery Scale scores; Better indicared by higher values)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	serious[2]	serious[1]	none	-	-	IRR - 0.80 (-2.23 to 0.62)	-	⊕⊕OO LOW	CRITICAL
Health-related quality of life (assessed with: Quality of life in Epilepsy Inventory-10; Better indicated by higher values)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	IRR 0.98 (-1.40 to 3.36)	-	⊕⊕⊕O MODERATE	CRITICAL
Depression (assessed with: Hospital anxiety and Depression scale scores; Better indicated by lower values)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	IRR -0.67 (-1.94 to 0.59)	-	⊕⊕⊕O MODERATE	IMPORTANT
Anxiety (assessed with: Hospital anxiety and Depression scale scores; Better indicated by lower values)												
1 (Noble 2014)	Observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	IRR -1.01 (-2.56 to 0.55)	-	⊕⊕⊕O MODERATE	IMPORTANT

1 95% CI crosses the line of no effect
2 Outcome is indirect

Table 11: Clinical evidence profile. Comparison 3: individual nurse-led intervention versus control group - stratified analyses for adults (>25 to 65 years old)

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual nurse-led intervention	Control group	Relative (95% CI)	Absolute		
Satisfaction with information and advice (measured with: Satisfaction with Epilepsy Care scores; Better indicated by higher values); adults (>25 to 65 years old)												
1 (Pfaffin 2016)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	76	-	MD 5.5 higher (4.83 to 6.17 higher)	⊕⊕OO LOW	CRITICAL
Satisfaction with patient-doctor relationship (measured with: Satisfaction with Epilepsy Care scores; Better indicated by higher values); adults (>25 to 65 years old)												
1 (Pfaffin 2016)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	76	-	MD 3 higher (2.31 to 3.69 higher)	⊕⊕OO LOW	CRITICAL
Satisfaction with organization of care (measured with: Satisfaction with Epilepsy Care scores; Better indicated by higher values); adults (>25 to 65 years old)												
1 (Pfaffin 2016)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	67	76	-	MD 3.9 higher (3.3 to 4.5 high-er)	⊕⊕OO LOW	CRITICAL
Number of people with anxiety (assessed with: Hospital Anxiety Rating Scale); adults (>25 to 65 years old)												
1 (Ridsdale 2000)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/47 (31.9%)	18/43 (41.9%)	RR 0.76 (0.44 to 1.32)	100 fewer per 1000 (from 234 fewer to 134 more)	⊕OOO VERY LOW	IMPORTANT
Number of people with depression (assessed with: Hospital Anxiety Rating Scale); adults (>25 to 65 years old)												
1 (Ridsdale 2000)	RCT	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/47 (19.1%)	8/43 (18.6%)	RR 1.03 (0.44 to 2.43)	6 more per 1000 (from 104 fewer to 266 more)	⊕OOO VERY LOW	IMPORTANT

[1] *Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 12: Clinical evidence profile. Comparison 3: individual nurse-led intervention versus control group - stratified analyses for people with learning disabilities

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Individual nurse-led intervention	Control group	Relative (95% CI)	Absolute		
Health-related quality of life (measured with: ELDQoL-SSS32 and Epilepsy and Learning Disabilities Quality of Life ; Better indicated by higher values); people with learning disabilities												
1 (Ring 2018)	Cluster RCT[a]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	160	109	-	MD 0.46 higher (1.76 lower to 2.68 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Admission to hospital (any); people with learning disabilities												
1 (Ring 2018)	Cluster RCT[a]	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[1]	none	30/135 (22.2%)	20/94 (21.3%)	RR 1.04 (0.63 to 1.72)	9 more per 1000 (from 79 fewer to 153 more)	⊕⊕OO LOW	IMPORTANT

[a] *Intraclass correlation coefficients (ICCs) were not available from the study, therefore external estimates were used to reduce the size of each trial to its "effective sample size", thus total Ns reported in the evidence table may differ from the ones reported in the clinical evidence profiles. For further information, please see "other information" section in Appendix D – Clinical evidence tables*

[1] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

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

1

1 Appendix H – Economic evidence tables

2 Economic evidence tables for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

3 **Table 13: Economic evidence tables for ESN led self-management intervention in people with epilepsy to reduce emergency visits**

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: • Noble 2014 **Country:** • UK **Type of economic analysis:** • CUA **Source of funding:** • NIHR Health Services and Delivery Research programme NIHR Dementia Biomedical Research Unit at South London Maudsley NHS Foundation Trust and King's College London	**Interventions in detail:** • ESN led self-management intervention plus TAU ○ The intervention was tailored to individual patient's needs, it was delivered by an ESN, and consisted of two 1-to-1 sessions delivered on an outpatient basis to PWE attending ED (lasting 45–60 and 30 minutes, respectively). Its goal was to improve PWE's self-care for their epilepsy's day-to-day management; therefore; the ESN role was to provide PWE with the knowledge, support and skills to mitigate disability and improve outcome • TAU alone ○ It was defined as 'standard medical review': this	**Population characteristics:** • Adults who attended an ED for establishing epilepsy. In the base case, patients were included if: had a documented diagnosis of epilepsy for more than 1 year; were older than 18 years of age; and resided within three areas of London (these are Lambeth, Southwark, or Lewisham) **Modelling approach:** • With-in trial economic evaluation (Noble 2004) **Source of base-line and effectiveness data:** RCT **Source of resource use:** RCT **Source of unit cost data:** • Cost data were obtained from different sources:	**QALYs** • 0.786 QALYs for ESN led self-management intervention plus TAU • 0.807 QALYs for TAU alone **Incremental costs with ESN led self-management intervention plus TAU:** • -£558 **Incremental QALYs with ESN led self-management intervention plus TAU:** • -0.02 QALYs **ICER:** • £26,445[1] **Sensitivity analysis:** When compared to TAU alone, the intervention was found to have:	**Perspective:** • UK NHS **Currency:** • UK pound sterling (£) **Cost year:** • 2010/11 **Time horizon:** • 12 months **Discounting:** • Not applicable **Applicability:** • Despite the analysed population did not include children and young people, the analysis was performed in the UK considering the NHS perspective, therefore the study was considered to be directly applicable

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
	consisted of a medical review of epilepsy at least yearly delivered by a generalist or specialist; with referral of PWE to secondary or tertiary services when seizures were being not controlled and/or treatment fails	○ Health care resource use (including primary care services, secondary care services, community health services and social care services), use of medication, and use of informal care were taken from CSRI. Included patients were asked through CSRI about the previous 12 months for baseline service use and previous 6 months for follow–up assessments ○ Service use costs were calculated by combining service use data with national unit cost (PSSRU 2010) ○ Medication costs were taken from routine Prescription Cost Analysis data (The Health and Social Care Information Centre 2012) ○ Intervention costs included ESN and was estimated at £50 per hour (including salaries, overheads, capital costs, training, and the ratio of direct to indirect contact time).	• 56% probability of being cost effective at a threshold of £20,000 per QALY • 50% probability of being cost effective at a threshold of £30,000 per QALY	**Limitations:** • The study fails to meet important quality criteria, and this might be likely to change the conclusions about its cost effectiveness results; therefore, it was considered as having very serious limitations: 1) the period of analysis of the study was not potentially long enough to include all relevant costs and outcomes; 2) none deterministic sensitivity analysis was performed to explore all potential uncertainties in the economic evaluation, for example about the cost estimation. Furthermore, the estimates of interventions' relative effects were likely to be biased, because the study was statistically underpowered in terms of participants recruited

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		○ Costs were all inflated to 2010/11 financial year **Source of QoL data:** • Utilities scores (based on EQ-5D-L5 data and UK weights) were used to estimate the QALYs gained during the follow-up period.		

CSRI: Client Services Receipt Inventory; CUA: Cost utility analysis; ED: Emergency department; EQ-5D-5L: EuroQoL-5 Dimensions, five-level; ESN: Epilepsy Specialist Nurse; ICER: Incremental cost effectiveness ratio; NIHR: National Institute for Health Research; PSSRU: Personal Social Services Research Unit; PWE: People with epilepsy; QALY: Quality adjusted life year; RCT: Randomised control trial; TAU: Treatment as usual
1 As both incremental costs and QALYs are negative this value represents a cost per QALY foregone

Table 14: Economic evidence tables for competency framework developed to optimise nurse management of epilepsy in people with an intellectual (learning) disability (ID) and epilepsy

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: • Ring 2018 **Country:** • UK **Type of economic analysis:** • CUA **Source of funding:** • NIHR • CLAHRC • East of England	**Interventions in detail:** • Learning disability ESN competency framework ○ It consisted of a series of interventions that can be taken in clinical, educational and professional domains relevant to the optimal delivery of epilepsy management in adults with an ID	**Population characteristics:** • Adults with an ID and epilepsy were recruited prospectively and entered the trial-based economic evaluation. In the base case, patients were included if: had a documented diagnosis of epilepsy with a developmental ID with an IQ of ≤ 70; were aged 18–65 years old; and had a history of at least one seizure in the 6 months preceding recruitment into the trial **Modelling approach:** • With-in trial economic evaluation	**QALYs** • 0.60 QALYs for learning disability ESN competency framework • 0.62 QALYs for TAU **Incremental costs with learning disability ESN competency framework:** • -£358[1] **Incremental QALYs learning disability ESN competency framework:** • -0.020 QALYs[1] **ICER:** • £220,000[2,3]	**Perspective:** • UK NHS **Currency:** • UK pound sterling (£) **Cost year:** • 2014/15 **Time horizon:** • 6 months **Discounting:** • Not applicable

at Cambridgeshire and Peterborough NHS Foundation Trust.	and epilepsy, it addresses nine skills domains, and it is tailored to the competency level of the nurse delivering the interventions: 1) Clinical diagnosis and management of epilepsy; 2) Assessing and managing risk; 3) Impact of epilepsy; 4) Capacity and consent to treatment; 5) Personal planning and organisation; 6) Multidisciplinary team working; 7) Personal and professional development; 8) Evidence-based practice; and 9) Development of educational programmes. Core element of the competency framework is that it is a list of what management a nurse should be able to deliver at their given level of competence. The nurses delivered	**Source of base-line and effectiveness data:** • Estimates of base-line clinical data were obtained from a 6-months cluster RCT (Ring 2018) **Source of cost data:** Cost data were obtained from different sources: • Health care resource use (including accommodation, respite including holidays, primary health and social care, day care, secondary health care including tests and investigations, mode of transport to healthcare appointments and informal care), use of medication, and use of informal care were taken from a modified version of the CSRI. Included patients were asked through CSRI for baseline and for follow–up service use • Data on medications use were collected separately • Service use costs were calculated by combining service use data with national unit costs, which were taken from 3 sources (that is: NHS Reference Costs, UCHSC, and the British National Formulary) Costs were all inflated to 2014/15 financial year **Source of QoL data:** • Utilities scores (based on EQ-5D-5L data and UK weights) were used to	**Probabilistic sensitivity analysis:** The results were sensitive to: • Patient ID level (with severe/profound ID leading to a greater chance of the competency framework to be cost effective if compared to control group) • Accommodation costs (with the exclusion of accommodation costs leading to a greater chance of the competency framework to be cost effective if compared to control group) When compared to TAU, the intervention was found to have: • 85% probability of being cost effective at a threshold of £20,000 per QALY • 83% probability of being cost effective at a threshold of £30,000 per QALY • 48% probability of being cost effective at a threshold of £50,000 per QALY, for patients with mild/moderate ID[4] • 88% probability of being cost effective at a threshold of £50,000 per QALY, for patients with severe/profound ID[4] • 85% probability of being cost effective at a threshold of £50,000 per QALY, when excluding accommodation costs	**Applicability:** Despite the population did not include children and young people, the analysis was performed in the UK considering the NHS perspective, therefore the study was considered to be directly applicable **Limitations:** The study was deemed as having potentially serious limitations. The analysis potentially does not meet a relevant quality criterion: the time horizon of the study was not potentially long enough to include all relevant costs and outcomes. Furthermore as noted by the authors, although base-case and sensitivity analyses indicate a potential for the competency framework to reduce costs, it is possible that there are additional costs associated with the implementation of the competency framework that were not captured by the overall study

	their interventions at a frequency determined by PWE individual's needs, through home visits, telephone clinics and visits to the local primary care or ID team base as appropriate. • TAU ○ It was defined as 'existing management approach for each participant'	estimate the QALYs gained during the follow-up period		

CLAHRC: Collaboration for Leadership in Applied Health Research and Care; CSRI: Client Services Receipt Inventory; CUA: Cost utility analysis; EQ-5D-5L: EuroQoL-5 Dimensions, five-level; ESN : Epilepsy Specialist Nurse; ICER: Incremental cost effectiveness ratio; ID: Intellectual (learning) disability; NIHR: National Institute for Health Research; PWE : People with epilepsy; QALY: Quality adjusted life year; RCT : Randomised control trial; TAU: Treatment as usual; UCHSC: Unit Costs of Health and Social Care
1 Values are adjusted for baseline variables, and missing values
2 An assumption of a linear interpolation between baseline and follow-up was made, as regard with the impact of treatment on costs and QALYs in the intervening 5 months. Relatively to the ICER, this is mathematically equivalent to assuming an immediate change in QoL and costs following commencement of the intervention
3 As both incremental costs and QALYs are negative this value represents a cost per QALY foregone
4 ID level was dichotomised into mild/moderate and severe/profound

