National Institute for Health and Care Excellence

Draft for consultation

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

[08] Evidence review: Therapeutic drug monitoring in women and girls

NICE guideline <number>

Evidence reviews underpinning recommendations 4.6.1 – 4.6.10 and a research recommendation in the NICE guideline

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1. Therapeutic drug monitoring in women and girls

1.1. Review question

What is the appropriate serial monitoring of drug levels, including timing, in girls or women who are thinking about conceiving, are pregnant or in the post-partum period?

1.1.1. Introduction

For some anti-seizure medications (ASMs), in particular phenytoin and lamotrigine, plasma concentrations can fall during pregnancy, and so it has been suggested that monitoring may be useful to inform dosing. A change in ASM level during pregnancy has the potential to worsen seizure control. If ASM doses are increased in pregnancy, this may have consequences on foetal drug exposure.

It is not known for which ASMs, if any, monitoring is beneficial in maintaining seizure control or how and when monitoring should be carried out before, during and after pregnancy. It is not known if pregnancy-associated ASM monitoring would be acceptable to women planning a pregnancy, who are pregnant or who are in the post-partum period. This review evaluates whether there should be therapeutic drug monitoring in girls and women prior to conception and through a pregnancy, when and by whom that monitoring should be performed, and how the results should be communicated.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: girls and women planning pregnancy, during pregnancy and postpartum up to 6 months. Exclusion: men, non-pregnant women not planning pregnancy.
Intervention	Drug monitoring (measurement of drug concentration in blood or saliva) of the following anti-seizure medications: • Brivaracetam • Carbamazepine (for focal motor status) • Chlormethiazole (clomethiazole) • Clobazam • Clonazepam (for myoclonic status) • Diazepam • Eslicarbazepine • Ethosuximide • Fosphenytoin • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Lorazepam • Midazolam • Oxcarbazepine • Perampanel • Phenobarbital (phenobarbitone) • Phenytoin • Pregabalin

	• Primidone • Rufinamide • Steroids (methylprednisolone, prednisolone) • Stiripentol • Sulthiame • Tiagabine • Topiramate • Valproate (sodium valproate/ valproic acid) • Zonisamide Dose according to prescriber discretion and / or local protocols.
Comparison	Usual care (dose adjustments made without measuring drug levels, based on symptoms).
Outcomes	• Mortality of mother or baby at study follow-up • Seizure freedom during pregnancy and at 6 months postpartum • Reduction in seizure frequency (50% or greater reduction in seizure frequency) • Time to first seizure in pregnancy up to 6 weeks and time to subsequent seizure up to 1 year • Anti-seizure medication exposure (mean daily) • Quality of life (any validated measures) at study follow-up • Adverse events – Anti-seizure medication-related (toxicity) – Pregnancy complications in mother and baby (admission to HDU/ICU for mother, admission to NICU for baby) – Seizures during labour – Attendance at ED – Congenital anomalies (neural tube defects (spina bifida), limb defects (club foot), cleft lip and palette etc) • Neurodevelopmental outcomes (Griffith Mental Development Scales and the Bayley Scales of Infant and Toddler Development scale)
Study design	• RCTs • Systematic reviews of RCTs • Published NMAs and IPDs will be considered for inclusion If insufficient RCT evidence is available, prospective observational comparative studies will be considered only if they adjust for key confounders of the age of epilepsy onset, classification (focal, generalised or epilepsy syndrome).

1.1.3. Methods and process

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

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

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

A search was conducted for randomised controlled trials comparing therapeutic monitoring to usual care, in which any necessary dose adjustments are made without knowledge of anti-seizure medication levels.

One Health Technology Assessment (comprising a randomised trial nested within a cohort study and a qualitative study) was included in the review.[151] Only data from the randomised

trial component of the study were extracted. The randomised trial is summarised in Table 2 below. Evidence from the trial is summarised in the clinical evidence summary below (Table 3). See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Thangaratinam 2018 UK	Therapeutic drug monitoring (n=130) versus clinical features monitoring (n=133)	Pregnant women of < 24 weeks gestation with a confirmed diagnosis of epilepsy, on monotherapy (lamotrigine, carbamazepine, phenytoin or carbamazepine) or polytherapy (lamotrigine with either carbamazepine, phenytoin or levetiracetam), and with ≥25% reduction in serum anti-seizure medication level at any time in pregnancy, compared with baseline or pre-pregnancy level.	Maternal mortality rate from randomisation to 6 weeks post-partum. Neonatal mortality rate. Rate of stillbirth from randomisation to end of pregnancy. Proportion of women who experienced no seizures from randomisation to 6 weeks post-partum. Time to first seizure from randomisation up to 6 weeks post-partum. Time to multiple seizures from randomisation up to 6 weeks post-partum. Mean daily dose of anti-seizure medication: monotherapy with carbamazepine, levetiracetam or lamotrigine, or polytherapy with lamotrigine and levetiracetam, from randomisation to 6 weeks post-partum.	One woman received phenytoin monotherapy and one woman received lamotrigine polytherapy with carbamazepine. No between-group comparisons were possible for these anti-seizure medication regimens. Participants were monitored for serum anti-seizure medication levels from baseline until 6 to 8 weeks post-partum. The time-period of observation for neonatal mortality was not stated. It was assumed to be from randomisation to 28 days after a live birth, in keeping with the established definition of the neonatal period. Period of observation for rate of admission to neonatal unit was not stated but assumed to be from randomisation to 4 weeks post-partum.

