3-year scoping report

Topic: Diagnosis and management of epilepsy in adults: SIGN 143 (2015)

Date of search: November 2018 (conducted by Carolyn Sleith, Evidence and Information Scientist)
Report prepared by: Julie Calvert, Health Services Researcher and Moray Nairn, Programme Manager

Background
The purpose of this scoping is to identify any information that may be relevant to the key questions or recommendations of the guideline on the diagnosis and management of epilepsy in adults (SIGN 143).

A rapid high-level search of the literature was conducted using a predefined list of resources. The search focused on secondary sources of evidence (health technology assessments, evidence-based guidelines, systematic reviews and meta-analyses) and was limited to evidence published, in English language, since 2013.

The results of the evidence review in section 2 are based mainly on information contained within the executive summaries or abstracts of the evidence identified. A comprehensive assessment and critical analysis of the evidence was not carried out.
The results of the review were discussed by Dr Moray Nairn, Programme Manager, SIGN, and Professor Martin Brodie, Chair of the guideline development group for SIGN 143: diagnosis and management of epilepsy in adults, to identify the priorities for review listed in section 1. The review and proposed updates were circulated to the original guideline development group for comment (see section 3).

Conclusion
While there is limited evidence for minor revisions to SIGN 143, none of these are judged to be essential. Clinical expert opinion suggests that, even where there is supporting evidence, revision of the recommendation may not be warranted.

Decision
The Guideline Programme Advisory Group considered the evidence and the feedback at a meeting on 29 May 2019. The group concluded that no evidence had been identified that would significantly change the key recommendations. The guideline is revalidated and will be considered for update again in 2023.

Section 1: Proposed action from the scoping summary

Guideline section	Details of update	Suggested priority (Desirable or Essential)
Section 4.2.3 **(AED – choice of formulation)**	The BMJ Best Practice; Generalised Seizures, 2018. '…for some women with epilepsy in whom it may not be possible to stop valproate, treatment may be continued during pregnancy with appropriate specialist care'. SIGN should consider adding 'with appropriate specialist care' to the valproate good practice point and consider referral to MHRA PPP and the Annual Risk Acknowledgment Form.	Desirable
Section 4.3.1 **(Drug-resistant focal epilepsy)**	Lattanzi et al 2016 – 'In adults with drug-refractory focal epilepsy, add-on brivaracetam was effective to reduce seizure frequency and fairly well tolerated. Further studies are needed to draw definitive conclusions about its efficacy in non-levetiracetam-naive participants and evaluate its long-term safety profile.' Brivaracetam is only approved for adjunctive therapy by SMC and not mentioned in SIGN 143. SIGN should consider brivaracetam as an option with recommended antiepileptic drugs (AEDs) for adjunctive treatment of drug-resistant focal epilepsy.	Desirable
Section 4.3.1 **(Drug-resistant focal epilepsy)**	Betts et al.2015 – 'Compared to other AEDs recently approved for adjunctive treatment of partial-onset seizures, eslicarbazepine acetate 1,200 mg had the highest overall efficacy and lowest number needed to treat (NNT) among the high-dose formulations, while eslicarbazepine acetate 800 mg had the second highest overall efficacy, and the second lowest NNT among the low-dose formulations.' SIGN 143 does not list eslicarbazepine acetate as an adjunctive therapy. SIGN should consider eslicarbazepine acetate as an option with recommended AEDs for adjunctive treatment of drug-resistant focal epilepsy.	Desirable

Section 4.9.1 (Vagus nerve stimulation)	Panebianco et al. 2015 - The surveillance report described a Cochrane review of 5 RCTs (439 participants) on vagus nerve stimulation (VNS) and seizures in adults and children with drug-resistant partial seizures or those who are not eligible for surgery or who have failed surgery. Results showed VNS was effective and well tolerated. VNS stimulation using the high-stimulation paradigm was better than low stimulation for reducing seizure frequency. However, evidence was limited and of moderate to low quality. The review authors note that further research is required in this area. SIGN should consider whether evidence supports inclusion of high- and low-stimulation paradigms.	Desirable
Section 4.10 (Management of prolonged seizures, including status epilepticus)	Prasad et al. 2014 – 'Intravenous (IV) lorazepam is better than IV diazepam or IV phenytoin alone for risk of non-cessation of seizures. The risk of continuation of *status epilepticus* requiring a different drug or general anaesthesia was lower with IV lorazepam than IV diazepam, but both IV lorazepam and diazepam were better than placebo for these outcomes'. This confirms the SIGN recommendation that lorazepam should be given if midazolam is unavailable, however suggests that lorazepam and diazepam may not have equivalent effectiveness. SIGN should consider whether recommendation requires rewording. (Clinical expert view is that this does not justify rewording of recommendation, see section 3)	Desirable
Section 5.1.2 (Emergency contraception)	Epilepsy in Pregnancy. Royal College of Obstetricians and Gynaecologists, 2016 – 'For emergency contraception for women with epilepsy taking enzyme-inducing AEDs, only the copper IUD is recommended. It is unclear whether a higher dose of levonorgestrel or ulipristal acetate is a sufficiently effective strategy. A double dose of levonorgestrel (3 mg as a single dose within 120 hours of unprotected sexual intercourse) may be used pragmatically. Ulipristal acetate should not be used.' SIGN should consider the importance placed on the IUD as an emergency contraception method.	Desirable
Section 5.4.3 (Pregnancy	Epilepsy in Pregnancy. Royal College of Obstetricians and Gynaecologists, 2016 – 'In women with epilepsy taking enzyme-inducing AEDs who are at risk of preterm delivery, doubling of the antenatal corticosteroid dose for prophylaxis against respiratory distress	Desirable

complications)	syndrome in the newborn is not recommended. Women with epilepsy taking enzyme-inducing AEDs, such as phenytoin, carbamazepine and phenobarbital, may increase their metabolism of corticosteroids, with reduced therapeutic effectiveness. No studies have assessed the effectiveness of higher or frequent doses of corticosteroids on neonatal outcomes in women with epilepsy exposed to enzyme-inducing AEDs and at risk of preterm delivery. In the absence of evidence of benefit with increased dose of steroids, and the potential harm with high steroid doses, routine doubling of steroid is not recommended.' This guideline conflicts with the SIGN recommendation for pregnant women with epilepsy taking enzyme-inducing AEDs to receive double the standard dose of betamethasone/dexamethasone (48 mg over 12–24 hours). One guideline group member queried this (see section 3). As both guidelines note that enzyme-inducing AEDs increase the metabolism of corticosteroids, the conflict is predicated on the actions advised to mitigate this effect. SIGN recommends steroid dosage increase, while RCOG note a lack of evidence of benefit or safety of this approach. Consider the impact of this advice on the current recommendation to double the standard dose (Clinical expert view is that this does not justify rewording of recommendation, see section 3)	
Section 5.6.3 **(Risks to the fetus associated with AED monotherapy)**	Weston et al. 2016 – A Cochrane review of prospective cohort controlled studies, cohort studies within pregnancy registries and RCTs reported no increased risk for major malformation with lamotrigine. Veroniki et al. 2017 – 'Lamotrigine and levetiracetam, were not associated with significant increased risks of congenital malformations compared to control, and were significantly less likely to be associated with children experiencing cardiac malformations than control.' While most statements in this Cochrane review support the statements in the guideline, the finding of "no increased risk associated with lamotrigine" differs from Table 4 in the guideline which notes absolute risk of major congenital malformation in those using lamotrigine ranging from 1.9% to 5.4%. SIGN should consider this new evidence. (Clinical expert view is that this does not justify rewording of recommendation, see section 3)	Desirable