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

Table 15: Economic evidence profile for ESN led self-management intervention in people with epilepsy to reduce emergency visits

Study and country	Limitations	Applicability	Other comments	Incremental costs	Incremental effects	ICER	Uncertainty
Author & year: • Noble 2014 **Country:** • UK **Interventions:** ESN led self-management intervention plus TAU *versus* TAU alone	• Potentially serious limitations[1]	• Directly applicable[2]	**Type of economic analysis:** • CUA **Time horizon:** • 12 months **Primary measure of outcome:** • QALY	• -£558	• -0.02 QALYs	• £26,445[3]	**Sensitivity analyses:** When compared to TAU alone, the intervention was found to have: • 56% probability of being cost effective at a threshold of £20,000 per QALY • 50% probability of being cost effective at a threshold of £30,000 per QALY

CUA: Cost utility analysis; ESN: Epilepsy Specialist Nurse; ICER: Incremental cost effectiveness ratio; QALY: Quality adjusted life year; TAU: Treatment as usual
1 The period of analysis of the study was not potentially long enough to include all relevant costs and outcomes; b) none deterministic sensitivity analysis was performed to explore all potential uncertainties in the economic evaluation, for example about the cost estimation. Furthermore, the estimates of interventions' relative effects were likely to be biased, because the study was statistically underpowered in terms of participants recruited
2 Despite the study population did not include children, young people, therefore, it was deemed to be similar with the scope of the decision problem
3 As both incremental costs and QALYs are negative this value represents a cost per QALY foregone

Table 16: Economic evidence profile for competency framework developed to optimise nurse management of epilepsy in people with an intellectual (learning) disability (ID) and epilepsy

Study and country	Limitations	Applicability	Other comments	Incremental costs[3]	Incremental effects[3]	ICER[4]	Uncertainty
Author & year: • Ring 2018 **Country:** • UK **Interventions:** Learning disability ESN competency framework *versus* TAU	• Potentially serious limitations[1]	• Directly applicable[2]	**Type of economic analysis:** • CUA **Time horizon:** • 6 months **Primary measure of outcome:** • QALY	• -£358	• -0.02 QALYs	• £220,000[5]	**PSA:** The intervention was found to have: • 85% probability of being cost effective at a threshold of £20,000 per QALY • 83% probability of being cost effective at a threshold of £30,000 per QALY • 48% probability of being cost effective at a threshold of £50,000 per QALY, for patients with mild/moderate ID[6] • 88% probability of being cost effective at a threshold of £50,000 per QALY, for patients with severe/profound ID[6] • 85% probability of being cost effective at a threshold of £50,000 per QALY, when excluding accommodation costs

CUA: Cost utility analysis; ESN: Epilepsy Specialist Nurse; ICER: Incremental cost effectiveness ratio; ID: Intellectual (learning) disability; PSA: probabilistic sensitivity analysis; QALY: Quality adjusted life year; TAU: Treatment as usual

1 The time horizon of the study was potentially too short to include all relevant costs and outcomes. Furthermore as noted by the Authors, although base-case and sensitivity analyses indicate a potential for the competency framework to reduce costs, it is possible that there are additional costs associated with the implementation of the competency framework that were not captured by the overall study

2 Despite the study population did not include children, young people, therefore, it was deemed to be similar with the scope of the decision problem

3 Values are adjusted for baseline variables, and missing values

4 An assumption of a linear interpolation between baseline and follow-up was made, as regard with the impact of treatment on costs and QALYs in the intervening 5 months. Relatively to the ICER, this is mathematically equivalent to assuming an immediate change in QoL and costs following commencement of the intervention

5 As both incremental costs and QALYs are negative this value represents a cost per QALY foregone

6 ID level was dichotomised into mild/moderate and severe/profound

1

Appendix J – Health economic model

Economic evidence analysis for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

1. Introduction

This appendix describes the economic model carried out to evaluate the cost effectiveness of epilepsy nurse specialist led intervention(s) in people with confirmed epilepsy, relative to the research question O: What is the effectiveness of a nurse specialist in the management of epilepsy?

The upfront costs incurred in delivering an epilepsy specialist nurse (ESN) led intervention to people with epilepsy who use hospital emergency departments (ED) may improve health and decrease long-term healthcare costs by enhancing ability to self-manage their epilepsy (Noble 2012, Noble 2014). Given the substantial use of healthcare services by people with epilepsy in the UK, which may be not always clinically necessary, this topic was prioritised for modelling by the guideline committee.

Two relevant studies were identified in the literature review of published economic evidence on this topic (Noble 2014, and Ring 2018). Noble (2014) considered the cost effectiveness of an ESN-led intervention in addition to the treatment as usual (TAU) in people with epilepsy compared to TAU alone, in adults with epilepsy attending an emergency department. Ring (2018) considered the cost effectiveness of an ESN-led intervention (that is 'Learning Disability Epilepsy Specialist Nurse Competency Framework) compared to TAU in adults with epilepsy and an intellectual (learning) disability. Both were performed in the UK from the NHS perspective and were considered to be directly relevant to the guideline's decision-making. However, both studies were characterised by potentially serious limitations and did not include children, and young people (CYP).

The committee focused their discussion on Noble 2014, as it was highlighted that this study reflects the wider population of people with epilepsy, besides its findings were believed more generalisable to the overall population of interest. Therefore, the committee was of a view that it would be more useful to use the economic model by Noble 2014 as a basis for any modelling for this topic. This economic evaluation found no evidence that an ESN led intervention reduced ED readmission rates or improved well-being –but it did lead to large overall cost savings, when compared to TAU (Noble 2014), by reducing ED visits. The committee also explained that the analysis by Noble 2014 potentially did not include all relevant long-term costs and outcomes.

In summary, based upon the data reported in Noble 2014, the primary analyses of the present economic model were carried out to:

- Update the cost estimates by using UK unit costs 2019
- Extend the cost effectiveness estimates to a population of CYP

Then two secondary analyses were performed in order to:

- Simulate costs and effectiveness data against a longer time horizon of 20 years
- Calculate the cost effectiveness estimates considering the epilepsy severity (seizure-free or not seizure-free)

2. Methods

In line with the NICE reference case (https://www.nice.org.uk/process/pmg20) for an intervention with health outcomes, the evaluation was undertaken from a NHS and Personal Social Services (PSS) perspective and, for the purposes of this analysis, the ESN led intervention was offered to all people with confirmed epilepsy. A time horizon of 20-years was chosen primarily as this timeframe is indicated to be the mean duration of epilepsy across the different ages of epilepsy onset (Moran 2004).

2.1 Population

The population of the economic model comprised people with confirmed epilepsy who present to emergency department (ED), although they may be subsequently referred to a generalist or specialist setting for a medical review of their epilepsy. This population was based upon the study population included in one economic evaluation found in the economic evidence review (Noble 2014).

Separate analyses were undertaken for adults and children and young people (CYP), in order to extend the cost effectiveness analysis to all groups of people of people with epilepsy of interest, as indicated by the committee.

Consistently with the overall evidence review, new-born babies (under 28 days) with acute symptomatic seizures were excluded from this economic analysis.

With the aim of assessing the impact of the epilepsy's severity on the cost effectiveness results, two hypothetical scenarios, reflecting two population's subgroups, have been explored by means of the present economic model:

- **Sub-group A*:*** "seizure-free" (SF) is defined as a situation in which people with epilepsy do not experience a seizure in the previous year before presenting to the ED
- **Sub-group B**: "Not seizure-free" (SF) is defined as a situation in which people with epilepsy do experience at least one seizure in the previous year before presenting to the ED

2.2 Strategies assessed and overview of model structure

This economic analysis was conducted to extrapolate and extend the findings of the Noble study (Noble 2014). This model compares treatment as usual (*TAU*) to TAU in addition to ESN led intervention (*ESN led intervention plus TAU*). TAU consisted of offering a yearly medical review to people with epilepsy, a yearly assessment of their epilepsy with their GP or an epilepsy specialist. Consistently with Noble 2014, the ESN led intervention had the following characteristics:

- It was delivered by an ESN (pay-scale 6), and consisted of two 1-to-1 sessions delivered on an outpatient basis to people with epilepsy attending ED (lasting 45–60 and 30 minutes)
- It was tailored to the person's needs
- It was aimed to improve people with epilepsy's self-care for the day-to-day management of epilepsy through improving knowledge, support and skills to mitigate adverse events and improve outcomes

Whilst not referring to any particular framework or approach for delivering the ESN intervention the committee noted that a number were available and in use with the NHS.

In order to allow for more flexibility in estimating the annual cost of the ESN intervention, we introduced costing scenarios supplementary to those assumed in Noble 2014, for example:

- Scenario 1: By adding 1 telephone contact lasting 10 minutes to the two 1-to1 face to face (F2F) sessions.
- Scenario 2: By extending the average length of each face-to-face session to 60 minutes.

- Scenario 3: By assuming a different nurse's salary (Pay scale 7) from that adopted in Noble 2014.

2.3 Model parameters

The economic analysis adopted the perspective of the NHS and personal social services (PSS), as recommended by NICE (NICE 2020). The measure of outcome was the Quality Adjusted Life Year (QALY), which incorporated utilities associated with the levels of epilepsy health related quality of life following treatment. Costs to the NHS & PSS consisted of ESN led intervention costs (healthcare professional time, number of sessions delivered by the ESN as part of intervention, as relevant) and use of health and social care services (for example emergency department contacts, inpatient stays, neurology outpatient contacts, primary care doctor/nurse contacts, etc.). The cost year was 2019.

2.4 Utility data and estimation of QALYs

For both adults and CYP with epilepsy the economic model used QALYs as the primary measure of outcomes. QALYs combine information on quantity of life and quality of life (QoL), with the latter measured on a scale anchored by 1 (full health) and 0 (death). Noble 2014 used the European Quality of Life-5 Dimensions (EQ-5D) combined with UK population preference weights to estimate the health-related QoL scores at baseline and each follow-up point.

At 1 year follow-up, the total QALYs accrued for each intervention group were calculated using those reported in Noble 2014.

At 20 years follow-up incremental QALYs were compared between the two groups using a linear interpolation assumption. That is, an assumption of a linear interpolation between baseline (1 year follow-up) and 20 years follow-up was made, as regard with the impact of treatment on incremental QALYs in the intervening group during the follow-up. Therefore for both adults and CYP with epilepsy, it was assumed that in both groups (ESN led intervention in addition to TAU care *versus* TAU alone), the relative effects of interventions remained constant overtime. This assumption favours TAU given the negative QALY estimate for ESN at 1 year. This assumption will increase the effectiveness of TAU over ESN. Whilst the committee did not believe that ESNs could lead to less QALYs or be clinically harmful, and consequently the assumption was not intended as an estimate of long term effect but as the most conservative plausible estimate for the effectiveness of ESNs given the clinical evidence identified.

Discounting, at a rate of 3.5% was applied to QALYs that accrued after the first year, as per the NICE reference case.

2.5 Cost data

Intervention costs, as well as other health care costs incurred by people with epilepsy, are based on cost data reported in the Noble 2014. Discounting, at a rate of 3.5% was applied to all costs that are incurred after the first year, as per the NICE reference case.

ESN led intervention cost was calculated by combining resource use estimates with respective national unit costs.

In both scenarios, for adults and CYP with epilepsy, the costing of TAU had the 10 components listed below:

- Emergency department (ED) attendance
- ED short-stay ward attendance
- Day care

- Inpatient stays
- Medication
- Neurology outpatient (O/P) visits
- Physiotherapist O/P visits
- Social worker O/P visits
- Other O/P visits
- Primary care doctor attendance
- Primary care nurse attendance

Also, in both economic models, the costing of the intervention differed from that of TAU because it included the costs of the delivery of the ESN led intervention; the costing of the intervention has been estimated by considering the elements listed in Table 17.

Table 17: Costing of the delivery of the ESN led intervention

A	Intensity and frequency of the ESN led intervention	A1	Number* of F2F contact delivered by the ESN as part of intervention and length of each session^
		A2	Number* of telephone contacts delivered by the ESN as part of intervention^^
B	ESN pay scale (Band 6 salary and on-costs) £47 per hour ESN pay scale (Band 7 salary and on-costs) £55 per hour		

** number per year; ^ length of 60 minutes per session; ^^ length of 10 minutes per contact*
F2F: face to face; ESN: epilepsy specialist nurse

Where the overall cost of the intervention is equivalent to A (Intensity and frequency of the ESN led intervention) multiplied by B (ESN pay scale); where A is equivalent to the sum of A1 (Number of F2F contact delivered by the ESN as part of intervention and length of each session) and A2 (Number of telephone contacts delivered by the ESN as part of intervention) (Table 17).

Table 18 reports the estimated costs of the ESN led intervention according to each hypothetical scenario.

Table 18: Costs of the ESN led intervention by varying its intensity, frequency, and delivery mode.