Study	Intervention and comparison	Population	Outcomes	Comments
			Quality of life (QOLIE-31 and QOLIE-31 Overall Health) from randomisation to 36 weeks gestation. Quality of life (EQ-5D) from randomisation to 6 weeks post-partum. Maternal admission to HDU/ICU from randomisation to 6 weeks post-partum. Rate of admission to neonatal unit. Rate of major congenital malformation from randomisation to 6 weeks post-partum.	

See Effectiveness evidence for full evidence tables.

1.1.6. Summary of the effectiveness evidence

Table 3: Clinical evidence summary: therapeutic drug monitoring versus clinical features monitoring

Outcomes	No of Participants Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Therapeutic drug monitoring versus clinical features monitoring (95% CI)
Quality of life (QOLIE-31 Overall Health)	225 Randomisation to 36 weeks gestation	LOW[a,b] due to risk of bias		The mean quality of life (QOLIE-31 Overall Health) in the control group was 7.3	The mean quality of life (QOLIE-31 Overall Health) in the intervention group was 0.35 lower (0.72 lower to 0.02 higher).

Quality of life (QOLIE-31)	224 Randomisation to 36 weeks gestation	LOW[a,c] due to risk of bias		The mean quality of life (QOLIE-31) in the control group was 73.7	The mean quality of life (QOLIE-31) in the intervention groups was 2.5 lower (5.1 lower to 0.1 higher).
Quality of life (EQ-5D)	201 Randomisation to 6 weeks post-partum	LOW[d,e] due to risk of bias		The mean quality of life (EQ-5D) in the control group was 0.9	The mean quality of life (EQ-5D) in the intervention groups was no higher or lower (0.05 lower to 0.05 higher).
Risk of first seizure	257 Randomisation to 6 weeks post-partum	VERY LOW[a,f] due to risk of bias, imprecision	HR 0.8 (0.55 to 1.16)	Not available	RD not calculable
Risk of multiple seizures	257 Randomisation to 6 weeks post-partum	VERY LOW[a,g] due to risk of bias, imprecision	HR 1.4 (0.73 to 2.68)	Not available	RD not calculable
Seizure freedom	257 Randomisation to 6 weeks post-partum	LOW[a,f] due to risk of bias	RR 1.01 (0.83 to 1.22)	615 per 1000	6 more per 1000 (from 105 fewer to 135 more)
Maternal mortality	263 Randomisation to 6 weeks post-partum	LOW[hn] due to risk of bias, imprecision			RD 0.00 (-0.01 to 0.01
Maternal admission to HDU/ICU	257 Randomisation to 6 weeks post-partum	VERY LOW[gh] due to risk of bias, imprecision	OR 1.8 (0.41 to 7.9)	23 per 1000	

Mean daily carbamazepine exposure (monotherapy)	36	VERY LOW[hi] due to risk of bias, imprecision		The mean daily carbamazepine exposure (monotherapy) in the control group was 695 mg	The mean daily carbamazepine exposure (monotherapy) in the intervention group was 12.1 lower (226.7 lower to 202.5 higher)
Mean daily lamotrigine exposure (monotherapy)	138	LOW[hj] due to risk of bias, imprecision		The mean daily lamotrigine exposure (monotherapy) in the control group was 252.6 mg	The mean daily lamotrigine exposure (monotherapy) in the intervention group was 32.3 higher (14.4 lower to 79 higher)
Mean daily levetiracetam exposure (monotherapy)	62	LOW[hk] due to risk of bias, imprecision		The mean daily levetiracetam exposure (monotherapy) in the control group was 1628.5 mg	The mean daily levetiracetam exposure (monotherapy) in the intervention group was 166.5 higher (229.8 lower to 562.8 higher)
Mean daily levetiracetam exposure (in women on levetiracetam plus lamotrigine polytherapy)	25	VERY LOW[hl] due to risk of bias, imprecision		The mean daily levetiracetam exposure (women on levetiracetam plus lamotrigine polytherapy) in the control group was 2122.2 mg	The mean daily levetiracetam exposure (women on levetiracetam plus lamotrigine polytherapy) in the intervention group was 137.3 lower (945.9 lower to 671.3 higher)
Mean daily lamotrigine exposure (in women on levetiracetam plus lamotrigine polytherapy)	25	LOW[hm] due to risk of bias, imprecision		The mean daily lamotrigine exposure (women on levetiracetam plus lamotrigine polytherapy) in the control group was 413.8 mg	The mean daily lamotrigine exposure (women on levetiracetam plus lamotrigine polytherapy) in the intervention group was 97.4 higher (28.7 lower to 223.5 higher)
Stillbirth	259	VERY LOW[gh] due to risk of bias, imprecision	Peto OR 0.14 (0.01 to 2.31)	15 per 1000	13 fewer per 1000 (from 15 fewer to 19 more)
Neonatal mortality	260	LOW[hn] due to risk of bias, imprecision			RD 0.0 (-0.01 to 0.01)

Major congenital malformation	259	VERY LOW[gh] due to risk of bias, imprecision	OR 0.66 (0.23 to 1.89)	75 per 1000	
Admission to Neonatal Intensive Care Unit	259	VERY LOW[gh] due to risk of bias, imprecision	OR 1.6 (0.29 to 8.83)	134 per 1000	

[a] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome.
[b] MID for this outcome was calculated as -/+ 0.8.
[c] The MID for this outcome was -/+6.75.
[d] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome. There was a high but similar rate of attrition in both groups.
[e] The MID for this outcome was -/+ 0.09.
[f] The MID for this outcome was 0.8 and 1.25.
[g] The MID for this outcome was 0.8 and 1.25. The outcome was downgraded by 2 increments as the confidence interval crossed both MIDs.
[h] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias.
[i] The MID for this outcome was -/+168.2. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[j] The MID for this outcome was -/+74.0. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[k] The MID for this outcome was -/+463.25. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[l] The MID for this outcome was -/+538.75. The outcome was downgraded by 2 increments as the confidence interval crossed both MIDs.
[m] The MID for this outcome was -/+45.55. The outcome was downgraded by 1 increment as the confidence interval crossed one MIDs.
[n] Downgraded by 1 increment as the outcome is from a single study with zero events in both arms, and sample size >70 and <350.