Section 3.2.4 **(The relevance of classification in clinical practice)**	Fisher et al. 2017 and Scheffer et al 2017 SIGN should consider an updated reference to the 2017 ILAE classification with any new clinically-relevant changes.	Desirable

Additional evidence suggested for inclusion by Professor Martin Brodie: None

Section 2: Summary of evidence by key questions

Topic: Diagnosis and management of epilepsy in adults: SIGN 143 (2015)
Date of search: November 2018
Prepared by: Carolyn Sleith (search), Julie Calvert and Moray Nairn (evidence selection and report writing)

KQ 3: In adults with newly diagnosed epilepsy are levetiracetam and zonisamide monotherapies more effective and well tolerated than existing AEDs at reducing seizure frequency, seizure duration, and adverse effects, and improving recovery time and QoL?

Reference and study type	Information likely to be relevant	Impact on guideline
Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Kaner et al. 2018 Neurology 91 (2) pg 74-81	Lamotrigine (LTG) should (Level B) and levetiracetam (LEV) and zonisamide (ZNS) may (Level C) be considered in decreasing seizure frequency in adults with new-onset focal epilepsy. LTG should (Level B) and gabapentin (GBP) may (Level C) be considered in decreasing seizure frequency in patients ≥60 years of age with new-onset focal epilepsy. No high-quality studies suggest clobazam, eslicarbazepine, ezogabine, felbamate, GBP, lacosamide, LEV, LTG, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or ZNS is effective in treating new-onset epilepsy because no high-quality studies exist in adults of various ages'.	Section 4.2.3 SIGN recommendation: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. <u>There are no differences in recommendations so no impact on guideline</u>
Efficacy and Tolerability of Antiepileptic Drugs in Patients with Focal Epilepsy: Systematic Review and Network Meta-analyses. Campos et al.	The authors examined the relative tolerability of all available AEDs for monotherapy of all types of epilepsy as well as their efficacy in the monotherapy of focal epilepsy. (65 studies, 16,025 patients). Clobazam, levetiracetam, lamotrigine, oxcarbazepine, sulthiame, topiramate, and valproate had the best efficacy profiles and	Section 4.2.3 SIGN recommendation: In patients with focal onset seizures, lamotrigine is the drug of choice. When lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable

Reference and study type	Information likely to be relevant	Impact on guideline
Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 2016 36 (12) 1255-1271	demonstrated no evidence of superiority or inferiority compared with CBZ. However, CBZ showed the greatest risk of patient discontinuation due to intolerable adverse reactions, whereas lamotrigine had the best safety profile and an 81% probability of being the best for the tolerability outcome of patient withdrawals from the study due to intolerable adverse reactions, followed by sulthiame (60%) and clobazam (51%). The newer AEDs (levetiracetam, lamotrigine, oxcarbazepine, sulthiame, and topiramate) should be considered for monotherapy of focal epilepsy because they were demonstrated to be as effective as the older ones (CBZ, clobazam, and valproate) for the treatment of focal epilepsy and were more tolerable. Lamotrigine was the AED with the best tolerability profile, suggesting that it may be the best option for the treatment of focal epilepsy in children and adults'.	alternatives. No impact on guideline
NICE surveillance 2018 reported: Nevitt, 2017 (Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data)	The surveillance report described a Cochrane review incorporating an individual patient data network meta-analysis (12,391 of 17,961 eligible patients from 36 of 77 RCTs) of AEDs used in monotherapy in children and adults with partial onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus) (5 of the 29 studies included were in children). The review looked at withdrawal of allocated treatment, remission and first seizure of 10 AEDs: carbamazepine, phenytoin, sodium valproate, phenobarbitone, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, zonisamide Partial onset seizures: For the primary outcome of time to withdrawal of allocated treatment, levetiracetam performed significantly better than carbamazepine. Lamotrigine performed better than all other treatments (aside from levetiracetam) and carbamazepine performed significantly better than gabapentin and phenobarbitone (high-quality evidence).	Section 4.2.3 SIGN recommendation: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. Clinical expert view (see section 3) is that this does not impact on SIGN recommendations. Further trial evidence (SANAD2) may be forthcoming in 2021. Section 4.2.3 SIGN recommendation: In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective

Reference and study type	Information likely to be relevant	Impact on guideline
	Generalised tonic-clonic seizures: sodium valproate performed significantly better than carbamazepine, topiramate and phenobarbitone (moderate- to high-quality evidence). For both partial and generalised onset seizures, phenobarbitone seems to perform worse than all other treatments (moderate- to high-quality evidence). For secondary outcomes of time to 12-month remission of seizures and time to six-month remission of seizures, the network meta-analysis showed few notable differences either partial or generalised seizure types (moderate- to high-quality evidence).	antiepileptic drug. <u>No impact on guideline</u>
NICE surveillance, 2018 reported: Nevitt, 2017 (Carbamazepine versus phenytoin monotherapy for epilepsy: an individual participant data review)	The surveillance report described a Cochrane individual patient data meta-analysis (595 of 1,192 eligible patients from 4 RCTs) on carbamazepine versus phenytoin in patients with partial onset or generalised onset tonic-clonic seizures. They found no significant differences between carbamazepine and phenytoin and there were more adverse events for phenytoin than for carbamazepine. Note: The studies included in this review are included in the Nevitt, 2017 review of 10 AEDs.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. <u>No impact on guideline</u>
NICE surveillance, 2018 reported: Nevitt, 2016 (Topiramate versus carbamazepine monotherapy for epilepsy: an individual participant	The surveillance report described a Cochrane review incorporating an individual patient data meta-analysis (1,151 of 1,239 eligible patients from 2 of 3 RCTs) on topiramate compared to carbamazepine in patients with partial onset or generalised onset tonic-clonic seizures. RCTs included both children and adults.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives.