Formulation of the ESN led intervention		Estimated cost
Base-case	Costing as for Noble 2014, using 2019' unit costs	£ 58.75
Scenario 1	Base-case + 1 telephone contact lasting 10 minutes	£ 66.58
Scenario 2	Scenario 1 + extending the average length of each face-to-face session to 60 minutes	£ 101,83
Scenario 3	Scenario 2 + assuming a band 7 nurse's salary (Pay scale 7)	£ 119,73

ESN: epilepsy specialist nurse

2.6 Resource use

In Noble 2014 resource use was captured using data recorded on a modified version of the Client Service Receipt Inventory (CSRI) (Beecham 1992) at baseline, at 6 months (time point T1; see Table 19), and again at 12 months (time point T2; Table 19). Data were collected on whether or not a service was used, the number of contacts and (when relevant) the typical contact duration. For inpatient care the number of days spent in hospital was recorded. Med-

ication taken as a result of epilepsy was recorded at each time point (Noble 2014). The committee believed that service use data for CYP were similar to those registered in adults by Noble 2014 (Table 19); therefore, an assumption was made about the equivalence between the CYP and adults subgroups in healthcare services usage following the interventions.

Table 19: Resource use

Resource use category (Noble 2014: Base-case [n=69])	Time point T1: First 6 Months from baseline				Time point T2: Second 6 Months from baseline			
	TAU group		ESN group		TAU group		ESN group	
	Contacts (Number)	Contacts (Mean per patient)	Contacts (Number)	Contacts (Mean per patient)	Contacts (Number)	Contacts (Mean per patient)	Contacts (Number)	Contacts (Mean per patient)
ED attendance	14	2.9	17	1.7	14	4	10	2.2
Inpatient stays	5	11.6	4	2.7	8	3.5	2	4.5
ED short-stay ward attendance	5	1.8	11	1.1	9	2.3	6	2
Neurology O/P visits	23	1.3	21	1.2	22	1.4	19	1.5
Other O/P visits	17	2.2	15	1.5	5	2	14	1.4
Day care	2	2.5	3	1	1	1	6	2
Primary care doctor attendance	27	3.6	25	3.6	22	3.6	23	4.1
ESN	0	0	0	0	0	0	69	1
Primary care nurse attendance	20	2	7	1.4	9	1.9	6	1.2
Physiotherapist visits	2	3	1	2	1	2	3	4.7
Social worker visits	0	0	6	3.3	1	1	3	2
*Medication**	*35*	*-*	*31*	*-*	*35*	*-*	*30*	*-*
ED: emergency department; ESN: epilepsy specialist nurse; N: number; TAU: treatment-as-usual								

When discussing these health care resource use categories the committee noted that there was not any omission, in terms of NHS services usage by people with confirmed epilepsy following the interventions.

2.7 Unit costs

Unit costs for each element of resource use were sought from appropriate national sources. All unit costs in the model are obtained from the Unit Costs of Health and Social Care 2019 data (Curtis and Burns 2020) or the 2018/19 National Cost Collection data (Department of health 2020); Table 20 reports the unit costs obtained for adults and CYP, respectively.

Table 20: Unit costs for adults and CYP

Resource use category	Value (£)	*Adults* / *CYP*	Source
ED attendance	189.00	*Adults*	National Schedule of NHS costs (VB08Z: Emergency Medicine, Category 2 Investigation with Category 1 Treatment – Total Unit Cost)
		CYP	
Inpatient stays	2,302.00*	*Adults*	National Schedule of NHS costs (AA26F: Muscu-

Resource use category	Value (£)	*Adults* / *CYP*	Source
		CYP	lar, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 6-8 – Non-elective Unit Cost)
ED short-stay ward attendance	459.00*	*Adults*	National Schedule of NHS costs (AA26F: Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 6-8 – Non-elective Short Stay Unit Cost)
		CYP	
Neurology O/P visits	136.00	*Adults*	PSSRU - Unit Costs of Health and Social Care, National Schedule of NHS costs for hospital services, (Weighted average of all outpatient attendances)
Other O/P visits	198.00	*CYP*	PSSRU - Unit Costs of Health and Social Care, National Schedule of NHS costs for children's health services (Weighted average of all outpatient attendances)
Day care	97.00	*Adults*	PSSRU - Unit Costs of Health and Social Care, Services for adults requiring physical support (Day care for adults requiring physical support)
		CYP	PSSRU - Unit Costs of Health and Social Care, National Schedule of NHS costs for children's health services (Day care for Child and Adolescent Mental Health Services, Average Cost Per Patient Contact)
Primary care doctor attendance	39.00	*Adults*	PSSRU - Unit Costs of Health and Social Care, Community-based health care staff (GP: Per surgery consultation lasting 9.22 minutes1)
		CYP	
Primary care nurse attendance	40.00	*Adults*	National Schedule of NHS costs (N02AF: District Nurse, Adult, Face to face)
	107.00	*CYP*	National Schedule of NHS costs (N12: Nursing Services for Children)
Physiotherapist visits	63.00	*Adults*	National Schedule of NHS costs (A08A1: Physiotherapist, Adult, One to One)
	101.00	*CYP*	National Schedule of NHS costs (A08C1: Physiotherapist, Child, One to One)
Social worker visits	51.00	*Adults*	PSSRU - Unit Costs of Health and Social Care, Community-based social care staff (Social worker - adult services)
	50.00	*CYP*	PSSRU - Unit Costs of Health and Social Care, Community-based social care staff (children worker -adult services)

ED: emergency department; CYP: children and young people; ESN: epilepsy specialist nurse; O/P: outpatient; TAU: treatment-as-usual

** Refers to the whole hospital stay*

2.8 Assumptions

Costing assumption

In both economic models, for adults and CYP with epilepsy, two major assumptions were used to estimate annual overall costs starting from the data extrapolated from Noble 2014 under the 20 years analytical time horizon:

- Convergence cost assumption: According to this assumption, the overall costs of TAU alone or combined with the ESN led intervention are assumed to differ at 1 year follow-up

and then to converge to the same amount over a 20-year follow-up. This was to reflect that patients receiving TAU were likely to incur less costs over the time, equalizing at the end those incurred by patients receiving the ESN led intervention.

- Remaining cost assumption: According to this more conservative assumption, the overall costs of TAU alone or combined with the ESN led intervention are assumed to differ at 1 year follow-up and to remain proportionally different over a 20-year follow-up. This assumption is that in the group with the highest costs (that is TAU) the difference would taper down at a constant rate until equal to the comparison group (this is, ESN led intervention) at 20 years. This assumption is the difference in intervention costs between the groups at one year would remain for the entirety of the 20- year time horizon reflecting that cost's differences may continue significantly past one year.

Epilepsy severity assumption

When developing the economic model, the committee outlined that people with epilepsy who are not SF will use healthcare services more than individuals who are SF. Therefore, one element of cost differences between interventions has been explored by assuming a dissimilar likelihood of uptake and healthcare use relative to seizures, that is on whether seizures were present or not. This different likelihood in the pattern of service use according to the epilepsy's severity has been estimated by extrapolating and using the data reported in a large UK prevalence study on epilepsy (Jacoby 1998). This study was believed by the committee as applicable to the decision-problem of the present economic model; therefore, its data were used in the economic analysis.

This cross-sectional study, which included a large sample of people with epilepsy (n = 1,341) -either adults or CYP, described both services use and associated costs. The data in the study was obtained from primary care doctors' records and patient surveys. These data were recorded relatively to the different health and social care settings (for example, inpatient, outpatient or community care settings); according to severity of the epilepsy (for example, seizure frequency reported in the last year by people with epilepsy); and by age groups (for example, adults and CYP). According to this study, people with epilepsy who experienced one or more seizures in a year reported higher use of all services than individuals who were seizure-free in the last year, although the differences were more marked for adult patients than for children (Table 21).

Table 21: Probabilities of using healthcare services by seizure frequency in the past year (SF *versus* not SF)

Use of healthcare services	CYP		ADULT	
	SF	Not SF	SF	Not SF
ED	0,02[1]	0,25	0,02	0,27
Inpatient stays	0,01[1]	0,29	0,01	0,16
ED short stay ward	0,02[2]	0,25[2]	0,02[2]	0,27[2]
Neurology O/P	0,85	0,92	0,18	0,49
Other O/P	0,85	0,92	0,18	0,49
Day care	0,21	0,51	0,01	0,01
Primary care doctor	0,36	0,47	0,18	0,61
Primary care nurse	0,04[1]	0,03	0,04	0,1
Physiotherapist	0,04	0,21	0,02	0,08
Social worker	0,04	0,15	0,01	0,02

CYP: children and young people; ED: emergency department; ESN: epilepsy specialist nurse; O/P: outpatient; N: number; SF: seizure free

1 missing values in Jacoby 1998, estimated from NICE guideline (NICE CG 137)

2 missing values in Jacoby 1998 and NICE guideline 137(NICE CG 137), assumed to be the same values as for inpatient admission by the committee

2.9 Data analysis and presentation of data

Deterministic and probabilistic analyses were used to analyse the input parameter data and present the results of the economic analysis.

A deterministic analysis was undertaken, where data are analysed as point estimates; results are presented as mean total costs and QALYs associated with each treatment option are assessed. Relative cost effectiveness between alternative treatments was estimated using incremental analysis. Incremental cost effectiveness ratios (ICERs) were calculated for the two intervention options in the analysis. ICERs expressed the additional cost per additional unit of benefit associated with one treatment option relative to its comparator. Estimation of such a ratio allowed consideration of whether the additional benefit was worth the additional cost when choosing one treatment option over another.

One-way sensitivity analyses explored the impact for each intervention group:

- of making different assumptions about the intensity and frequency of the ESN led intervention as described in Noble 2014; that is, using either intervention costs from scenario 1 (this is, by adding 1 telephone contact lasting 10 minutes to the two 1-to1 face to face (F2F) sessions); intervention costs from scenario 2 (this is, by extending the average length of each face to face session to 60 minutes); or intervention costs from scenario 3 (this is, by assuming a different nurse's salary (Pay scale 7) from that adopted in Noble 2014
- of omitting from the overall estimated costs those related to ED services use
- of omitting from the overall estimated costs those related to inpatient stays

Additionally, one-way sensitivity analyses, each of the following model inputs was varied ±25% around the baseline value:

- ED cost per patient
- ED short-stay ward cost per patient
- ESN cost per patient
- Inpatient stays cost per patient
- Medication cost per patient
- Neurology O/P cost per patient
- Other O/P cost per patient
- Primary care doctor cost per patient

Most the unit costs were taken from national databases with a large number of observations and consequently we would not expect there to be a large degree of uncertainty around them. Given the weaknesses of the underlying clinical evidence we expected there to be some uncertainty around the mean use of these services. There would also be great uncertainty around costs extrapolated beyond the first year given this was done through assumption. It would be difficult to capture all these in a conventional statistical distribution with 95% confidence intervals for the tornado diagram values. Given this the ±25% change was considered a wide, conservative estimate for a plausible range for these costs.

In addition to deterministic analyses, probabilistic analyses were also conducted, probabilistic analyses were also conducted. In these cases, all model input parameters were assigned probability distributions (rather than being expressed as point estimates), to reflect the uncertainty characterising the available clinical and cost data. Subsequently, 1,000 iterations were performed, each drawing random values out of the distributions fitted on to the model input

parameters. This exercise provided more accurate estimates of mean costs and benefits for each intervention assessed (averaging results from the 1,000 iterations), by capturing the non-linearity characterising the economic model structure (Briggs 2006). Table 22 provides information on the distributions assigned to specific parameters in probabilistic sensitivity analyses.

Table 22: Distributions assigned to specific parameters in probabilistic sensitivity analyses.

Input parameter	Probability distribution*
Incremental QALY (TAU group – ESN group)	
Baseline	Log Normal, SE=0.10 of mean
20 years' time horizon	Uniform ("+-10%")
Unit costs	
ED cost	Gamma (Assumes 0.3*Mean as 1SD)
Inpatient stays cost	Gamma (Assumes 0.3*Mean as 1SD)
ED short-stay ward cost	Gamma (Assumes 0.3*Mean as 1SD)
Neurology O/P cost	Uniform ("+-25%")
Other O/P cost	Uniform ("+-25%")
Day care cost	Uniform ("+-25%")
Primary care doctor cost	Uniform ("+-25%")
ESN cost	Uniform ("+-25%")
Primary care nurse cost	Gamma (Assumes 0.3*Mean as 1SD)
Physiotherapist cost	Gamma (Assumes 0.3*Mean as 1SD)
Social worker cost	Uniform ("+-25%")

** based on assumption.*
ED: emergency department; ESN: epilepsy specialist nurse; O/P: outpatient; N: number; TAU: treatment-as-usual

Results of probabilistic analyses were presented in the form of cost effectiveness acceptability curves (CEACs), which demonstrated the probability of each treatment option being the most cost effective among the strategies assessed at different levels of willingness-to-pay per unit QALY (that is, at different cost effectiveness thresholds the decision maker may set). Also, cost effectiveness planes (CEPs) were used to show the uncertainty around cost effectiveness outcomes of the model, uncertainty represented as a cloud of points on the plane corresponding to the different 1,000 iterations of the economic model in the probabilistic sensitivity analysis. Basically, the CEPs were used to visually represent the differences in costs and QALYs between treatment alternatives in two dimensions, by plotting the costs against QALYs on a graph.