Table 4: Clinical evidence summary: therapeutic drug monitoring versus clinical features monitoring

See Appendix F for full GRADE tables.

1.1.7. Economic evidence

1.1.7.1. Included studies

No health economic studies were included.

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8. Economic model

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

1.1.9. Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness.

Cost of staff time

Resource	Unit costs
Hospital-based nurse, Band 6: Cost per hour	£53
Hospital-based doctor, Speciality registrar: Cost per hour	£58

Source: PSSRU 2020[1], including qualification costs

Cost of test for therapeutic drug monitoring

Therapeutic drug monitoring can be conducted by epilepsy centres internally if they have the appropriate resources. In addition, epilepsy centres that can undertake testing internally can also charge for these tests if they are requested externally.

The unit costs provided are illustrative of the costs observed for one epilepsy centre and indicate the cost of external testing for those epilepsy centres that are unable to provide therapeutic drug monitoring through use of internal resources.

Resource	Internal testing	External testing
Cost of tests for Lamotrigine, Phenytoin, and Carbamazepine	£9.50	£12.50
Levetiracetam	£22.50	£30

Source: Guideline Committee member

1.1.10. Committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

The selection of outcomes in the protocol reflected concern that physiological changes during pregnancy can have a marked effect on the serum concentrations of ASMs, that deterioration in seizure control can be harmful to both the mother and foetus, and that there are foetal risks associated with exposure to ASMs. The outcomes comprised: mortality of mother or baby at study follow-up, seizure freedom during pregnancy and at six months post-partum, reduction in seizure frequency (50% or more), time to first seizure in pregnancy and

up to up to six weeks post-partum, time to subsequent seizures (within an observation period of up to one year), ASM exposure (mean daily), and quality of life (using any validated measures) at study follow-up. Also included were the following adverse events: ASM toxicity, pregnancy complications in the mother or baby (maternal admission to a high dependency or intensive care unit or admission of the baby to a neonatal intensive care unit), seizures during labour, attendance at an emergency department, congenital anomalies, and neurodevelopmental outcomes.

There was no evidence found for the following outcomes: reduction in seizure frequency, ASM toxicity, seizures during labour and neurodevelopmental impairment.

1.1.10.2. The quality of the evidence

Evidence was provided by a single randomised controlled trial of therapeutic drug monitoring (TDM) versus clinical features monitoring (CFM) among women under 24 weeks gestation in whom ASM concentrations had fallen by 25% or more. In the TDM group, monthly ASM concentrations were communicated to the responsible clinician. In the CFM group, the mother and responsible clinician were unaware of the ASM concentrations. The quality of evidence for protocol-specified outcomes ranged from low to very low. This was due to risk of bias and low precision. The risk of bias arose from a lack of clarity about allocation concealment and a lack of blinding among outcome assessors. Low precision arose from a failure to recruit the target number of participants. Four outcomes were reasonably precise: quality of life measured using QOLIE-31 and QOLIE-31 (Overall Health) favoured CFM rather than TDM, but the effects were very small; and neither quality of life measured using EQ-5D nor seizure freedom differed between TDM and monitoring based on clinical features alone. The committee noted that the control (CFM) group had background measurement of ASM concentrations, and that clinicians managing the care of those women made dosing decisions in the knowledge that those measurements could be revealed in certain circumstances. These circumstances included, for example, if levels were found to be above the therapeutic range with risks of toxicity. Knowledge of the background drug levels for the control group could potentially underestimate any benefit observed by performing therapeutic drug monitoring. Some discrepancies in the reporting of the study were also highlighted. For example, the mean ASM exposures in each group for women on both levetiracetam and lamotrigine appear to have been entered in reverse order. This impacted the confidence of the committee in making recommendations based on this trial. It was agreed that the trial was inconclusive, neither providing clear evidence in favour of TDM in pregnancy, nor providing clear evidence against it. A research recommendation was therefore made for further study to address the clinical and cost effectiveness of decisions about TDM in girls, young women, and women with epilepsy.

No evidence was found for drug monitoring in women or girls pre-conception or in the post-partum period beyond 6 weeks.

1.1.10.3. Benefits and harms

The committee agreed that there was no clinically important difference seen in any of the included outcomes. For most outcomes, this was because of a lack of precision, a risk of bias, or both.

There were, however, four outcomes with reasonably precise estimates. Quality of life measured on the QOLIE-31 scale (maximum score 100) yielded an adjusted mean difference of 2.5 points lower with TDM, with a 95% confidence interval of 5.1 lower to 0.1 higher. This most likely indicates better quality of life with clinical features monitoring, but by a very small amount of 5.1 points at best. Quality of life measured on the overall health item of the QOLIE-31 scale (maximum score 10) yielded an adjusted mean difference of 0.35 points lower with TDM, with a 95% confidence interval of 0.72 points lower to 0.02 points higher. Again, this potentially indicates better quality of life with CFM, but by a very small degree. Quality of life measured on the EQ5-D scale (maximum score 1) showed no difference

between groups (adjusted mean difference 0.0, 95% confidence interval -0.05 to 0.05). The effect (if any) was therefore very small and of indeterminate direction. Lastly, the proportion of women without any seizures over the whole period of observation was similar in each group, yielding an absolute risk difference of only six more women per thousand in the TDM group. The maximum and minimum plausible values (105 women fewer to 135 women more) could be clinically important, but the point estimate suggests very little difference, and the direction of effect (if any) was unclear.