Reference and study type	Information likely to be relevant	Impact on guideline
data review)	The primary outcome was time to withdrawal of allocated treatment, and secondary outcomes were time to first seizure post randomisation, time to 6-month remission, time to 12-month remission and incidence of adverse events. For partial seizures, carbamazepine was less likely to be withdrawn and the 12 month remission was achieved earlier, than with topiramate. Evidence showed no difference between carbamazepine and topiramate in patients with generalised onset tonic-clonic seizures, but there was only a limited number of patients in this group. Note: The studies included in this review are included in the Nevitt, 2017 review of 10 AEDs.	In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. <u>No impact on guideline</u>
NICE surveillance, 2018 reported: Nevitt, 2016 (Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review)	The surveillance report described a Cochrane review incorporating an individual patient data meta-analysis (2,572 of 3,394 eligible patients from 9 of 14 trials) on lamotrigine monotherapy compared to carbamazepine in patients with partial onset or generalised onset tonic-clonic seizures. 7 of the 14 studies were in children. For partial seizures, lamotrigine was less likely to be withdrawn than carbamazepine but the authors report that carbamazepine may be superior in terms of seizure control. Carbamazepine was superior at 6 months, but there was no difference at 12 months or 24 months and only 2 trials followed participants for more than one year. As data is limited, more long-term data is required. Note: The studies included in this review were included in the Nevitt, 2017 review of 10 AEDs.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. <u>No impact on guideline</u>
NICE surveillance, 2018 reported:	The surveillance report described a Cochrane review of IPD (836 of 1,455 eligible patients from 6 of 13 trials) which evaluated	Section 4.2.3 SIGN recommendations:

Reference and study type	Information likely to be relevant	Impact on guideline
Nevitt, 2016 (Carbamazepine versus phenobarbitone monotherapy for epilepsy: an individual participant data review)	phenobarbitone compared to carbamazepine in patients with partial onset or generalised onset tonic-clonic seizures. Carbamazepine may be more effective (seizure control and adverse events) than phenobarbitone. For time to first seizure recurrence, phenobarbitone was superior for partial seizures and carbamazepine for generalised seizures. Evidence was low quality. Note: All but one of the studies included in this review were included in the Nevitt, 2017 review of 10 AEDs.	In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. Phenobarbitone is not currently recommended. Clincial expert view (see section 3) is that given rarity of phenobarbital as a new adjunct this has no impact on SIGN recommendations.
NICE surveillance, 2018 reported: Nevitt, 2018 (Oxcarbazepine versus phenytoin monotherapy for epilepsy: an individual participant data review)	The surveillance report described a Cochrane review of individual patient data (480 of 517 eligible patients in 2/3 trials, one study included adults, the other children) compared oxcarbazepine and phenytoin monotherapy in patients with partial onset or generalised onset tonic-clonic seizures. Treatment failure due to adverse events occurred significantly later with oxcarbazepine than phenytoin. There were no other differences between the drugs. Note: The studies included in this review were included in the Nevitt, 2017 review of 10 AEDs.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. No impact on guideline
NICE surveillance, 2018 reported: Nolan, 2016 (Phenytoin	The surveillance report described a Cochrane review of individual patient data (669 of 1,119 eligible patients from 5 of 14 trials) on phenytoin compared to valproate in patients with partial onset or generalised onset tonic-clonic seizures.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where

Reference and study type	Information likely to be relevant	Impact on guideline
versus valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures: an individual participant data review)	There were no differences between the drugs for outcomes measured. However, the authors noted that misclassification of seizure type may have confounded the results of this review.	lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. Phenytoin is not currently listed as a monotherapy choice. No impact on guideline / clinical expert view notes that other difficulties with phenytoin preclude use as first line in this setting.
NICE surveillance, 2018 reported: Nolan, 2013 (Phenobarbitone versus phenytoin monotherapy for epilepsy)	The surveillance report described a Cochrane review of individual participant data (599 of 1,119 eligible patients from 4 of 8 trials) on phenobarbitone versus phenytoin in patients with partial onset or generalised onset tonic-clonic seizures. There was no differences in seizure outcomes between the two drugs. There was a clinical advantage for phenytoin for treatment withdrawal. There were no differences between the drugs for outcomes measured.	Section 4.2.3 SIGN recommendations: In patients with focal onset seizures, lamotrigine is the drug of choice. Where lamotrigine is poorly tolerated, carbamazepine and levetiracetam may be reasonable alternatives. In genetic generalised epilepsy or unclassified epilepsy, sodium valproate is the most effective antiepileptic drug. Phenobarbitone not currently recommended. No impact on guideline
The BMJ Best Practice; Generalised Seizures, 2018 paper reported:	Although, the BMJ report that eslicarbazepine acetate was approved for monotherapy in adults, the SMC notes that eslicarbazepine acetate (Zebinix ®) is not recommended for use	The SIGN guideline addresses eslicarbazepine acetate only as an adjunctive therapy and it is not included in the list of recommended drugs.

Reference and study type	Information likely to be relevant	Impact on guideline
Willems et al. 2018 (Eslicarbazepine acetate in epilepsies with focal and secondary generalised seizures: systematic review of current evidence) Sperling et al. 2015 (Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a randomized historical control phase III study based in North America) Jacobson et al. 2015 (Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a historical-control phase III study)	within NHSScotland. https://www.scottishmedicines.org.uk/medicines-advice/eslicarbazepine-acetate-zebinix-non-sub-smc2090/	No impact on guideline
The BMJ Best Practice; Generalised Seizures, 2018 paper reported: Wechsler et al. 2014 (Conversion to lacosamide	Although, the BMJ report that lacosamide was recently approved for monotherapy in adults, SMC states that lacosamide (Vimpat®) is not recommended for use within NHS Scotland as monotherapy. (https://www.scottishmedicines.org.uk/medicines-advice/lacosamide-vimpat-non-submission-132418/) March 2018	The SIGN guideline addresses lacosamide only as an therapy No impact on guideline

Reference and study type	Information likely to be relevant	Impact on guideline
monotherapy in the treatment of focal epilepsy: results from a historical-controlled, multicenter, double-blind study) Giráldez et al. 2-15 (Long-term efficacy and safety of lacosamide monotherapy in the treatment of partial-onset seizures: A multicenter evaluation)		
The BMJ Best Practice; Generalised Seizures, 2018 paper reported: French et al. 2015 (Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy: a randomized trial) Krauss et al. 2014 (Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307)	Perampanel has shown efficacy as monotherapy for both generalised-onset and secondary generalised seizures however, SMC has not considered perampanel as monotherapy.	The SIGN guideline addresses perampanel only as an adjunctive therapy <u>No impact on guideline</u>

KQ 5: Once monotherapy has failed what adjunctive drugs (eslicarbazepine acetate, lacosamide, pregabalin, retigabine, rufinamide, perampanel) are most effective and well tolerated compared to existing add-on therapies or to placebo?