3. Results

3.1 Primary analyses results

Deterministic results

Table 23 shows the costs and QALYs for the TAU alone or combined with ESN led intervention for the (deterministic) primary analyses in adults with epilepsy (Table 23 – Part A). In addition, it provides the incremental cost and incremental effectiveness expressed as QALY gains.

On average, adults receiving the ESN led intervention incurred £2,422 lower costs and got 0.02 fewer QALYs than TAU participants, within a 1-year timeframe (Table 23 – Part A). Compared with ESN led intervention, the additional cost of gaining a QALY for adults using

TAU equalled £115,329, so TAU would not be considered cost-effective; that is, the ESN led intervention produce considerable cost savings but fewer QALYs than TAU, which would justify its use given the accepted principle of opportunity cost. In other words, the ESN led intervention is well within the recommended threshold currently specified for NICE decision-making in England and Wales (£20,000 per QALY gain), even though it produces fewer QALYs, i.e. if NHS is willing to pay £20,000 per QALY gain, it should be willing to accept anything above £20,000 for a QALY lost.

Similar cost effectiveness estimates have been determined for CYP (Table 23 – Part B). On average, CYP with epilepsy receiving the ESN led intervention incurred £2,468 lower costs and got 0.02 fewer QALYs than TAU participants, at 1-year. Therefore, within a 1-year timeframe the ICER equalled £117,514 saved per QALY lost, which is acceptable in terms of the recommended threshold currently specified for NICE decision-making.

Table 23: Deterministic cost effectiveness estimates for the ESN led intervention compared with TAU at 1-year time horizon

PART A (Adults)		PART B (CYP)	
TAU alone		*TAU alone*	
Costs (£), mean	£ 4,263	Costs (£), mean	£ 4,420
QALY, mean	0.81	QALY, mean	0.81
TAU + ESN intervention		*TAU + ESN intervention*	
Costs (£), mean	£ 1,841	Costs (£), mean	£ 1,952
QALY, mean	0.79	QALY, mean	0.79
TAU + ESN intervention vs. TAU alone		*TAU + ESN intervention vs. TAU alone*	
Incremental cost, mean	-£ 2,422	Incremental cost, mean	-£ 2,462
Incremental QALY, mean	- 0.02	Incremental QALY, mean	-0.02
ICER (£/QALY)	*£ 115,329*[a]	*ICER (£/QALY)*	*£117,514*[a]

ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; SD: standard deviation; TAU: treatment-as-usual; £: pound sterling
a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.

Probabilistic results

Figure 2 shows the cost effectiveness plane for the ESN intervention compared with TAU at 1-year follow up based on 1,000 bootstrapped iterations. The diagonal line represents a willingness to pay per QALY threshold of £20,000. The average costs from the bootstrapped estimates were £4,262 (SD 62.8) and £1,856 (SD 29.6) for the TAU and ESN arms, respectively. The corresponding mean incremental QALY was -0.02 (SD 0.03) for the ESN led intervention compared to TAU alone.

Both for adults and CYP, all the simulation estimates are all well below the x-axis, showing that the ESN intervention is always less costly than TAU. In addition, most of simulated estimates are very close to the y-axis and were spread in the south-west quadrant, showing that the ESN intervention led always to slightly fewer QALYs than TAU; although some estimates are in the south-east quadrant, where the ESN intervention results in more QALYs than TAU. These results suggest that the ESN led intervention is either cost effective compared to TAU, or is likely to be dominant (this is, the intervention is both clinically superior and cost saving compared to the TAU).

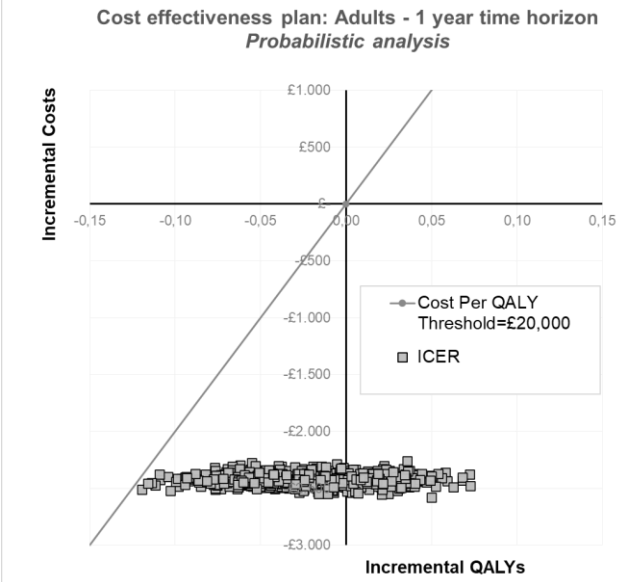
A cost effectiveness acceptability curve of the ESN led intervention compared with TAU is presented in Figure 3. At a threshold of £20,000, the ESN led intervention had a 100% chance of being cost effective, and this percentage decreased to 97.5% when the threshold was £30,000.

There is a negative relationship between the cost effectiveness threshold and the chance of the ESN intervention being cost effective, and this is because the ESN intervention was, on average, less effective (in terms of QALY gains) than TAU, but cost significantly less.

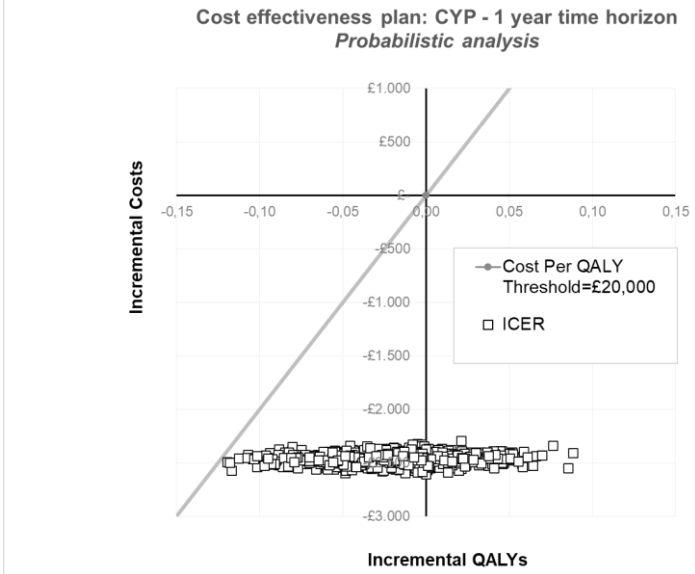
The results for CYP are similar to those estimated for adults (Figure 3 – Part A for adults, and Figure 3 – Part B for CYP, respectively).

Figure 2: Cost effectiveness plan for the ESN led intervention compared with TAU at 1 year time horizon

PART A (Adults)



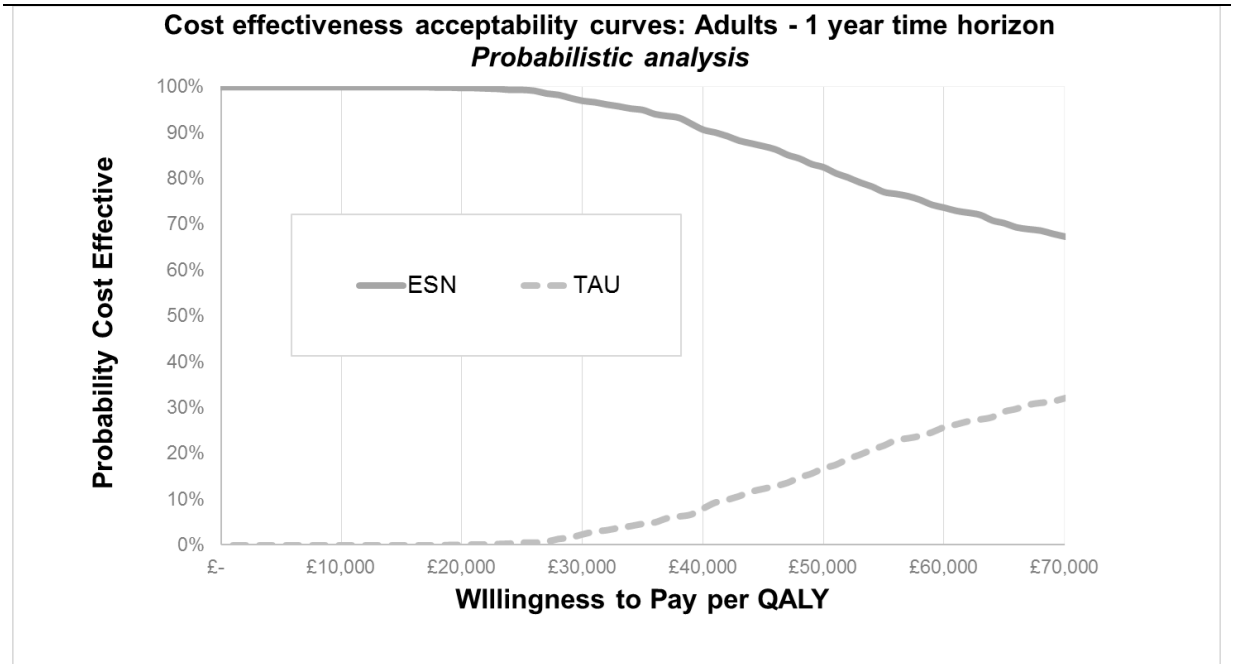
PART B (CYP)



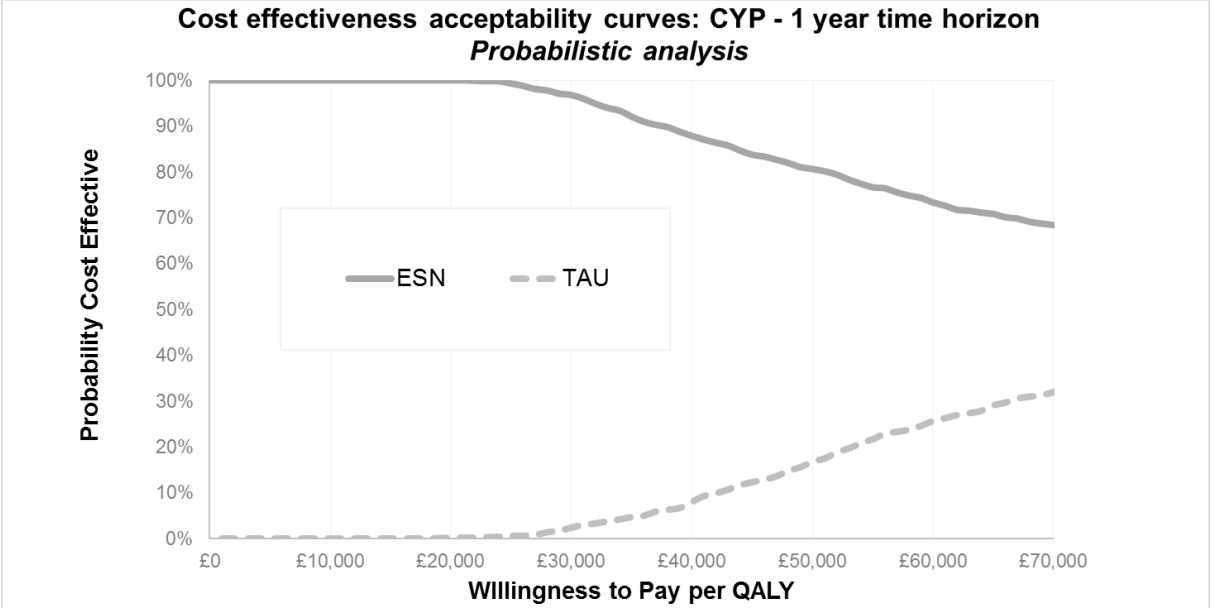
ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

Figure 3: Cost effectiveness acceptability curves for the ESN led intervention compared with TAU at 1 year time horizon

PART A (Adults)



PART B (CYP)



ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

3.1.1 Sensitivity analysis

The population of the economic model included people with confirmed epilepsy who present to ED. Subsequently, we did a one-way sensitivity analysis to investigate the influence of including the whole population with epilepsy not just those using hospital emergency services. The results of these sensitivity analyses are summarized in Table 24 and Figure 4 and suggest that the population included in the model does not affect considerably the cost effectiveness results

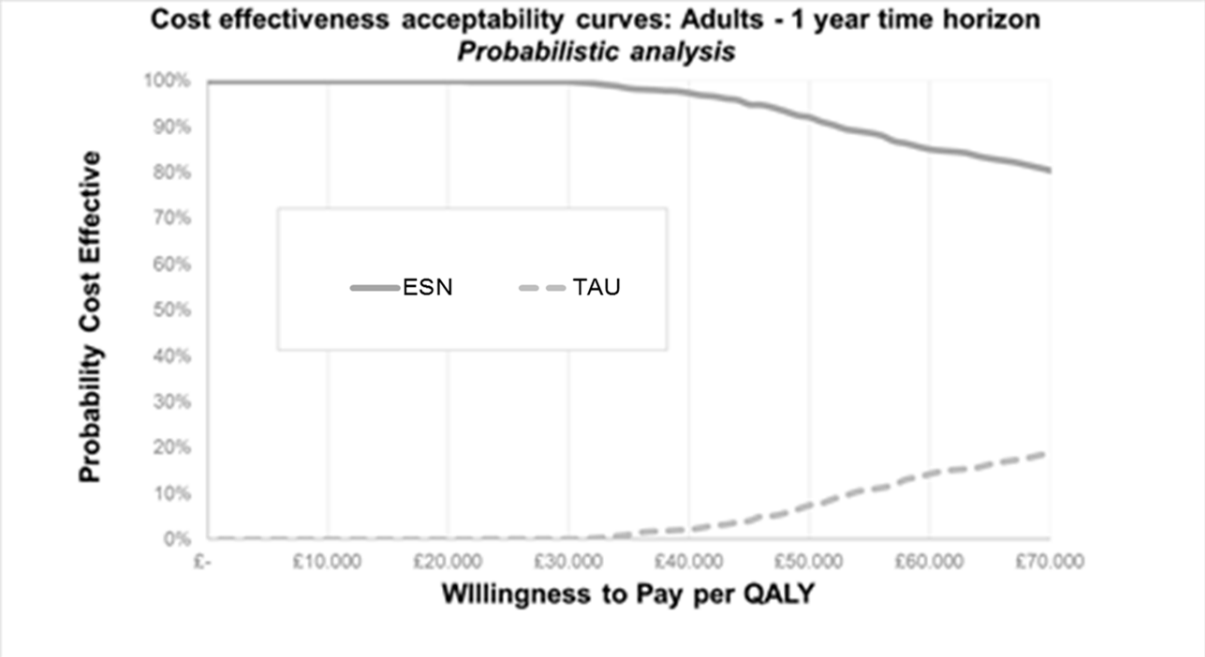
Table 24: Deterministic cost effectiveness estimates for the ESN led intervention compared with TAU at 1 year time horizon, assuming the general population with epilepsy non included in the base-case analyses.