The committee agreed to reflect MHRA safety advice on monitoring of ASMs in pregnancy in their recommendations. However, given the limited and inconclusive evidence included in this review, the committee felt a research recommendation was needed to encourage more research in this area.

The committee highlighted the importance of obtaining preconception levels of antiseizure medication as a baseline level to compare and titrate against when monitoring drug levels during pregnancy. Where preconception levels were not possible, the committee recommended using levels recorded as early as possible in pregnancy. The committee agreed informal consensus recommendations were needed to ensure the preference of the women and girls was considered, that adequate information for the care of women and girls with epilepsy who are pregnant is accessible to all the healthcare teams involved. Furthermore, more frequent monitoring should be offered to vulnerable groups i.e., women and girls with learning disabilities, under the age of 16 years, with active epilepsy (a seizure within the past 12 months) and/or who have bilateral tonic-clonic seizures. The committee agreed, the care of women and girls who are pregnant, or planning pregnancy should be within an epilepsy specialist team, who can provide advice on any adjustments to the ASM prescribed. They also noted the importance of providing advice on not stopping medication without first discussing with a clinician.

The committee highlighted questions or concerns often raised about breastfeeding after the birth. They agreed published data is limited but has shown the amount of drugs in breast milk is extremely small and has not demonstrated any harm to the baby. They agreed that the advantages of breastfeeding outweighed any small risk of the drug affecting the baby.

1.1.10.4. Cost effectiveness and resource use

No health economic evidence was identified for this review question. The committee agreed that current practice is not consistent nationally with regards to therapeutic drug monitoring pre-conception and during pregnancy. In some centres, women will have their drug levels assessed pre-conception and then receive regular monitoring throughout their pregnancy. Conversely, in other centres drug monitoring is rarely or never done. The drug levels are measured through blood tests. The committee noted that for some of the drugs, the tests need to be sent away at high cost and take time to come back limiting their clinical value. It was thought that most centres would be able to obtain concentrations of levetiracetam, lamotrigine, carbamazepine, phenytoin, phenobarbitone and sodium valproate within a reasonable time frame.

The committee noted that monitoring should typically be conducted three months prior to actively trying to conceive and once the dosage of ASMs are stable. An additional appointment would then be required once a person has conceived. Subsequent monitoring is then dependent on how the initial ASM concentration compares to pre-conception dosing. If the ASM concentration has not changed, monitoring may only be undertaken once per trimester. However, if the ASM concentration has dropped substantially, therapeutic drug monitoring is required more frequently.

Because therapeutic drug monitoring is variable in current practice, the committee concluded it was difficult to determine which health care professional would typically undertake therapeutic drug monitoring in current practice. However, the committee noted that therapeutic drug monitoring would likely either be undertaken by an epilepsy nurse or doctor. The cost of an epilepsy nurse is £53 per hour, and the cost of a doctor is £58 per hour. Therefore, assuming a 15-minute appointment, the cost of staff time for monitoring per appointment is £13.25 and £14.50, respectively. The overall cost of monitoring based on the unit costs provided indicates that monitoring would cost between £23.00 - £44.50 per monitoring appointment.

The committee made recommendations which are in line with the MHRA safety advice on monitoring in pregnancy. Because there are a proportion of people who do not currently receive therapeutic drug monitoring there may be an increase in drug monitoring compared to current practice.

1.1.10.5. Other factors the committee took into account

The committee discussed the current MHRA guidance that includes advice to monitor lamotrigine concentration before, during, and after pregnancy (including shortly after birth), to ensure appropriate clinical management of pregnant women treated with levetiracetam, to 'consider' monitoring concentrations of the active metabolite of oxcarbazepine (including postpartum if the dose was changed during pregnancy), and that monitoring of phenytoin concentrations may be valuable as a guide to appropriate adjustment of dosage. The committee decided, therefore to make a recommendation to monitor drug levels in women or girls who are planning a pregnancy or are pregnant and prescribed these particular ASMs in line with guidance provided by the MHRA guidance and also given in the BNF. It was noted that routine care already includes more frequent monitoring of women and girls who are pregnant if they are under the age of sixteen, have very active epilepsy, have bilateral tonic-clonic seizure or have learning disabilities. For further discussion of MHRA guidance, see evidence review F Safety of ASM in women and girls.

The committee also discussed the MBRRACE-UK 2019 report 'Saving Lives, Improving Mothers' Care' which highlighted that maternal deaths have occurred after ASM concentrations have been monitored but not subsequently acted upon. This was of considerable concern to the committee who agreed that were an ASM level to be checked, it was essential that level was checked and acted on appropriately.

The committee considered that there is variation in practice with the recommendations reflecting current practice in some areas but not in others. They agreed that risk perceptions differ among clinicians, and that ASM prescribing also varies across healthcare settings. These can all influence the advice given to women and girls and their experience of care. These variations make it difficult to make judgements about resource impact.

1.1.11. Recommendations supported by this evidence review

This evidence review supports recommendations 4.6.1 – 4.6.10 and a research recommendation on therapeutic drug monitoring in women and girls in the NICE guideline.