Reference and study type	Information likely to be relevant	Impact on guideline
NICE surveillance 2018 reported: Biton et al. 2015 (Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials)	The surveillance report described a Cochrane review of 3 RCTs (1,308 participants) on the safety and tolerability of lacosamide as an add-on treatment for drug-resistant partial epilepsy. The most common adverse events were dizziness (30.6% for lacosamide *v* 8.2% for placebo), nausea (11.4% *vs*4.4%), and diplopia (10.5% *v* 1.9%). Adverse events led to discontinuation in 8.1%, 17.2%, and 28.6% of the lacosamide 200-, 400-, and 600-mg/day groups, respectively (*v* 4.9% of placebo). Discontinuations due to adverse events based on most commonly used AEDs taken in combination with lacosamide (all doses combined) were carbamazepine (15.3% [51/334] *v* 3.9% [5/129] placebo), lamotrigine (19.2% [56/291] *v* 4.3% [5/117]), and levetiracetam (10.1% [28/278] *v* 3.9% [4/103]).	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy No impact on guideline
NICE surveillance 2018 reported: Weston et al. 2015 (Lacosamide add-on therapy for partial epilepsy)	The surveillance report described a Cochrane review of 3 RCTs (1,311 participants) on the efficacy and tolerability of lacosamide as an add-on treatment for drug-resistant partial epilepsy. Lacosamide was effective and well tolerated in the short term compared to placebo. Higher doses produced more adverse effects and withdrawal compared with lower doses.	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy No impact on guideline
NICE surveillance 2018 reported: Chang et al. 2017	The surveillance report described a Cochrane review of 5 RCTs (1,799 participants) on the efficacy and tolerability of eslicarbazepine acetate as an add-on treatment for drug-resistant partial epilepsy.	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine,

Reference and study type	Information likely to be relevant	Impact on guideline
(Eslicarbazepine acetate add-on for drug-resistant partial epilepsy)	Eslicarbazepine acetate reduced seizure frequency in the short term compared to placebo but was associated with adverse effects.	perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy <u>No impact on guideline</u>
Brivaracetam add-on for refractory focal epilepsy: A systematic review and meta-analysis Lattanzi et al. 2016. Neurology 86 (14) 1344-52	OBJECTIVE: To evaluate the efficacy and safety of the new antiepileptic drug brivaracetam (BRV) as add-on treatment for drug-resistant partial epilepsy using meta-analytical techniques. METHODS: Randomized, placebo-controlled, single- or double-blind, add-on trials of BRV in adult patients with drug-resistant partial epilepsy were identified through a systematic literature search. The following outcomes were assessed: 50% or greater reduction in seizure frequency, seizure freedom, incidence of treatment-emergent adverse events (TEAEs), and treatment withdrawal. Risk ratio (RR) with 95% confidence interval was estimated for each outcome. RESULTS: Six trials were included involving 2,399 participants according to the intent-to-treat, 1,715 for BRV, and 684 for placebo groups, respectively. The pooled RRs for the 50% responders and seizure freedom were 1.79 (1.51-2.12) and 4.74 (2.00-11.25), respectively. The subanalysis by levetiracetam (LEV) status did not show a statistically significant difference in the 50% responder rate when comparing BRV with placebo in patients with concomitant assumption of LEV. The TEAEs significantly associated with BRV were irritability (2.99 [1.28-6.97]), fatigue (2.19 [1.44-3.33]), somnolence (1.97 [1.45-2.68]), and dizziness (1.66 [1.19-2.31]). The overall RRs for treatment withdrawal due to TEAEs or any reason were 1.58 (1.04-2.40) and 1.27 (0.93-1.73), respectively. CONCLUSIONS: In adults with drug-refractory focal epilepsy, add-on BRV was effective to reduce seizure frequency and fairly well-tolerated. Further studies are needed to draw definitive	Brivaracetam is only approved for adjunctive therapy by SMC and not mentioned in SIGN guideline. <u>May wish to consider listing as adjunctive therapy</u>

Reference and study type	Information likely to be relevant	Impact on guideline
	conclusions about its efficacy in non-LEV-naive participants and evaluate its long-term safety profile. MHRA include brivaracetam in their list of drugs for epilepsy MHRA include brivaracetam (https://www.gov.uk/drug-safety-update/antiepileptic-drugs-updated-advice-on-switching-between-different-manufacturers-products) Brivaracetam has FDA approval for monotherapy or adjunctive therapy for focal seizures (https://www.biospace.com/article/releases/ucb-announces-briviact-brivaracetam-now-approved-by-fda-to-treat-partial-onset-focal-seizures-in-pediatric-epilepsy-patients/)	
Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. Kanner et al. 2018 Neurology 91 (82-90)	Aim: To update the 2004 American Academy of Neurology guideline for managing treatment-resistant (TR) epilepsy with second- and third-generation antiepileptic drugs (AEDs). Results Forty-two articles were included. Recommendations The following are established as effective to reduce seizure frequency (Level A): immediate-release pregabalin and perampanel for TR adult focal epilepsy (TRAFE); vigabatrin for TRAFE (not first-line treatment); rufinamide for Lennox-Gastaut syndrome (LGS) (add-on therapy). The following should be considered to decrease seizure frequency (Level B): lacosamide, eslicarbazepine, and extended-release topiramate for TRAFE (ezogabine production discontinued); immediate- and extended-release lamotrigine for generalized epilepsy with TR generalized tonic-clonic (GTC) seizures in adults; levetiracetam (add-on therapy) for TR childhood focal epilepsy (TRCFE) (1 month–16 years), TR GTC seizures, and TR juvenile myoclonic epilepsy; clobazam for LGS (add-on therapy); zonisamide for TRCFE (6–17 years); oxcarbazepine for TRCFE (1 month–4 years). The text presents Level C recommendations. AED selection depends on seizure/syndrome type, patient age,	Section 4.3.2 SIGN recommendations: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy. Lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy. No impact on guideline

Reference and study type	Information likely to be relevant	Impact on guideline
	concomitant medications, and AED tolerability, safety, and efficacy. This evidence-based assessment informs AED prescription guidelines for TR epilepsy and indicates seizure types and syndromes needing more evidence.	
A systematic review and network meta-analysis of eslicarbazepine acetate and other recently-approved anti-epileptic drugs for adjunctive treatment of partial-onset seizures in adults. Betts et al.2015 Epilepsy Currents 1 pg 161	The objective of this review was to compare the relative effectiveness of eslicarbazepine acetate (ESL) to that of recently-approved anti-epileptic drugs (AEDs) for adjunctive treatment of partial-onset seizures (POS) in adults. Results: Fourteen studies met inclusion/exclusion criteria (3 each for ESL, lacosamide (LAC), ezogabine (EZO), and perampanel (PMP); one each for oxcarbazepine extended-release (OXC) and levetiracetam extended-release (LEV)). The estimated R50 for the high-dose formulations were 41.8% for ESL 1200 mg, 39.3% for EZO 1200 mg, 38.8% for LAC 400 mg, 37.1% for PMP 12 mg, 33.9% for LEV 1,000 mg, and 32.6% for OXC 2400 mg (see table). Among the low-dose formulations, the R50 were 35.2% for EZO 600 mg, 33.2% for ESL 800 mg, 32.3% for PMP 4 mg, 31.6% for LAC 200 mg, and 28.5% for OXC 1200 mg. The NNTs for the high doses were: 4.9 for ESL 1200 mg, 5.5 for EZO 1,200 mg, 5.7 for LAC 400 mg, 6.3 for PMP 12 mg, 7.9 for LEV 1,000 mg, and 8.8 for OXC 2,400 mg. The NNTs for the low doses were: 7.1 for EZO 600 mg, 8.3 for ESL 800 mg, 9.0 for PMP 4 mg, 9.6 for LAC 200 mg, and 13.7 for OXC 1,200 mg. Conclusions: This network meta-analysis found that higher medication doses were associated with increased efficacy, compared to lower doses. Compared to other AEDs recently approved for adjunctive treatment of partial-onset seizures, ESL 1200 mg had the highest overall efficacy and lowest NNT among the high dose formulations, while ESL 800 mg had the second	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy. SIGN do not list eslicarbazepine acetate as an adjunctive therapy. <u>May wish to consider as an adjunctive therapy</u>