ESN + TAU *versus* TAU	ICER (£/QALY) [a]	
Adults	£156.136	Figure 4 – PART A
	£115.329[b]	
CYP	£159.129	Figure 4 – PART B
	£117.514[b]	

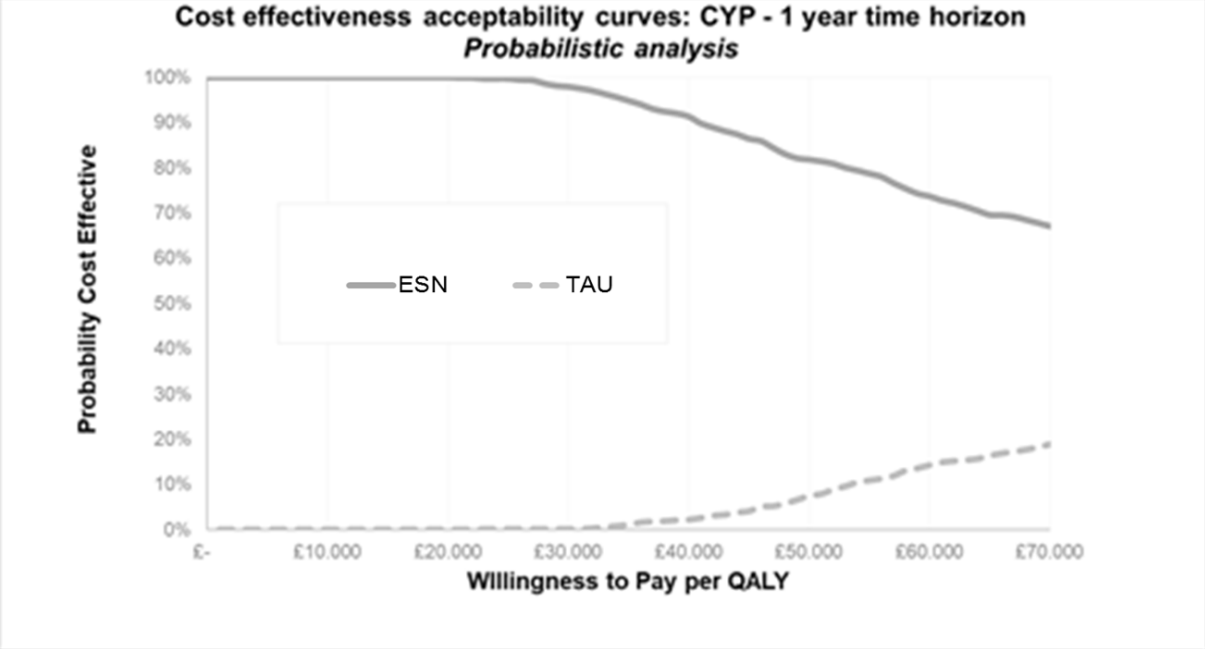
ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling
a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.
b: the values are relative to the deterministic ICERs estimated in the baseline primary analysis.

Figure 4: Cost effectiveness acceptability curves for the ESN led intervention compared with TAU at 1 year time horizon, assuming the general population with epilepsy non included in the base-case analyses.

PART A (Adults)



PART B (CYP)



ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

To account for uncertainty in the incremental costs and QALYs estimation, a number of further sensitivity analyses were conducted (Table 25**Error! Reference source not found.**, and Figure 5). The first sensitivity analyses included making different assumptions about the intensity and frequency of the ESN led intervention, that is, using either intervention costs from scenario 1, intervention costs from scenario 2, or intervention costs from scenario 3 as defined earlier in the methods (chapter 2.2). By adding these scenarios, the delivery of the ESN intervention remained likely to be cost effective both in adult and CYP with epilepsy at 1 year time horizon (Table 25**Error! Reference source not found.**). As for the base-case analyses, these results indicate the ESN led intervention is less effective than the TAU, and so, as the value placed on a QALY increases, the likelihood that the intervention is cost effective falls – but not by much because the differential impact on QALYs is small compared with costs (Figure 5: A, B, and C).

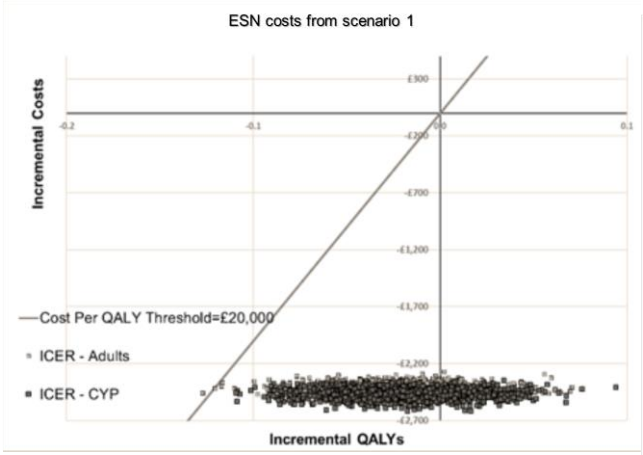
Table 25: Deterministic cost effectiveness estimates for the ESN led intervention compared with TAU at 1-year time horizon– univariate sensitivity analysis

PART A (Adult)		PART B (CYP)		
ESN + TAU *versus* TAU	ICER (£/QALY)	ESN + TAU *versus* TAU	ICER (£/QALY)	
Baseline analysis	*£115.329*[a]	*Baseline analysis*	*£117.514*[a]	
ESN costs from scenario 1	£114,956[a]	ESN costs from scenario 1	£117,141[a]	Figure 5*: A*
ESN costs from scenario 1 + 2	£113,278[a]	ESN costs from scenario 1 + 2	£115,463[a]	Figure 5*: B*
ESN costs from scenario 1 + 2 + 3	£112,452[a]	ESN costs from scenario 1 + 2 + 3	£114,637[a]	Figure 5*: C*
Omission of ED costs	£109,368[a]	Omission of ED costs	£111,453[a]	Figure 5*: D*
Omission of inpatient stays costs	**£10,158***	Omission of inpatient stays costs	**£12,344***	Figure 5*: E*
Omission of both inpatient stays and ED costs	**£4,198***	Omission of both inpatient stays and ED costs	**£6.383***	Figure 5*: F*

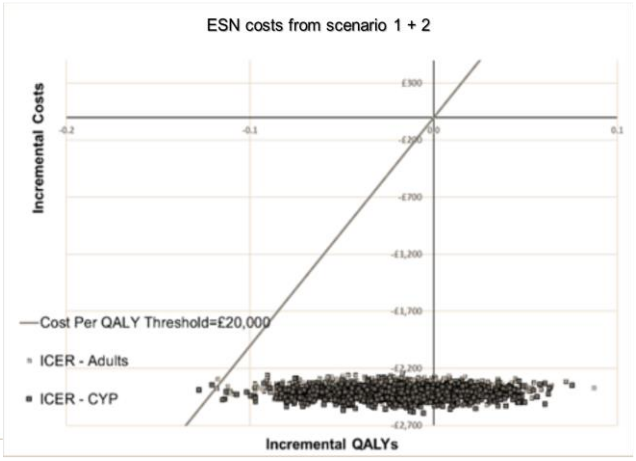
ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling
** non cost effective results*
a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.

Figure 5: Deterministic cost effectiveness estimates for the ESN led intervention compared with TAU at 1-year time horizon– univariate sensitivity analysis

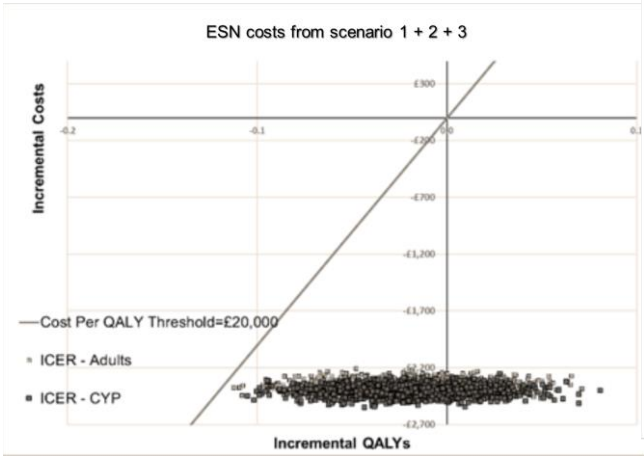
A



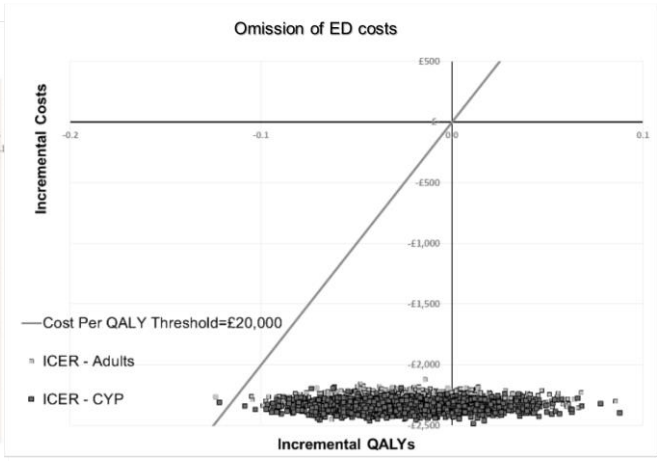
B



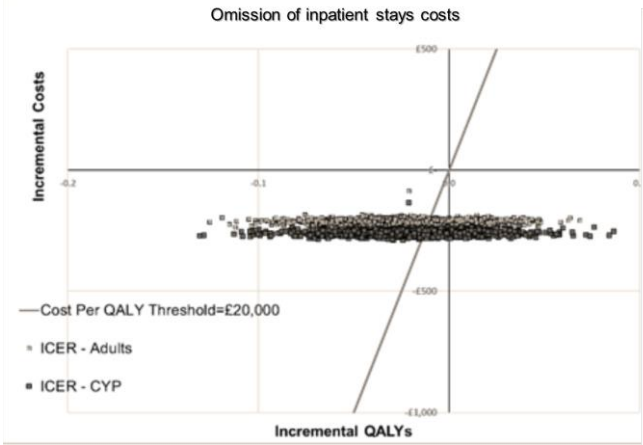
C



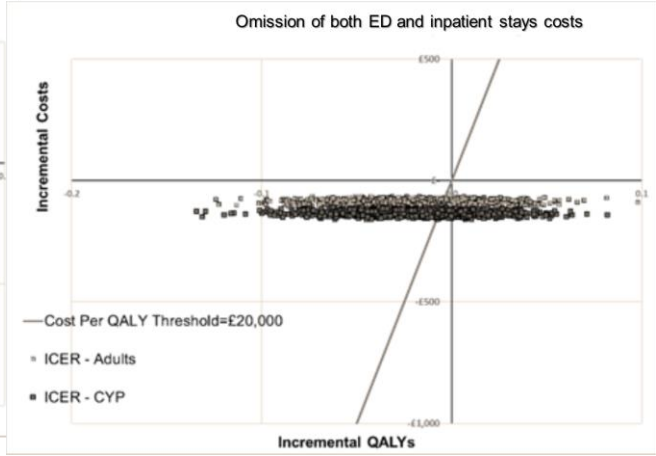
D



E



F



ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

When omitting from the overall estimated costs those related to ED services use, the ICER was £ £109,368 and £111,453 for adults and CYP, respectively. Thus, the addition the ESN intervention was likely to be cost effective compared to TAU also when not considering the ED's costs, and as shown in figure result 3 most of the simulation estimates were all below the x-axis, suggesting that the ESN intervention combined to TAU was less costly than TAU alone, also in this scenario (Table 25**Error! Reference source not found.**, Figure 5: D).