References

1. Curtis L, Burns A. Unit costs of health and social care 2020. Canterbury. Personal Social Services Research Unit University of Kent, 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

2. 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 & Behavior. 2005; 7(3):451-457

3. Islamiyah WR, Suharjono, Jaya HP, Ernawati I. Analysis relationship of self-medication card administration with adherence (ARMS score), phenytoin serum levels and frequency of seizures in patients using phenytoin monotherapy. Research Journal of Pharmacy and Technology. 2019; 12(12):5991-6000

4. Jacob S, Nair AB. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. Drugs in R & D. 2016; 16(4):303-316

5. Jacob S, Nair AB, Shah J. Revisiting clinical practice in therapeutic drug monitoring of first-generation antiepileptic drugs. Drugs and Therapy Perspectives. 2019; 35(10):500-517

6. Jannuzzi G, Cian P, Fattore C, Gatti G, Bartoli A, Monaco F et al. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. Epilepsia. 2000; 41(2):222-230

7. Jarvie D, Mahmoud SH. Therapeutic drug monitoring of levetiracetam in select populations. Journal of Pharmacy & Pharmaceutical Sciences. 2018; 21(1S):149s-176s

8. Jimenez M, Grau-Lopez L, Ciurans J, Garcia-Esperon C, Fumanal A, Barambio S et al. Epilepsy and pregnancy. Factors associated with epileptic seizures during pregnancy. Neurologia. 2020; S0213-4853(20):30135-30133

9. Johannessen SI, Landmark CJ. Value of therapeutic drug monitoring in epilepsy. Expert Review of Neurotherapeutics. 2008; 8(6):929-939

10. Kelly TE. Teratogenicity of anticonvulsant drugs. I: Review of the literature. American Journal of Medical Genetics. 1984; 19(3):413-434

11. Kim K, Magness JW, Nelson R, Baron V, Brixner DI. Clinical utility of pharmacogenetic testing and a clinical decision support tool to enhance the identification of drug therapy problems through medication therapy management in polypharmacy patients. Journal of Managed Care and Specialty Pharmacy. 2018; 24(12):1251-1259

12. Koch S, Göpfert-Geyer I, Jäger-Roman E, Jakob S, Huth H, Hartmann A et al. Anti-epileptic agents during pregnancy. A prospective study on the course of pregnancy, malformations and child development. Deutsche medizinische wochenschrift (1946). 1983; 108(7):250-257

13. Kusznir Vitturi B, Barreto Cabral F, Mella Cukiert C. Outcomes of pregnant women with refractory epilepsy. Seizure. 2019; 69:251-257

14. Larkin JG, McGuire GM, Percy-Robb I, Brodie MJ. Anticonvulsant monitoring at the epilepsy clinic: A prospective study. British Journal of Clinical Pharmacology. 1988; 25(5):627P-628P

15. Leenen LAM, Wijnen BFM, Kessels AGH, Chan H, de Kinderen RJA, Evers S et al. Effectiveness of a multicomponent self-management intervention for adults with epilepsy (ZMILE study): A randomized controlled trial. Epilepsy & Behavior. 2018; 80:259-265

16. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Annals of Neurology. 2001; 49(3):336-344

17. Longo B, Forinash AB, Murphy JA. Levetiracetam use in pregnancy. Annals of Pharmacotherapy. 2009; 43(10):1692-1695

18. Losada-Camacho M, Guerrero-Pabon MF, Garcia-Delgado P, Martinez-Martinez F. Impact of a pharmaceutical care programme on health-related quality of life among women with epilepsy: a randomised controlled trial (IPHIWWE study). Health & Quality of Life Outcomes. 2014; 12:162

19. Maguire M, Jackson C, Marson A, Nevitt S. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD011792. DOI: 10.1002/14651858.CD011792.pub2.

20. Mauri Llerda JA, Suller Marti A, de la Pena Mayor P, Martinez Ferri M, Poza Aldea JJ, Gomez Alonso J et al. The Spanish Society of Neurology's official clinical practice guidelines for epilepsy. Special considerations in epilepsy: comorbidities, women of childbearing age, and elderly patients. Neurologia. 2015; 30(8):510-517

21. McAuley JW, Anderson GD. Treatment of epilepsy in women of reproductive age: pharmacokinetic considerations. Clinical Pharmacokinetics. 2002; 41(8):559-579

22. Mehrotra TN, Aneja GK, Arora V, Goel S, Singh VS. Valproate sodium in epilepsy. A clinical trial including monitoring of drug levels. Journal of the Association of Physicians of India. 1990; 38(4):277-279

23. Mikov S, Gjergja Juraski R, Fuhic A, Bonjak Paic M, Ivihevic Bakulic T, Cvitanovic-ojat LJ et al. Prospective surveillance of croatian pregnant women under lamotrigine monotherapy-aspects of pre-pregnancy counseling and drug monitoring. Acta Clinica Croatica. 2010; 49(Suppl 2):99

24. Miskov S, Gjergja-Juraski R, Cvitanovic-Sojat L, Bakulic TI, Fucic A, Bosnjak-Pasic M et al. Prospective surveillance of Croatian pregnant women on lamotrigine monotherapy--aspects of pre-pregnancy counseling and drug monitoring. Acta Clinica Croatica. 2009; 48(3):271-281

25. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2020]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

26. Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. Epilepsia. 2001; 42(5):667-673

27. Nonoda Y, Iwasaki T, Ishii M. The efficacy of gabapentin in children of partial seizures and the blood levels. Brain and Development. 2014; 36(3):194-202