Reference and study type	Information likely to be relevant	Impact on guideline
	highest overall efficacy, and the second-lowest NNT among the low-dose formulations.	
NICE surveillance 2018 reported: Al-Bachari et al. 2013 (Gabapentin add-on for drug-resistant partial epilepsy)	The surveillance report described a Cochrane review of 11 RCTs (2,125 participants) on the efficacy and tolerability of gabapentin as an add-on treatment for drug-resistant partial epilepsy. A meta-analysis using data from 6 of these (1,206 participants) showed a significant reduction in seizure frequency (compared to placebo) and increased efficacy with increased dose. It was associated with significantly more adverse effects.	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy <u>No impact on guideline</u>
NICE surveillance 2018 reported: Ramaratnam et al. 2016 (Lamotrigine add-on for drug-resistant partial epilepsy)	The surveillance report described a Cochrane review of 14 RCTs (1,958 participants) on the effectiveness of lamotrigine as an add-on treatment for refractory partial epilepsy. Lamotrigine reduced seizure frequency (compared to placebo) and was fairly well tolerated.	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy This was an update of a 2010 Cochrane review with no new studies so this doesn't provide new evidence. <u>No impact on guideline</u>
NICE surveillance 2018 reported: Pulman et al. 2014 (Pregabalin add-on for drug-resistant partial	The surveillance report described a Cochrane review of 6 RCTs (2,009 participants) on the efficacy and tolerability of pregabalin as an add-on treatment for drug-resistant partial epilepsy. Pregabalin was significantly more effective than placebo at reducing seizure frequency (by 50% or more) and increased	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the

Reference and study type	Information likely to be relevant	Impact on guideline
epilepsy)	seizure freedom.	adjunctive treatment of focal epilepsy No impact on guideline
NICE surveillance 2018 reported: Pulman et al. 2014 (Topiramate add-on for drug-resistant partial epilepsy)	The surveillance report described a Cochrane review of 11 RCTs (1,401 participants) on the effectiveness of topiramate as an add-on treatment for drug-resistant partial epilepsy. Topiramate reduced seizure frequency (compared to placebo) in the short term but was associated with significantly more side effects.	Section 4.3.2 SIGN recommendation: Carbamazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, sodium valproate and zonisamide may be used in the adjunctive treatment of focal epilepsy No impact on guideline

KQ 8: In adults with drug resistant epilepsy is VNS or DBS more effective than current treatment or placebo for reducing seizure frequency, seizure duration and adverse effects and improving recovery and QoL?

Reference and study type	Information likely to be relevant	Relevance to guideline
NICE surveillance 2018 reported: Panebianco et al. 2015 (Vagus nerve stimulation for partial seizures)	The surveillance report described a Cochrane review of 5 RCTs (439 participants) on VNS and seizures in adults and children with drug-resistant partial seizures or those who are not eligible for surgery or who have failed surgery. Results showed VNS was effective and well tolerated. VNS stimulation using the high stimulation paradigm was better than low stimulation for reducing seizure frequency. However, NICE note that evidence was limited and of moderate to low quality. The review authors note that further research is required in this area.	Section 4.9.1 SIGN recommendation: Vagus nerve stimulation may be considered in adult patients who have been found to be unsuitable for resective surgery May wish to consider adding detail of high/low stimulation
BMJ Best Practice: Generalised seizures 2018 reported:	The responsive neurostimulation (RNS) system is a seizure detection device for refractory patients with one to two unresectable foci.	May wish to consider including RNS

Reference and study type	Information likely to be relevant	Relevance to guideline
Jobst BC, Kapur R, Barkley GL, et al. 2017 (Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas) Geller et al. 2017 (Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy)		

KQ 9: In adult patients with status epilepticus what is the best drug regime for stopping seizures?

Reference and study type	Information likely to be relevant	Relevance to guideline
NICE surveillance 2018 reported: Prasad et al. 2014 (Anticonvulsant therapy for staus epilepticus)	The surveillance report described a Cochrane review of 18 RCTs (2,755 participants) which looked at the effectiveness and safety of drugs for status epilepticus. 'Intravenous (IV) lorazepam is better than IV diazepam or IV phenytoin alone for risk of non-cessation of seizures. The risk of continuation of status epilepticus requiring a different drug or general anaesthesia was lower with IV lorazepam than IV diazepam, but both IV lorazepam and diazepam were better than placebo for these outcomes. Although IV lorazepam was better than IV phenytoin for reducing risk of noncessation of seizures, it was not clear whether IV valproate had any benefit over IV	Section 4.10.1 SIGN recommendation: Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given: • midazolam 10 mg buccally or intranasally, or • lorazepam 4 mg IV if midazolam is unavailable, or • diazepam 10 mg if midazolam and lorazepam are unavailable.

Reference and study type	Information likely to be relevant	Relevance to guideline
	phenytoin. For pre hospital management, midazolam IM appeared more effective than lorazepam IV for control of seizures, frequency of hospitalisation and ICU admissions. However the Cochrane authors noted 'it was unclear whether the risk of recurrence of seizures differed between treatments'. Because of the low numbers of studies and participants in each comparison, differences in adverse effects between anticonvulsants are unclear. The quality of included studies was acceptable but risk of bias could not be determined because of incomplete and selective reporting of data in the individual studies'.	Section 4.10.4 SIGN Good practice point Patients with non-convulsive status epilepticus should be managed as follows: • maintain or reinstate usual oral antiepileptic drug treatment • consider benzodiazepine treatment (midazolam 10 mg buccally or intranasally, lorazepam 4 mg IV, or diazepam 10 mg IV) • refer for specialist advice. This confirms the SIGN recommendation that lorazepam should be given if midazolam is unavailable, however suggests that lorazepam and diazepam may not have equivalent effectiveness. <u>May wish to consider</u>
Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society Epilepsy Curr Glauser et al. 2016. 16 (1) 48-61	'OBJECTIVE: To analyze efficacy, tolerability and safety data for anticonvulsant treatment of children and adults with convulsive status epilepticus RESULTS: A total of 38 randomized controlled trials were identified, rated and contributed to the assessment. Only four trials were considered to have class I evidence of efficacy. Two studies were rated as class II and the remaining 32 were judged to have class III evidence. In adults with convulsive status epilepticus, intramuscular midazolam, intravenous lorazepam, intravenous diazepam and intravenous phenobarbital are established as efficacious as initial therapy (Level A). Intramuscular midazolam has superior effectiveness compared to	Section 4.10.1 SIGN recommendation: Patients with prolonged tonic-clonic seizures that have lasted five minutes or more should be given: • midazolam 10 mg buccally or intranasally, or • lorazepam 4 mg IV if midazolam is unavailable, or • diazepam 10 mg if midazolam and lorazepam are unavailable.