The impact of excluding inpatient stays costs, from the overall costs, is to decrease the likelihood that the ESN led intervention is cost effective compared to TAU alone, and this is true both for adults and CYP (Table 25**Error! Reference source not found.**, Figure 5: E, and F). This is to some extent intuitive when one considers the data on hospital usage included in the Noble trial (Noble 2014, Risdale 2013), which suggest that the duration of hospital admissions following ED visits was shorter for the group who were offered the ESN intervention than TAU.

3.2 Secondary analyses results – time horizon extended to 20 years

Deterministic results

Table 26 shows the deterministic results for each of the model arms at 20 years for adults and children and young people. The results are stratified according to the costing assumptions, i.e. converging and remaining. The results reinforce the findings observed at 1 year, i.e. intervention was cost savings but also led to fewer QALYs gained with an ICER of ESN-led intervention ranging from £ 64,553 to £ 115,329 per QALY lost (vs TAU) depending on the costing approach adopted. See Table 23 and Table 26.

For adults, the aforementioned is true both assuming a converging or remaining costing's assumption, as suggested by the estimated results (Table 26 – Part A). These findings are analogous to those estimated for CYP (Table 26 – Part B).

Table 26: Deterministic cost effectiveness for the ESN led intervention compared with TAU estimates at 20-year time horizon

Part A (Adults)		
Costing assumption	**Converging**	**Remaining**
TAU alone		
Costs (£), mean	£ 47,018	£ 62,703
QALY, mean	11.87	11.87
TAU + ESN intervention		
Costs (£), mean	£ 27,077	£ 27,077
QALY, mean	11.56	11.56
TAU + ESN intervention vs. TAU alone		
Incremental cost, mean	-£ 19,941	-£ 35,626
Incremental QALY, mean	-0.31	-031
ICER (£/QALY)	£ 64, 553[a]	£ 115,329[a]
Part B (CYP)		
Costing assumption	**Converging**	**Remaining**
TAU alone		
Costs (£), mean	£ 49,030	£ 65,012
QALY, mean	11.87	11.87
TAU + ESN intervention		

Costs (£), mean	£ 28,711	£ 28,711
QALY, mean	11.56	11.56
TAU + ESN intervention vs. TAU alone		
Incremental cost, mean	-£ 19,275	-£ 34,435
Incremental QALY, mean	-0.31	-0.31
ICER (£/QALY)	£ 62,396[a]	£ 117,514[a]

ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling
a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.

Probabilistic results

Considering uncertainty around the model inputs (this is, looking at the probabilistic results), TAU was associated with an extra cost of £19,922 (under a converging costing assumption) and a 20-year QALY gain of 0.39 (equivalent to 23.7 extra days of full health) compared with the ESN intervention, in adult population. The ICER indicated that 1 QALY would be gained for every £62,396 spent by *not* adopting the ESN led intervention; the ICER was below the NICE-recommended threshold (£20,000) and, therefore, the ESN led intervention added to TAU was expected to be cost effective in the longer term, compared to TAU alone. The obtained estimates favoured even strongly the ESN led intervention arm rather than the TAU arm, when taking into account a remaining costing assumption (Table 27 – Part A). The results for CYP are similar to those already described for adults (Table 27 – Part B).

Table 27: Probabilistic cost effectiveness for the ESN led intervention compared with TAU estimates at 20-year time horizon

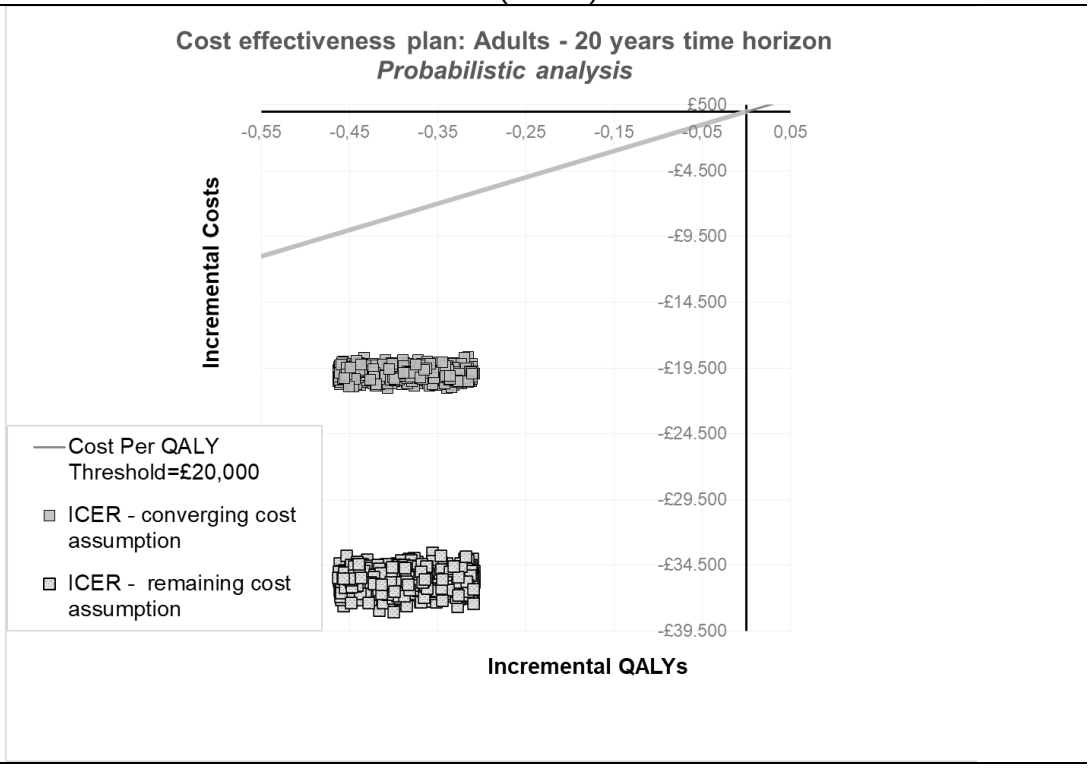
Part A (Adults)		
Costing assumption	**Converging**	**Remaining**
TAU alone		
Costs (£), mean (SD)	£ 47,002 (699.1)	£ 62,668 (957.9)
QALY, mean	11.87	11.87
TAU + ESN intervention		
Costs (£), mean (SD)	£ 27,079 (437.6)	£ 27,065 (440.8)
QALY, mean	11.56	11.56
TAU + ESN intervention vs. TAU alone		
Incremental cost, mean (SD)	-£ 19,922 (384.7)	-£ 35,626 (685.7)
Incremental QALY, mean (SD)	-0.39 (0.04)	-0.39 (0.04)
ICER (£/QALY)	£ 52,103[a]	£ 92,851[a]
Part B (CYP)		
Costing assumption	**Converging**	**Remaining**
TAU alone		
Costs (£), mean (SD)	£ 49,046 (798.2)	£ 64,997 (1,023.6)
QALY, mean	11.87	11.87
TAU + ESN intervention		
Costs (£), mean (SD)	£ 28,711 (541.9)	£ 28,695 (527.3)
QALY, mean	11.56	11.56
TAU + ESN intervention vs. TAU alone		
Incremental cost, mean (SD)	-£ 20,329 (396.3)	-£ 34,435 (692.7)
Incremental QALY, mean (SD)	-0.31	-0.38 (0.04)
ICER (£/QALY)	£ 53,486[a]	£ 96,069[a]

ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling
a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.

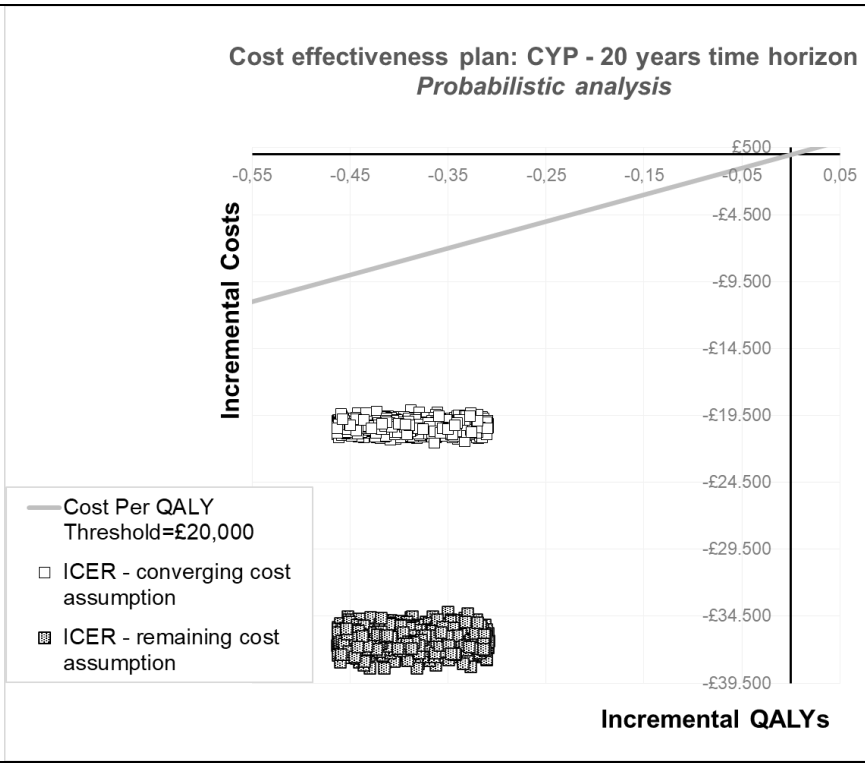
Figure 6 shows the results of the probabilistic analysis, either for a converging or remaining costing assumption. Each point on the graphs represents the result of one probabilistic simulation of the model and indicates a potential incremental cost and decremental QALY for the ESN intervention compared with TAU. The diagonal line represents the NICE willingness-to-pay threshold of £20,000 per QALY. Most points were distributed well below the origin, both for the simulated analysis of adults (Figure 6 – part A), and CYP (Figure 6– part B). This indicates that the ESN intervention is always less costly than TAU. In most cases, the simulated ICERs were spread in the south-west region close to the y-axis, which indicated that the intervention is less effective than the TAU. Therefore, probabilistic data suggest that ESN led intervention might reduce substantially the cost of supporting people with epilepsy but provide slightly worse outcomes than TAU; as a result, from the perspective of the UK health and social care, the ESN led intervention is likely to be cost effective at a willingness-to-pay threshold of £20,000 at a 20 years' time horizon. For those with severe epilepsy (i.e. Not SF) there is a higher likelihood that the ESN led intervention is cost effective and the ESN led intervention was cost effective for all cost per QALY thresholds in this population.

Figure 6: Cost effectiveness planes for the ESN led intervention compared with TAU at 20-year time horizon

PART A (Adults)



PART B (CYP)



ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

3.2.1 Sensitivity analysis

Figure 7 shows the tornado diagrams for a one-way sensitivity analyses where input parameters for models' variables were varied ±20% around their baseline values.

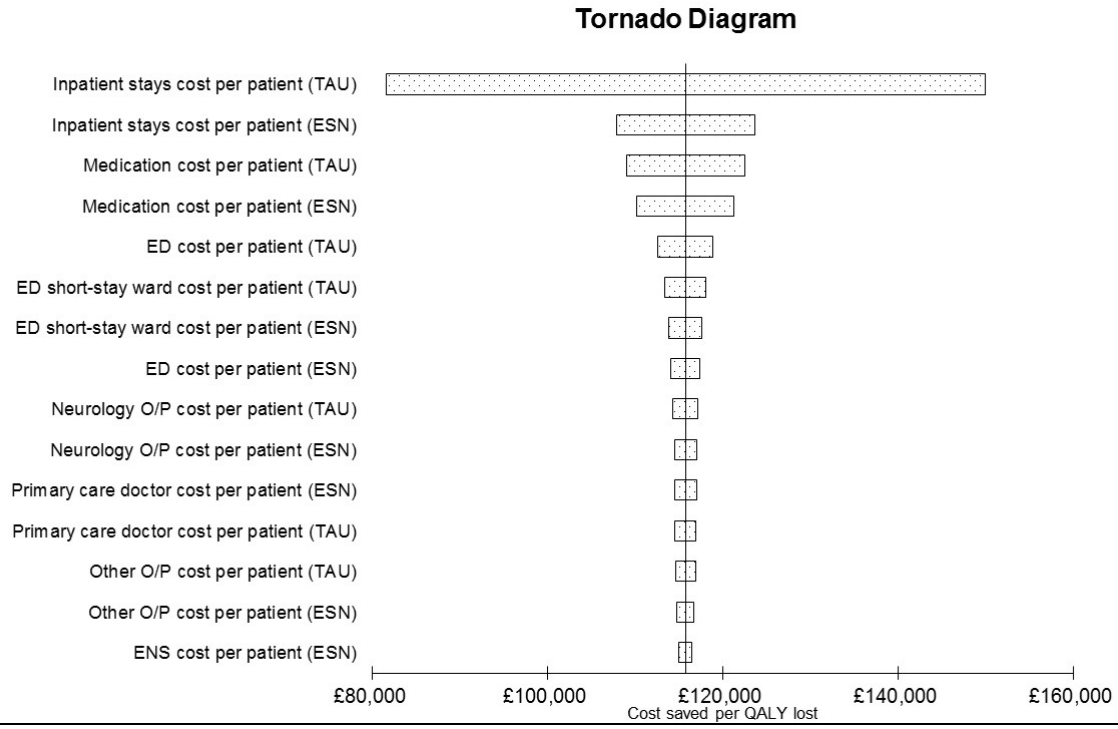
These tornado diagrams, relative to the simulated data against a time horizon of 20 years with a converging costing assumption, indicate graphically how variations in each input affect the baseline outcome of the economic models (that are the baseline ICERs).