28. Otani K. Risk factors for the increased seizure frequency during pregnancy and puerperium. Folia Psychiatrica et Neurologica Japonica. 1985; 39(1):33-41

29. Pack AM. Therapy Insight: Clinical management of pregnant women with epilepsy. Nature Clinical Practice Neurology. 2006; 2(4):190-200

30. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008; 49(7):1239-1276

31. Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: A 2018 update. Therapeutic Drug Monitoring. 2018; 40(5):526-548

32. Pennell PB. 2005 AES annual course: evidence used to treat women with epilepsy. Epilepsia. 2006; 47(Suppl 1):46-53

33. Pennell PB. Antiepileptic drugs during pregnancy: what is known and which AEDs seem to be safest? Epilepsia. 2008; 49(Suppl 9):43-55

34. Pennell PB. Pregnancy in women who have epilepsy. Neurologic Clinics. 2004; 22(4):799-820

35. Pennell PB. Use of antiepileptic drugs during pregnancy: Evolving concepts. Neurotherapeutics. 2016; 13(4):811-820

36. Pennell PB, French JA, Harden CL, Davis A, Bagiella E, Andreopoulos E et al. Fertility and birth outcomes in women with epilepsy seeking pregnancy. JAMA Neurology. 2018; 75(8):962-969

37. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2008; 70(22 Pt 2):2130-2136

38. Perucca E. Current trends in antiepileptic drug therapy. Epilepsia. 2003; 44(Suppl 4):41-47

39. Pirie DA, Al Wattar BH, Pirie AM, Houston V, Siddiqua A, Doug M et al. Effects of monitoring strategies on seizures in pregnant women on lamotrigine: a meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2014; 172:26-31

40. Plumpton CO, Brown I, Reuber M, Marson AG, Hughes DA. Economic evaluation of a behavior-modifying intervention to enhance antiepileptic drug adherence. Epilepsy & Behavior. 2015; 45:180-186

41. Pulliam C, Pait L, Winslow J. How to give phenytoin safely. Report from a long-term care facility in North Carolina. North Carolina Medical Journal. 1996; 57(5):292-295

42. Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC, Ramaswamy K, Rahmathullah R et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. New England Journal of Medicine. 1990; 323(14):929-935

43. Rajadhyaksha S, Shah KN, Kanhere S, Naik N, Mehta R. Does treatment change the outcome of seizures and computerized tomographic lesions in intracranial granulomas? Journal of Tropical Pediatrics. 1999; 45(3):161-165

44. Raju GB, Behari M, Prasad K, Ahuja GK. Randomized, double-blind, placebo-controlled, clinical trial of D-alpha-tocopherol (vitamin E) as add-on therapy in uncontrolled epilepsy. Epilepsia. 1994; 35(2):368-372

45. Ramsay RE, Uthman BM, Augustinsson LE, Upton AR, Naritoku D, Willis J et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and

tolerability. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994; 35(3):627-636

46. Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as Intensive Care Unit sedatives in postoperative electively ventilated eclamptic patients. Journal of Anaesthesiology Clinical Pharmacology. 2017; 33(3):331-336

47. Rath W, Fischer T. The diagnosis and treatment of hypertensive disorders of pregnancy: New findings for antenatal and inpatient care. Deutsches Arzteblatt. 2009; 106(45):733-738

48. Reardon DA, Lassman AB, Van Den Bent M, Kumthekar P, Merrell R, Scott AM et al. Efficacy and safety results of ABT-414 in combination with radiation and temozolomide in newly diagnosed glioblastoma. Neuro-Oncology. 2017; 19(7):965-975

49. Reid SM, Johnstone BR, Westbury C, Rawicki B, Reddihough DS. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling in children with neurological disorders. Developmental Medicine and Child Neurology. 2008; 50(2):123-128

50. Rektor I, Krauss GL, Inoue Y, Kaneko S, Williams B, Patten A et al. Assessment of the long-term efficacy and safety of adjunctive perampanel in tonic-clonic seizures: Analysis of four open-label extension studies. Epilepsia. 2020; 61(7):1491-1502

51. Remy C, Beaumont D. Efficacy and safety of vigabatrin in the long-term treatment of refractory epilepsy. British Journal of Clinical Pharmacology. 1989; 27(Suppl 1):125S-129S

52. Rentmeester T, Janssen A, Hulsman J, Scholtes F, van der Kleij B, Overweg J et al. A double-blind, placebo-controlled evaluation of the efficacy and safety of loreclezole as add-on therapy in patients with uncontrolled partial seizures. Epilepsy Research. 1991; 9(1):59-64

53. Rentmeester T, Janssen A, Hulsman J, Scholtes F, van der Kleij B, Overweg J et al. Long-term evaluation of the efficacy and safety of loreclezole as add-on therapy in patients with uncontrolled partial seizures: a 1-year open follow-up. Epilepsy Research. 1991; 9(1):65-70

54. Rezaei F, Nasseri K, Esfandiari GR, Sadeghi SM, Fathie M, Gharibi F. Remifentanil added to propofol for induction of anesthesia can reduce reorientation time after electroconvulsive therapy in patients with severe mania. Journal of ECT. 2012; 28(2):124-127

55. Riaz IB, Dhoble A, Mizyed A, Hsu CH, Husnain M, Lee JZ et al. Transcatheter patent foramen ovale closure versus medical therapy for cryptogenic stroke: A meta-analysis of randomized clinical trials. BMC Cardiovascular Disorders. 2013; 13:116