Reference and study type	Information likely to be relevant	Relevance to guideline
	intravenous lorazepam in adults with convulsive status epilepticus without established intravenous access (Level A). In children, intravenous lorazepam and intravenous diazepam are established as efficacious at stopping seizures lasting at least 5 minutes (Level A) while rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam are probably effective (Level B). No significant difference in effectiveness has been demonstrated between intravenous lorazepam and intravenous diazepam in adults or children with convulsive status epilepticus (Level A). Respiratory and cardiac symptoms are the most commonly encountered treatment-emergent adverse events associated with intravenous anticonvulsant drug administration in adults with convulsive status epilepticus (Level A). The rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convulsive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus (Level A). When both are available, fosphenytoin is preferred over phenytoin based on tolerability but phenytoin is an acceptable alternative (Level A). In adults, compared to the first therapy, the second therapy is less effective while the third therapy is substantially less effective (Level A). In children, the second therapy appears less effective and there are no data about third therapy efficacy (Level C). The evidence was synthesized into a treatment algorithm. CONCLUSIONS: Despite the paucity of well-designed randomized controlled trials, practical conclusions and an integrated treatment algorithm for the treatment of convulsive status epilepticus across the age spectrum (infants through adults) can be constructed. Multicenter, multinational efforts are needed to design, conduct and analyze additional randomized controlled trials that can answer the many outstanding clinically relevant questions identified in this guideline'.	Clinical expert view (see section 3) is that different delivery methods were already accounted for in SIGN 143 – no need for marked rewording but might reaffirm place of MDZ in early treatment.

KQ 14: In women with epilepsy taking hepatic enzyme-inducing AEDs or non-inducing AEDs, what advice should be given regarding contraception, including postnatal contraception, and emergency contraception? Consider: combined oral contraceptive pill, progesterone only pill, progesterone implant, levonorgestrel intrauterine system, transdermal patches, condoms, IUCD, levonorgestrel emergency contraceptive pill

The Medicines and Healthcare products Regulatory Agency (MHRA) states that valproate must no longer be used in any woman or girl able to have children unless she has a pregnancy prevention programme in place.
An expert panel was convened to review the sections of the guideline affected by this advice and an updated guideline was published in September 2018.

Reference and study type	Information likely to be relevant	Relevance to guideline
Valproate in the treatment of epilepsy in women and girls 2015) https://www.ilae.org/files/ilaeGuideline/ValproateCommentILAE-0315.pdf	Offers guidance based on the valproate warning.	SIGN may wish to link to this guidance.
The BMJ Best Practice; Generalised Seizures, 2018 paper reported: European Medicines Agency. New measures to avoid valproate exposure in pregnancy endorsed. March 2018 [internet publication].	'…for some women with epilepsy in whom it may not be possible to stop valproate, treatment may be continued during pregnancy with appropriate specialist care'.	Section 4.3.2 SIGN Good Practice Point Sodium valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and a Pregnancy Prevention Programme is in place. May wish to consider adding in 'with appropriate specialist care' to the valproate advice
Epilepsy in Pregnancy. Royal College of Obstetricians and Gynaecologists, 2016	'WWE taking enzyme-inducing AEDs should be informed that a copper IUD is the preferred choice for emergency contraception. For emergency contraception for WWE taking enzyme-inducing AEDs, only the copper IUD is recommended. It is unclear whether a higher dose of levonorgestrel or ulipristal acetate is a sufficiently	Section 5.1.2 SIGN recommendation: Women with epilepsy who require emergency contraception while using enzyme-inducing antiepileptic drugs, or who have stopped taking these within the last 28 days:

Reference and study type	Information likely to be relevant	Relevance to guideline
	effective strategy.A double dose of levonorgestrel (3 mg as a single dose within 120 hours of unprotected sexual intercourse) may be used pragmatically. Ulipristal acetate should not be used. Faculty of Sexual and Reproductive Healthcare. Faculty of Sexual & Reproductive Healthcare Clinical Guidance: Drug Interactions with Hormonal Contraception. [London]: FSRH; 2011 (updated 2012)'.	• should be prescribed a single dose of levonorgestrel 3 mg (as opposed to 1.5 mg), ideally as soon as possible, and within 72 hours of unprotected intercourse • should not be offered ulipristal acetate (ellaOne®) because of a risk of reduced efficacy • may be offered insertion of a non-hormonal intrauterine device within 5 days of intercourse as an alternative option. May wish to consider the importance placed on the IUD as an emergency method

KQ 18: In pregnant women with epilepsy taking AEDs how should management differ during the antenatal period, labour, delivery and the postnatal period, compared to pregnant women without epilepsy? Consider: multidisciplinary shared care

Reference and study type	Information likely to be relevant	Relevance to guideline
Epilepsy in Pregnancy. Royal College of Obstetricians and Gynaecologists, 2016	'WWE who are planning their pregnancy should have a clinician competent in the management of epilepsy take responsibility for sharing decisions around choice and dose of AEDs, based on the risk to the fetus and control of seizures. Women should be informed that the risk of congenital abnormalities in the fetus is dependent on the type, number and dose of AEDs.	This guideline contains more detailed recommendations than SIGN 143. SIGN may wish to consider adding some of this advice

Reference and study type	Information likely to be relevant	Relevance to guideline
	The lowest effective dose of the most appropriate AED should be used. Exposure to sodium valproate and other AED polytherapy should be minimised by changing the medication prior to conception, as recommended by an epilepsy specialist after a careful evaluation of the potential risks and benefits'.	

KQ 19: In pregnant women with epilepsy who receive AEDs as monotherapy or in combination what evidence is there that there is an increased risk of adverse pregnancy outcomes, teratogenicity and epilepsy in offspring, compared to pregnant women with epilepsy not on AEDs, and pregnant women without epilepsy?

Reference and study type	Information likely to be relevant	Relevance to guideline
NICE surveillance 2018 reported: Weston et al. 2016 (Monotherapy treatment of epilepsy in pregnancy:congenital malformation outcomes in the child)	The surveillance report described a Cochrane review of prospective cohort controlled studies, cohort studies within pregnancy registries and RCTs (50 studies, 31 for meta-analysis). The review looked at prenatal exposure to AEDs and the prevalence of congenital malformations. They reported the following findings: • Children exposed to valproate, carbamazepine or phenytoin were at a higher risk of malformation than children born to women without epilepsy and women with untreated epilepsy • Children exposed to phenobarbital or topiramate were at a higher risk of malformation than children born to women without epilepsy. • There was no increased risk for major malformation with lamotrigine. • Gabapentin, levetiracetam, oxcarbazepine, primidone and zonisamide were not associated with an increased risk,	Section 5.6.3 Table 4: The SIGN guideline notes absolute rates of major congenital malformations associated with sodium valproate, carbamazepine, phenytoin, lamotrigine, gabapentin, topiramate and levetiracetam. While most statements in this Cochrane review support the statements in the guideline, the finding of "no increased risk associated with lamotrigine" differs from the guideline which notes absolute risk of major congenital malformation in those using lamotrigine ranging from 1.9% to 5.4%. Clinical expert review notes that SIGN 143 takes account of doses and rate of