Both for adults and CYP, the one-way sensitivity analyses suggest that the ICERs are most sensitive to variation in the inpatient stays costs per patient, and least sensitive to variation in the cost of the delivery of the ESN intervention. However, under all assumptions the conclusions were unchanged, i.e. the ESN intervention remained the preferred choice.

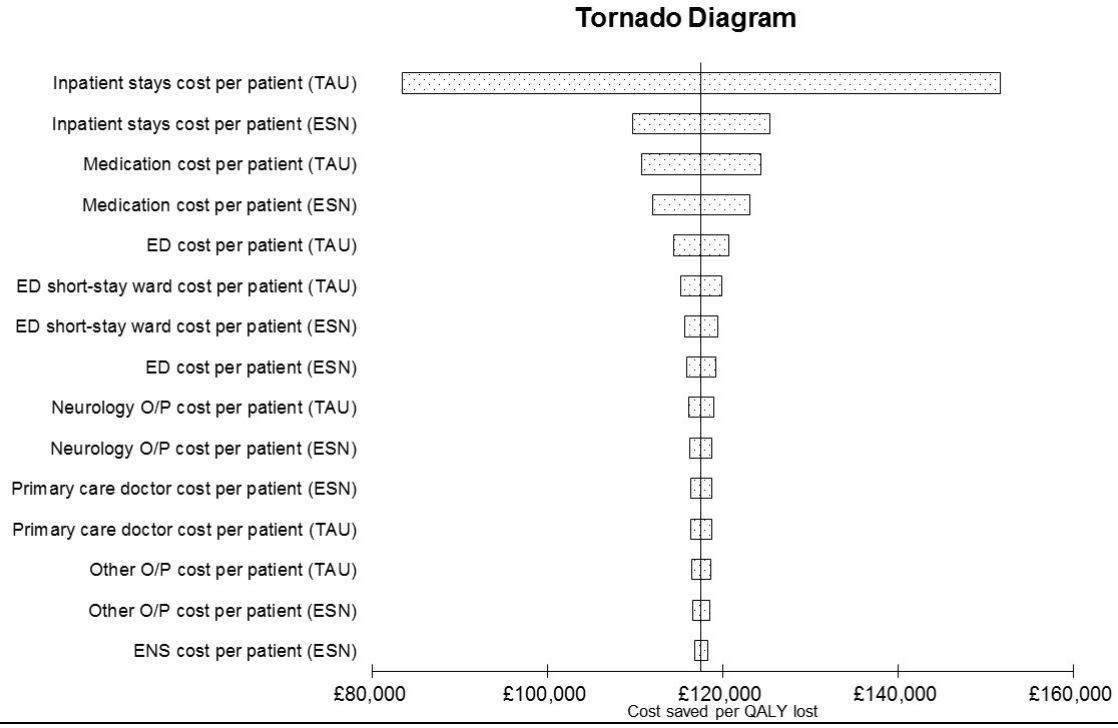
Figure 7: Tornado diagrams for deterministic one-way sensitivity analyses -at 20-year time horizon, with a 'converging' costing assumption*

PART A (Adults) [a,b]

PART A (Adults) [a,b]



PART A (CYP) [a, c]



£: pound sterling; CYP: children and young people; ED: emergency department; ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; O/P: outpatient; TAU: treatment-as-usual.

** each of model input was varied ±25% around the baseline value.*

a: the positive value of the ICER reflects negative effectiveness outcomes and large cost saving of the intervention compared to TAU, indicating an acceptable cost effective situation.

b: baseline ICER (at 20-year time horizon, with a 'converging' costing assumption): £ 64,553.

c: baseline ICER (at 20-year time horizon, with a 'converging' costing assumption): £ 65,776.

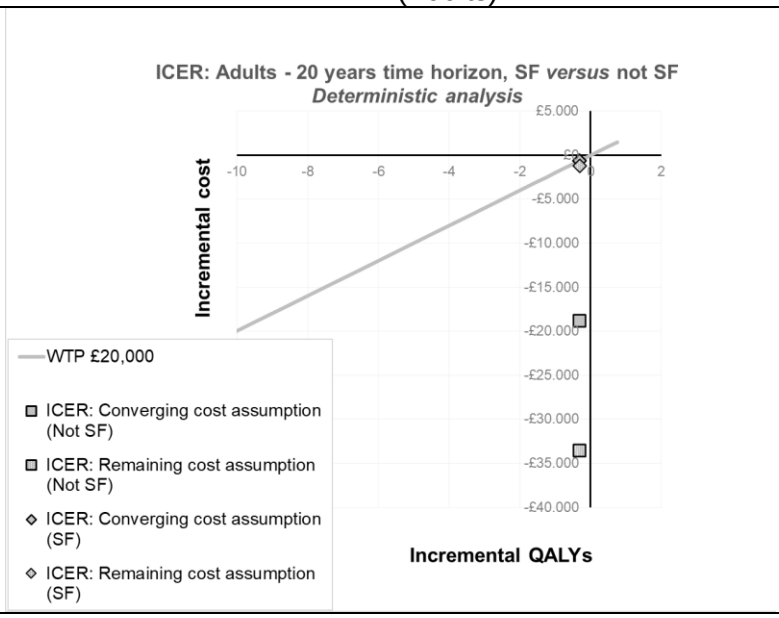
Subgroup analysis according to the severity of epilepsy.

The impact of the severity of epilepsy was investigated in subgroup analysis. The resulting deterministic estimates for the 'seizure-free' (SF) and 'not seizure-free' (not SF) subgroups are shown in Figure 8, both for adults (Figure 8– Part A), and for CYP (Figure 8– Part B). As shown by the deterministic cost effectiveness plans in Figure 8, people with epilepsy who experienced one or more seizures in a year reported higher use of all services than individuals who were seizure-free in the last year, with this differences being slightly more marked for adult patients than for CYP.

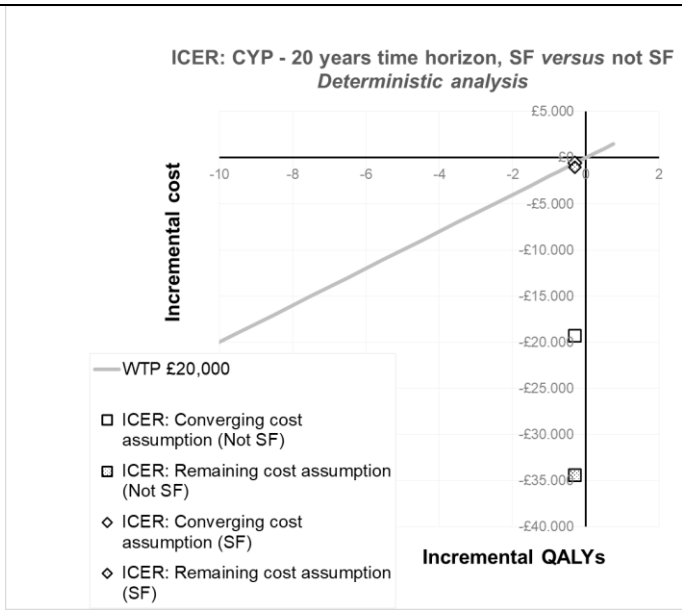
In the SF group, either for adults or for CYP, there is considerable uncertainty regarding the cost effectiveness of the ESN intervention regardless of the costing assumption. In contrast, for those with severe epilepsy (not SF group) there is a greater likelihood that the ESN intervention is cost effective and the value placed on costing the alternative interventions has no influence on cost effectiveness of any kind. The analysis suggests large cost differences in magnitude between the ESN led intervention and TAU, along with very small QALY loss. When observing these findings, the committee thought that implementing the ESN led intervention was likely to lead to large cost savings primarily due to a reduction in the health care costs of supporting people with epilepsy compared with TAU, with only uncertain and tiny reductions in health outcomes. Therefore, they agreed that overall the ESN led intervention would be beneficial for people with epilepsy, specifically for those with severe epilepsy (not SF group).

Figure 8: Deterministic cost effectiveness plans at 1-year time horizon

PART A (Adults)



PART B (CYP)

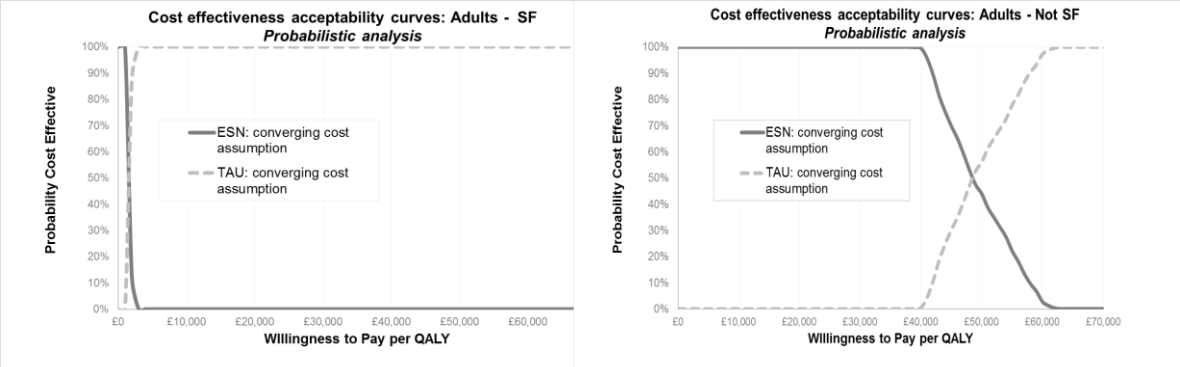


ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

Error! Reference source not found. explores the probabilistic results of the economic model, when accounting for the disease's severity. The cost effectiveness acceptability curves presented in **Error! Reference source not found.** show the proportion of model simulation points being under different cost effectiveness threshold values and indicated the probability that each treatment was cost effective at given willingness-to-pay values, for a converging cost assumption, which was suggested by the committee to be more conservative and realistic than the remaining cost assumption. Both in the case of adults and CYP with a non-severe epilepsy (SF), the ESN intervention was associated with a low probability of being cost effective (vs TAU) at threshold values less than £ 20,000 per QALY.

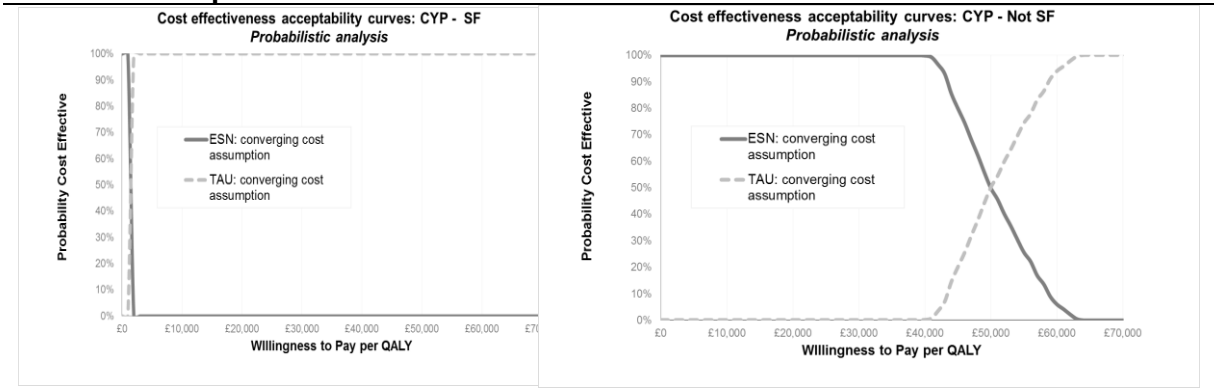
Figure 9: Cost effectiveness acceptability curves for the ESN led intervention compared with TAU at 20-year time horizon, with a 'converging' costing assumption

PART A (Adults)



PART B (CYP)

Figure 9: Cost effectiveness acceptability curves for the ESN led intervention compared with TAU at 20-year time horizon, with a 'converging' costing assumption



ESN: epilepsy specialist nurse; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year; TAU: treatment-as-usual; £: pound sterling

4. Discussions and conclusions

The primary purposes of this economic model were to update the economic evaluation carried out by Noble and colleagues (Noble 2014); by updating its cost estimates by using UK unit costs 2019; and by extending its cost effectiveness estimates to a population of CYP, beyond adults.

When considering a population of adults, our results suggest that the ICER for TAU with the ESN led intervention was below the NICE threshold of £20,000 per QALY. The findings of our simulation for CYP are similar to those estimated for adults. The committee pointed this similarity out, when discussing the evidence and drafting the recommendations.