56. Rich TL, Menk J, Krach LE, Feyma T, Gillick BT. Repetitive transcranial magnetic stimulation/behavioral intervention clinical trial: Long-term follow-up of outcomes in congenital hemiparesis. Journal of Child and Adolescent Psychopharmacology. 2016; 26(7):598-605

57. Richardson MP, Koepp MJ, Brooks DJ, Duncan JS. 11C-flumazenil PET in neocortical epilepsy. Neurology. 1998; 51(2):485-492

58. Richens A, Davidson DL, Cartlidge NE, Easter DJ. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Journal of Neurology, Neurosurgery and Psychiatry. 1994; 57(6):682-687

59. Ridsdale L, Kwan I, Cryer C. Newly diagnosed epilepsy: can nurse specialists help? A randomized controlled trial. Epilepsy Care Evaluation Group. Epilepsia. 2000; 41(8):1014-1019

60. Ridsdale L, McKinlay A, Wojewodka G, Robinson EJ, Mosweu I, Feehan SJ et al. Self-Management education for adults with poorly controlled epILEpsy [SMILE (UK)]: a randomised controlled trial. Health technology assessment (Winchester, England). 2018; 22(21):1-142

61. 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. Epilepsy Care Evaluation Group. BMJ. 1997; 314(7074):120-122

62. Ridsdale L, Wojewodka G, Robinson EJ, Noble AJ, Morgan M, Taylor SJC et al. The effectiveness of a group self-management education course for adults with poorly controlled epilepsy, SMILE (UK): A randomized controlled trial. Epilepsia. 2018; 59(5):1048-1061

63. Rieckmann P, Heidenreich F, Sailer M, Zettl UK, Zessack N, Hartung HP et al. Treatment de-escalation after mitoxantrone therapy: Results of a phase IV, multicentre, open-label, randomized study of subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis. Therapeutic Advances in Neurological Disorders. 2012; 5(1):3-12

64. Ring H, Howlett J, Pennington M, Smith C, Redley M, Murphy C et al. Training nurses in a competency framework to support adults with epilepsy and intellectual disability: the EpAID cluster RCT. Health Technology Assessment. 2018; 22(10):1-104

65. Riveau G, Schacht AM, Dompnier JP, Deplanque D, Seck M, Waucquier N et al. Safety and efficacy of the rSh28GST urinary schistosomiasis vaccine: A phase 3 randomized, controlled trial in Senegalese children. PLoS Neglected Tropical Diseases. 2018; 12:e0006968

66. Rivera-Castano L, Leal-Cantu R, Abreu P, Guerrero M, Davila G. A 21-week open-label clinical trial of pregabalin as adjunctive therapy in partial seizures at multiple centers in Mexico (PREPS Mexico). Epilepsy Research. 2012; 100(1-2):74-79

67. Robinson BJ, Robinson GM, Maling TJ, Johnson RH. Is clonidine useful in the treatment of alcohol withdrawal? Alcoholism: Clinical & Experimental Research. 1989; 13(1):95-98

68. Rogin J, Wheless J, Abou-Khalil B, Wolter KD, Pixton GC, Sherman NA et al. Safety and effectiveness of long-term treatment with diazepam auto-injector administered by caregivers in an outpatient setting for the treatment of acute repetitive seizures. Epilepsia. 2014; 55(9):1444-1451

69. Romo ML, Wyka K, Carpio A, Leslie D, Andrews H, Bagiella E et al. The effect of albendazole treatment on seizure outcomes in patients with symptomatic neurocysticercosis. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2015; 109(11):738-746

70. Rosati A, Ilvento L, L'Erario M, De Masi S, Biggeri A, Fabbro G et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01). BMJ Open. 2016; 6:e011565

71. Rosenfeld W, Conry J, Lagae L, Rozentals G, Yang H, Fain R et al. Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a

combined extension study. European journal of paediatric neurology: EJPN. 2015; 19(4):435-445

72. Rosman NP, Colton T, Labazzo J, Gilbert PL, Gardella NB, Kaye EM et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. New England Journal of Medicine. 1993; 329(2):79-84

73. Rosman NP, Douglass LM, Paolini JL. Preventing febrile seizures in children with oral diazepam: can a controlled trial truly be "double-blind?". Journal of Pediatrics. 2001; 138(4):548-552

74. Rossetti AO, Jeckelmann S, Novy J, Roth P, Weller M, Stupp R. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. Neuro-Oncology. 2014; 16(4):584-588

75. RTS.S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015; 386(9988):31-45

76. RTS.S Clinical Trials Partnership, Agnandji ST, Lell B, Soulanoudjingar SS, Fernandes JF, Abossolo BP et al. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. New England Journal of Medicine. 2011; 365(20):1863-1875

77. Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014; 55(1):47-56

78. Sabers A, Moller A, Dam M, Smed A, Arlien-Soborg P, Buchman J et al. Cognitive function and anticonvulsant therapy: effect of monotherapy in epilepsy. Acta Neurologica Scandinavica. 1995; 92(1):19-27

79. Sabna M, Thomas A. Impact of pharmaceutical care on bone health in epileptic women taking antiepileptic drugs: An interventional trial. International Research Journal of Pharmacy. 2018; 9(7):173-176

80. Saccone G, Schuit E, Amer-Wahlin I, Xodo S, Berghella V. Electrocardiogram ST analysis during labor: A systematic review and meta-analysis of randomized controlled trials. Obstetrics and Gynecology. 2016; 127(1):127-135