Reference and study type	Information likely to be relevant	Relevance to guideline
	but there were fewer data for these medications. • When AEDs were compared, children exposed to valproate had the greatest risk of malformation, while levetiracetam and lamotrigine exposure carried the lowest risk of overall malformation; however, data pertaining to specific malformations are lacking'.	malformation in untreated patients with epilepsy, however, this new evidence may supersede the information on lamotrigine. SIGN should consider this new evidence
NICE surveillance 2018 reported: Bromley et al. 2014 (Treatment for epilepsy in pregnancy: neurodevelopmental outcomes in the child)	The surveillance report described a Cochrane review of 22 prospective cohort studies, and 6 registry based studies. The review looked at prenatal exposure to AEDs and the prevalence of neurodevelopmental outcomes in children. They reported the following findings: • Use of sodium valproate led to a reduction in IQ. • There may be a dose-relationship, with higher doses of sodium valproate (800 to 1000 mg daily or above) associated with a poorer cognitive outcome in the child.	Section 5.6.7 A prospective multicentre study assessing intelligence quotient (IQ) at six years of age in 224 children born to women taking carbamazepine, lamotrigine, phenytoin or sodium valproate monotherapy, reported that IQ was significantly lower after exposure to sodium valproate (with a dose-dependent relationship) than to the other AEDs, with verbal and memory abilities being particular problems (see section 5.2.1). No impact on guideline
Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes Veroniki et al. 2017 BMC Medicine 15 (1), 95	Veroniki et al. 2017 carried out a systematic review and network meta-analysis to investigate safety of AED exposure in utero. They looked at the risk of congenital malformations (CMs) and prenatal outcomes in 96 eligible studies (n = 58,461 patients). For major CMs, ethosuximide (OR, 3.04; 95% CrI, 1.23–7.07), valproate (OR, 2.93; 95% CrI, 2.36–3.69), topiramate (OR, 1.90; 95% CrI, 1.17–2.97), phenobarbital (OR, 1.83; 95% CrI, 1.35–2.47), phenytoin (OR, 1.67; 95% CrI, 1.30–2.17), carbamazepine (OR, 1.37; 95% CrI, 1.10–1.71), and 11 polytherapies were significantly more harmful than control, but lamotrigine (OR, 0.96; 95% CrI, 0.72–1.25) and levetiracetam (OR, 0.72; 95% CrI, 0.43–	Section 5.6.3 Table 4: The SIGN guideline notes absolute rates of major congenital malformations associated with sodium valproate, carbamazepine, phenytoin, lamotrigine, gabapentin, topiramate and levetiracetam. While most statements in this review support the statements in the guideline, the finding of "no increased risk associated with lamotrigine"

Reference and study type	Information likely to be relevant	Relevance to guideline
	1.16) were not. Lamotrigine and levetiracetam, were not associated with significant increased risks of CMs compared to control, and were significantly less likely to be associated with children experiencing cardiac malformations than control.	differs from the guideline which notes absolute risk of major congenital malformation in those using lamotrigine ranging from 1.9% to 5.4%. SIGN should consider this new evidence
Epilepsy in Pregnancy. Royal College of Obstetricians and Gynaecologists, 2016	In WWE taking enzyme-inducing AEDs who are at risk of preterm delivery, doubling of the antenatal corticosteroid dose for prophylaxis against respiratory distress syndrome in the newborn is not recommended. WWE taking enzyme-inducing AEDs, such as phenytoin, carbamazepine and phenobarbital, may increase their metabolism of corticosteroids, with reduced therapeutic effectiveness. No studies have assessed the effectiveness of higher or frequent doses of corticosteroids on neonatal outcomes in WWE exposed to enzyme-inducing AEDs and at risk of preterm delivery. In the absence of evidence of benefit with increased dose of steroids, and the potential harm with high steroid doses, routine doubling of steroid is not recommended.	Section 5.4.3 SIGN recommendation: Pregnant women with epilepsy receiving hepatic enzyme-inducing antiepileptic drugs who require antenatal corticosteroids for the prevention of neonatal respiratory morbidity, should receive double the standard dose of betamethasone/dexamethasone (48 mg over 12–24 hours). May wish to consider the advice to double the standard dose

KQ 30: In adults with epilepsy what is the evidence that risk factors, interventions and methods of communication affect the incidence and management of SUDEP? Consider: drug adherence, bed alarms, night-time supervision, seizure type and frequency, information given, pillows etc.

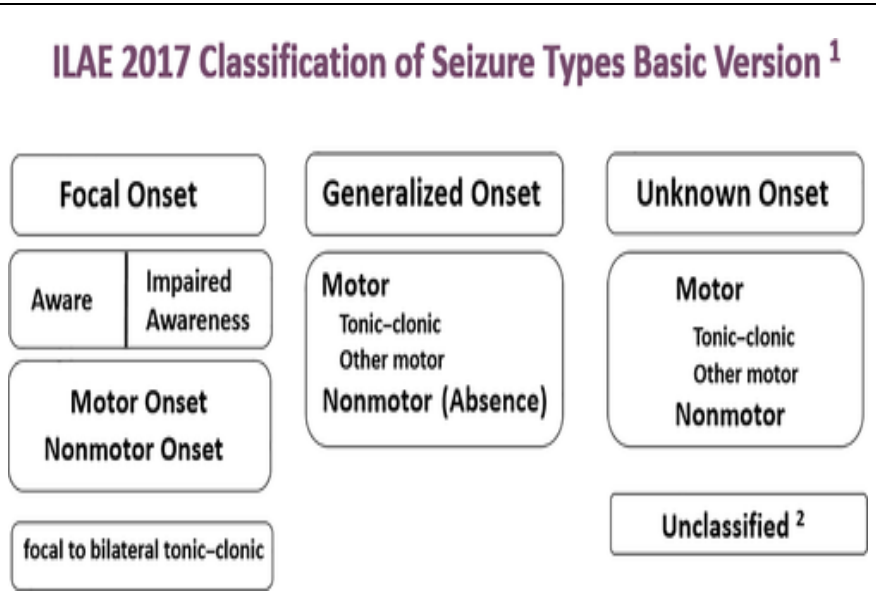
Reference and study type	Information likely to be relevant	Relevance to guideline
NICE surveillance 2018 reported: Maguire et al. 2016 (Treatments for the	The surveillance report described a Cochrane review which evaluated the effectiveness of interventions in preventing SUDEP in epilepsy They found 1 case-control study at serious risk of bias (n=154 cases of SUDEP and 616 controls). The study showed that nocturnal supervision, a supervising person sharing the same	This study was at serious risk of bias. No need to consider

Reference and study type	Information likely to be relevant	Relevance to guideline
prevention of Sudden Unexpected Death in Epilepsy (SUDEP))	bedroom, or taking special precautions such as using a listening device had a protective effect against SUDEP, independent of seizure control.	
NICE surveillance 2018 reported: Maguire et al. 2016 (Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP))	The surveillance report described a Cochrane review which evaluates interventions in SUDEP. One case-control study at serious risk of bias was reported; norcturnal supervision, a supervising person sharing the same bedroom or taking special precautions such as a listening device have a protective effect against SUDEP (independently of seizure control).	This was a case-control study at serious risk of bias. No need to consider

KQ 32: Do adults with epilepsy, who are educated in self management, when compared with those who are not, have better health outcomes in terms of seizure frequency, seizure severity, patient satisfaction and quality of life?