Secondarily, starting with our base case economic scenario, we aimed to simulate costs and effectiveness data against a longer time horizon (that is 20 years); and to calculate the cost effectiveness estimates considering the epilepsy severity (that is seizure-free versus not seizure-free).

Over long-term, the analysis suggest that TAU is more effective but far more expensive than the ESN led intervention and, hence, is not cost effective – both for CYP and adults.

In other words, the intervention results in a reduction in QALYs but generates considerable cost savings, which would justify its introduction at currently accepted thresholds. The results of this economic analysis further suggest that the ESN led intervention is more likely to be cost saving in people with a severe epilepsy (this is, people with epilepsy not seizure free or with ongoing seizures) than in people who are seizure free.

Starting upon the main methodological limitations of the previous economic evidence on the role of ESNs in epilepsy' management, one major strength of the present model is that costs and effectiveness data were estimated over a longer time horizon of 20 years, considering the epilepsy severity (seizure-free or not seizure-free). Also, additionally to the previous evidence identified in the health economic review (Noble 2014, Ring 2018), the current work extends its cost effectiveness findings to a population of CYP with confirmed epilepsy.

The present analysis makes an important contribution to the existing evidence on the cost effectiveness of ESN led intervention(s) in patients with epilepsy. However, it should be interpreted in light of some limitations, which may also limit generalisability of its findings. A first limitation is that results can be biased from likely baseline differences between intervention groups, as allocation of people with epilepsy to TAU or to the ESN led intervention was

not randomised (Noble 2014). However, as noted by Noble (2014), this bias was minimised by focusing the recruitment of people with epilepsy from similar hospitals and areas, therefore reducing the likelihood of baseline differences. A second potential limitation is that the sample of people included in the present analysis was recruited from hospital emergency departments, therefore it was unlikely to be representative of the overall spectrum of people with epilepsy. In order to manage this drawback, we did a sensitivity analysis to investigate the influence of including the whole population with epilepsy, i.e. those not using hospital emergency services. The main change made to the input parameters in order to capture the whole population with epilepsy concerned the usage of healthcare services, as reported in Jacoby 1998.

Overall, the data indicated that the ESN led intervention in addition to TAU is likely to be cost effective compared with TAU alone, and that it is more likely to be cost effective when considering the overall population of people with epilepsy.

The overall economic analysis was judged as very conservative by the committee. They discussed the evidence published in the existing economic evaluations presented in the evidence review (Noble 2014, and Ring 2018), highlighting how the findings reported in these studies are consistent with those resulted with the present economic model; they recognised that these data suggest that the ESN led intervention might reduce substantially the cost of supporting people with epilepsy providing slightly worse outcomes than TAU. So, the committee agreed that from the perspective of the UK NHS and PSS, the ESN led intervention added to TAU is likely to be cost effective at a willingness-to-pay threshold of £20,000, compared to TAU alone. These findings remained when extrapolated out beyond Noble 2014 including in increasing the time horizon to 20 years, splitting the population into seizure free and not seizure free and also expanding to a population of CYP. The model did not identify any scenarios for which ESN would not be a cost effective approach suggesting the conclusions were robust to alternative assumptions. It was noted though that the positive results of the model are almost entirely driven by cost savings taken from Noble 2014. If large reductions in resource use as identified in Noble 2014 were not realised then the conclusions of the model may not hold.

In discussing the economic findings when drafting the recommendations, the committee noted some potential factors driving healthcare transformation, including fragmentation and access problems, suboptimal outcomes and relevant costs. Cost concerns along with changing epilepsy continuity of care and management created the greatest urgency for the need for change. According with the findings of the Noble's economic analysis, and based on the present economic model the committee highlighted how greater coordination of care—across providers and across settings—may improve quality care, improve outcomes, while reduce health care spending.

Based on their knowledge and supplemented by the findings of the economic model, the committee pointed out the vital role played by ESNs in epilepsy management, continuity of care and in fostering the coordination of the planning pathway of people with epilepsy across care services. Partly based on the evidence (Noble 2014) and partly based on the economic model, they agreed that people with epilepsy should have access to an ESN who they could contact between scheduled reviews and after emergency department visits. The evidence supported the committee´s experience that people with epilepsy and their families valued the approachable nature of epilepsy specialist nurses, so the recommendations reflect the need to offer information in a timely manner. The committee also acknowledged in the recommendations made, that people´s information needs may vary from time to time and more contact may be needed when seizures are ongoing or after an emergency department visit. The cost-effectiveness of ESN intervention was supported by the findings of the sensitivity, which suggested that the ESN intervention added to TAU was cost effective in both CYP and adults with epilepsy regardless of the severity. intensity or frequency of the intervention delivery, and only for people with ongoing seizures.

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Noble AJ, Goldstein LH, Seed P, Glucksman E, Ridsdale L. Characteristics of people with epilepsy who attend emergency departments: prospective study of metropolitan hospital attendees. Epilepsia. 2012;53(10):1820-8.

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1 Jacoby A, Buck D, Baker G, McNamee P, Graham-Jones S, Chadwick D. Uptake and costs
2 of care for epilepsy: findings from a U.K. regional study. Epilepsia. 1998;39(7):776-86. doi:
3 10.1111/j.1528-1157.1998.tb01164.x.

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Appendix L – Research recommendations

Research recommendations for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

No research recommendations were made for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question: What is the effectiveness of a nurse specialist in the management of epilepsy?

Clinical studies

Table 28: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
The effectiveness of the holistic nursing care model on quality of life of the epilepsy patients at tertiary epilepsy center of Thailand, Epilepsia, 60, 203-2019	Conference Paper
Adamolekun, B., Mielke, J., Ball, D., Mundanda, T., An evaluation of the management of epilepsy by primary health care nurses in Chitungwiza, Zimbabwe, Epilepsy Research, 39, 177-81, 2000	Study design does not meet the inclusion criteria - before-and-after study
Appleton, R. E., Sweeney, A., The management of epilepsy in children: The role of the clinical nurse specialist, Seizure, 4, 287-291, 1995	Narrative review
Bradley, P. M., Lindsay, B., Care delivery and self-management strategies for adults with epilepsy, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	Systematic review; included other types of interventions apart from those delivered by epilepsy nurse specialists. References checked for inclusion
Callanan, Mimi, Spencer, David C., Measuring the Value of Epilepsy Nurses, Epilepsy currents, 16, 384-385, 2016	Summary only (study summarised has already been included in NGA review)
Cote, J., Beaudet, L., Auger, P., Rouleau, G., Chicoine, G., Leger, V., Keezer, M., Reid, M. A., Nguyen, D. K., Evaluation of a web-based virtual nursing intervention to support self-management among adults with epilepsy: a mixed-methods study, Epilepsy & behavior, 2020	Intervention does not include support from a nurse specialist
Dunkley, C., Down, C., Calvin-Mwingirwa, F., David-Feveck, M., Stacey, H., Epilepsy12: Improving care for children with epilepsy, Developmental Medicine and Child Neurology, 63, 67, 2021	Conference abstract
Ek Hauge, N. C., Henning, O., Nakken, K. O., Bjorge, H., Patient satisfaction with information provided by epilepsy specialist nurses: Results of an online survey, Epilepsy and Behavior, 112 (no pagination), 2020	Cross-sectional survey
Ghosh, R., Gandhi, V., MacKinnon, L., Paediatric epilepsy and core evaluation service (PEACES): A quality improvement initiative, Archives of disease in childhood, 104, A76-A77, 2019	Conference abstract
Hansen, O. A., Harboe, L., Dossing, M. K., Kjeldsen, M. J., Beier, C. P., Safety and feasibility of an intensive epilepsy nurse-based treatment course, Seizure, 86, 35-40, 2021	Not comparative
Higgins, A., Downes, C., Varley, J., Doherty, C. P., Begley, C., Elliott, N., Supporting and empowering people with epilepsy: Contribution of the Epilepsy Specialist Nurses (SENsE study),	Study design does not meet the inclusion criteria - qualitative study

Study	Reason for Exclusion
Seizure, 71, 42-49, 2019	
Higgins, A., Downes, C., Varley, J., Tyrell, E., Normand, C., Doherty, C. P., Begley, C., Elliott, N., Patients with epilepsy care experiences: Comparison between services with and without an epilepsy specialist nurse, Epilepsy & behavior, 85, 85-94, 2018	Study design does not meet the inclusion criteria - cross-sectional study
Higgins, A., Murphy, R., Downes, C., Varley, J., Begley, C., Elliott, N., Factors influencing the implementation of Epilepsy Specialist Nurse role: Using the Consolidation Framework for Implementation Research, Journal of clinical nursing, 29, 1352-1364, 2020	Study design does not meet the inclusion criteria - qualitative study
Kengne, A. P., Fezeu, L. L., Awah, P. K., Sobngwi, E., Dongmo, S., Mbanya, J. C., Nurse-led care for epilepsy at primary level in a rural health district in Cameroon, Epilepsia, 49, 1639-1642, 2008	Does not report outcomes of interest
Locatelli, G., The multifaceted role of the Epilepsy Specialist Nurse: Literature review and survey study on patient and medical Staff Perceptions, Professioni Infermieristiche, 72, 34-41, 2019	Unavailable
Locatelli, G., Ausili, D., Stubbings, V., Di Mauro, S., Luciani, M., The epilepsy specialist nurse: A mixed-methods case study on the role and activities, Seizure, 85, 57-63, 2021	Describes activities of specialist nurses. Does not report on effectiveness of intervention
Manzanares, I., Sevilla-Guerra, S., Pena-Ceballos, J., Carreno, M., Palanca, M., Lombrana, M., Conde-Blanco, E., Centeno, M., Donaire, A., Gil-Lopez, F., Khawaja, M., Lopez Poyato, M., Zabalegui, A., THE EMERGING ROLE OF THE ADVANCED PRACTICE EPILEPSY nurse: A COMPARATIVE STUDY BETWEEN TWO COUNTRIES, Journal of clinical nursing, 2021	Describes activities of specialist nurses. Does not report on effectiveness of intervention.
Mills, N., Bachmann, M. O., Campbell, R., Hine, I., McGowan, M., Effect of a primary care based epilepsy specialist nurse service on quality of care from the patients' perspective: Results at two-years follow-up, Seizure, 8, 291-296, 1999	Study design does not meet the inclusion criteria - controlled before-and-after study
Mills, N., Bachmann, M. O., Harvey, I., Hine, I., McGowan, M., Effect of a primary-care-based epilepsy specialist nurse service on quality of care from the patients' perspective: Quasi-experimental evaluation, Seizure, 8, 1-7, 1999	Study design does not meet the inclusion criteria - controlled before-and-after study
Mills, N., Bachmann, M., Harvey, I., McGowan, M., Hine, I., Patients' experience of epilepsy and health care, Family practice, 14, 117-123, 1997	This study did not have an intervention and control group; had a cross-sectional design and assessed the effect of epilepsy on people's lives
Patel, Anup D., Terry, Debbie, Moore, Jayne Pacheco, Sale, Jacy, Wood, Eric G., Grinspan, Zachary M., Cohen, Daniel M., Reduction of emergency department visits using an urgent clinic for children with established epilepsy, Neurology. Clinical practice, 6, 480-486, 2016	Intervention does not include support from a nurse specialist
Ridsdale, L., Kwan, I., Cryer, C., The effect of a special nurse on patients' knowledge of epilepsy and their emotional state. Epilepsy Evaluation Care Group, British Journal of General Practice,	Relevant outcomes overlap with those reported in Ridsdale 2000

Study	Reason for Exclusion
49, 285-9, 1999	
Ridsdale, L., Morgan, M., O'Connor, C., Promoting self-care in epilepsy: the views of patients on the advice they had received from specialists, family doctors and an epilepsy nurse, Patient Education & Counseling, 37, 43-7, 1999	Study design does not meet the inclusion criteria – qualitative
Ridsdale, L., Robins, D., Cryer, C., Williams, H., Feasibility and effects of nurse run clinics for patients with epilepsy in general practice: Randomised controlled trial, British Medical Journal, 314, 120-122, 1997	No relevant outcomes were reported
Ridsdale, L., Robins, D., Fitzgerald, A., Jeffery, S., McGee, L., Close, J., Free, A., Hart, Y., Hughes, C., Ogden, J., Orme-Smith, A., Stott, P., Story, N., Epilepsy monitoring and advice recorded: General practitioners' views, current practice and patients' preferences, British journal of general practice, 46, 11-14, 1996	No interventions were assessed
Sarkissian, S., Wennberg, R., Effects of the acute care nurse practitioner role on epilepsy monitoring outcomes, Outcomes management for nursing practice, 3, 161-166, 1999	Study design does not meet inclusion criteria - controlled before-and-after study
Scambler, A., Scambler, G., Ridsdale, L., Robins, D., Towards an evaluation of the effectiveness of an epilepsy nurse in primary care, Seizure, 5, 255-258, 1996	No relevant outcomes were reported
Schull, D. E., Tosch, P., Wood, M., Clinical nurse specialists as collaborative care managers, Nursing management, 23, 30-33, 1992	Does not report outcomes of interest
Stephen, L. J., Maxwell, J., Brodie, M. J., Outcomes from a nurse-led clinic for adolescents with epilepsy, Seizure, 12, 539-544, 2003	Single-arm study; the intervention was not compared with a control group

Economic studies

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