Reference and study type	Information likely to be relevant	Relevance to guideline
NICE surveillance 2018 reported: Bradley et al. 2016 (Care delivery and self-management strategies for adults with epilepsy)	The surveillance report described a 2016 Cochrane review of 18 studies (RCTs, controlled or matched trials, cohort studies or other prospective studies with a control group, and time series studies; n=NR) which identified 16 interventions beyond usual care. Specialist epilepsy nurse and self-management education had some evidence of benefit, but most of the studies had methodological weaknesses and no single model of service provision could be recommended.	Section 9.3 SIGN recommendation: Each epilepsy team should include epilepsy specialist nurses. No impact on guideline

Additional evidence that SIGN may wish to include in an update

Reference and study type	Information likely to be relevant	Impact on guideline
Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-30. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-21.		Section 3.2.4 SIGN recommendation: The seizure type(s) and epilepsy syndrome should be identified. SIGN should include an updated reference to the 2017 ILAE classification with any new clinically-relevant changes.
Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Powell, G. Saunders, M. Rigby, A. Marson, A. G. 2016	Updated Cochrane review	References: Powell G, Saunders M, Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database of Systematic Reviews 2010, Issue 1. SIGN could update reference
Evidence on the efficacy of primary radiosurgery or	Although the majority of adult epilepsy patients respond well to the current antiepileptic drug treatment, 20–40% of them are drug-	Radiotherapy is not included in the remit of

Reference and study type	Information likely to be relevant	Impact on guideline
stereotactic radiotherapy for drug-resistant non-neoplastic focal epilepsy in adults: A systematic review. Eekers et al. Seizure: European Journal of Epilepsy, 2018-02-01, Volume 55, Pages 83-92	resistant. In these patients, resective epilepsy surgery is a curative treatment option, for which, however, only a limited number of patients is eligible. The purpose is to summarize the outcome of radiotherapy for drug-resistant non-neoplastic focal epilepsy and to elucidate its efficacy for seizure outcome and long-term toxicity in adults. RESULTS: Sixteen out of 170 initially identified studies were included in this systematic literature study (n=170 patients). Twelve of the 16 studies described a positive effect of radiotherapy on seizure frequency reduction, with 98 of the patients (on average 58%, range 25%–95%) reporting no or rare seizures (defined as radiotherapy-adapted Engel class [RAEC] I and II. In total, 20% (34 patients) of the patients needed subsequent surgery due to radionecrosis, cysts formation, edema, and intracranial hypertension or remaining seizures. A dose-effect model was fitted to the available response data in an attempt to derive a relationship between prescribed dose and RAEC frequency. CONCLUSIONS: Radiotherapy is a possible non-invasive treatment option for patients with drug-resistant focal non-neoplastic epilepsy. This systematic review showed that there is only level 4 evidence of primary radiotherapy reducing seizure frequency in adult patients. Prospective randomized trials are needed to determine its exact value compared to other treatment approaches.	SIGN 143. SIGN could consider adding radiotherapy as a new key question, however based on this systematic review, the available evidence is very weak.

Section 3: Consultation feedback

Former members of the SIGN 143 guideline development group were invited to comment on the report and the proposed areas for update.

Reviewer	Comments
Professor John Paul Leach Consultant Neurologist and Honorary Professor, Head of Undergraduate Medicine, University of Glasgow	KQ3 (section 4.2.3) Nevitt, et al 2017 - This does not change the guidance in my opinion – further trial evidence may be forthcoming – SANAD2 in 2021 KQ3 (section 4.2.3) Nevitt, et al 2016 - Given rarity of Phenobarbital as a new adjunct I do not think this impacts on SIGN 143 KQ3 (section 4.2.3) Nolan et al 2016 - No effect on guidance – other difficulties with PHT preclude use as first line in this setting KQ5 (Section 4.3.1) Lattanzi et al 2016 – Agree, as licensed drug for refractory epilepsy (brivaracetam) – could add as possible adjunctive treatment KQ5 (Section 4.3.1) Betts et al 2015 – Agree, as licensed drug for refractory epilepsy (eslicarbazepine acetate) – could add as possible adjunctive treatment KQ8 (Section 4.9.1) Panebianco et al. 2015 - Could update current references to include mention of High and low vagus nerve stimulations KQ9 (Section 4.10.1) Prasad et al 2014 - This confirms place of LRZ and would not require rewording of guideline KQ9 (Section 4.10.1) Glauser et al 2016 - Different delivery methods were already accounted for in SIGN 143 – no need for marked rewording but might reaffirm place of MDZ in early treatment KQ14 (Section 4.3.2) BMJ Best Practice; Generalised Seizures, 2018 - Agree – should refer to MHRA PPP and the Annual Risk Acknowledgment Form KQ18 Epilepsy in Pregnancy, Royal College of Obstetricians and Gynaecologists, 2016 – Agree that some advice may be incorporated KQ 19 (Section 5.4.3) - Disagree: the wording of the RCOG guidance is pasted below – I think the text above is a typo and the advice in 143 stands ***In WWE on enzyme-inducing AEDs, and are at risk of preterm delivery, consideration should be given to administering twice the usual dose of corticosteroids. [D]*** *WWE on enzyme-inducing AEDs such as phenytoin, carbamazepine and phenobarbitone may increase their metabolism of corticosteroids and reduce their therapeutic effectiveness.*[71] *No studies have assessed the effectiveness of higher or frequent doses of corticosteroids on neonatal outcomes in WWE at risk of preterm delivery and enzyme-inducing AEDs. Given the theoretical possibility of reduced effectiveness of steroids, an increase in the dose of steroids is recommended, with a total of 48 mg of betamethasone or dexamethasone given in two 24 mg*

	doses 12 hours apart. Evidence level 4 SIGN comment – we were not able to verify this extract. It does not match the RCOG guideline document cited in this report. KQ19 (Section 5.6.3) Weston et al. 2016 - SIGN 143 takes account of doses and rate of malformation in untreated patients WE. New - Eekers et al 2018 (radiotherapy) - Given long term risks, I do not think this would bear inclusion as a key question. (Section 3.2.4) Scheffer et al 2017, Fisher et al 2017 (ILEA classification) - SIGN should include an updated reference to the 2017 ILAE classification with any new clinically-relevant changes. - Agree
Ms Yvonne Leavy Epilepsy Specialist Nurse Western General Hospital, Edinburgh	I agree with the conclusions in this report.
Jane Stuart Learning Disability Psychiatrist Edinburgh	I would agree with the attached report. I think that Brivaracetam is likely to be a relevant addition to our list of AED options as it is already being quite widely used, so would be worth reviewing in the guideline. Updated information on Valproate and the pregnancy prevention plans would be very useful to add. We should also include the updated information on classification. I suspect there will be increasing amounts of evidence on cannabidol to consider in the near future. All potential prescribers will be looking for practical guidelines on this as patients are asking regularly about this in clinics. Given all the media and political interest in this it will be essential to have pragmatic, evidence based guidelines for clinicians.