81. Sacevich C, Semakuba B, McKay WP, Thakore S, Twagirumugabe T, Nyiligira J. Subcutaneous ketamine for postoperative pain relief in Rwanda: a randomized clinical trial. Canadian Journal of Anaesthesia. 2018; 65(2):170-177

82. Sachdeo R, Kramer LD, Rosenberg A, Sachdeo S. Felbamate monotherapy: controlled trial in patients with partial onset seizures. Annals of Neurology. 1992; 32(3):386-392

83. Sachdeo RC, Reife RA, Lim P, Pledger G. Topiramate monotherapy for partial onset seizures. Epilepsia. 1997; 38(3):294-300

84. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. New England Journal of Medicine. 1993; 328(12):839-846

85. Sackellares JC, Ramsay RE, Wilder BJ, Browne TR, 3rd, Shellenberger MK. Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures. Epilepsia. 2004; 45(6):610-617

86. Sáez-Llorens X, McCoig C, Feris JM, Vargas SL, Klugman KP, Hussey GD et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatric Infectious Disease Journal. 2002; 21(1):14-22

87. Sahjpaul RL, Mahon J, Wiebe S. Dexamethasone for morbidity after subdural electrode insertion--a randomized controlled trial. Canadian Journal of Neurological Sciences. 2003; 30(4):340-348

88. Saida T, Itoyama Y, Kikuchi S, Hao Q, Kurosawa T, Ueda K et al. Long-term efficacy and safety of fingolimod in Japanese patients with relapsing multiple sclerosis: 3-year results of the phase 2 extension study. BMC Neurology. 2017; 17:17

89. Salinsky M, Storzbach D, Munoz S. Cognitive effects of pregabalin in healthy volunteers: a double-blind, placebo-controlled trial. Neurology. 2010; 74(9):755-761

90. Salinsky MC. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995; 45(2):224-230

91. Salinsky MC, Uthman BM, Ristanovic RK, Wernicke JF, Tarver WB. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. Archives of Neurology. 1996; 53(11):1176-1180

92. Salloway S, Marshall GA, Lu M, Brashear HR. Long-term safety and efficacy of bapineuzumab in patients with mild-to-moderate alzheimer's disease: A phase 2, open-label extension study. Current Alzheimer Research. 2018; 15(13):1231-1243

93. Saposnik G, Cohen LG, Mamdani M, Pooyania S, Ploughman M, Cheung D et al. Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. Lancet Neurology. 2016; 15(10):1019-1027

94. Saygin MZ, Sungur MZ, Sabol EU, Cetinkaya P. Nefazodone versus sertraline in treatment of posttraumatic stress disorder. Klinik Psikofarmakoloji Bulteni. 2002; 12(1):1-5

95. Schachter SC, Leppik IE, Matsuo F, Messenheimer JA, Faught E, Moore EL et al. Lamotrigine: A six-month, placebo-controlled, safety and tolerance study. Journal of Epilepsy. 1995; 8(3):201-209

96. Schechtmann G, Lind G, Winter J, Meyerson BA, Linderoth B. Intrathecal clonidine and baclofen enhance the pain-relieving effect of spinal cord stimulation: A comparative placebo-controlled, randomized trial. Neurosurgery. 2010; 67(1):173-181

97. Schonenberg M, Wiedemann E, Schneidt A, Scheeff J, Logemann A, Keune PM et al. Neurofeedback, sham neurofeedback, and cognitive-behavioural group therapy in adults with attention-deficit hyperactivity disorder: a triple-blind, randomised, controlled trial. The Lancet Psychiatry. 2017; 4(9):673-684

98. Schougaard LM, Mejdahl CT, Petersen KH, Jessen A, de Thurah A, Sidenius P et al. Effect of patient-initiated versus fixed-interval telePRO-based outpatient follow-up: study protocol for a pragmatic randomised controlled study. BMC Health Services Research. 2017; 17(1):83

99. Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet. 1999; 353(9153):623-626

100. Sedman AJ, Gilmet GP, Sayed AJ, Posvar EL. Initial human safety and tolerance study of a GABA uptake inhibitor, CI-966: Potential role of GABA as a mediator in the pathogenesis of schizophrenia and mania. Drug Development Research. 1990; 21(3):235-242

101. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios--comparison of 3:1 with 4:1 diet. Epilepsia. 2007; 48(4):801-805

102. Sethi A, Chandra D, Puri V, Mallika V. Gabapentin and lamotrigine in Indian patients of partial epilepsy refractory to carbamazepine. Neurology India. 2002; 50(3):359-363

103. Seynaeve L, Devroye A, Dupont P, Van Paesschen W. Randomized crossover sham-controlled clinical trial of targeted low-frequency transcranial magnetic stimulation comparing a figure-8 and a round coil to treat refractory neocortical epilepsy. Epilepsia. 2016; 57(1):141-150

104. Shaw L, Rodgers H, Price C, van Wijck F, Shackley P, Steen N et al. BoTULS: A multicentre randomized controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Health Technology Assessment. 2010; 14(26):i-141

105. Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P et al. Childhood-onset schizophrenia: A double-blind, randomized clozapine-olanzapine comparison. Archives of General Psychiatry. 2006; 63(7):721-730

106. Shefner J, Meininger V, Rothstein J, Chio A, Ludolph A, Genge A et al. A double blind, multi-national, placebo controlled trial of talampanel in amyotrophic lateral sclerosis: study design and subject baseline characteristics. Amyotrophic Lateral Sclerosis. 2009; 10(Suppl 1):72

107. Shi J, Zhou C, Liu S, Sun H, Wang Y, Yan F et al. Outcome impact of different tranexamic acid regimens in cardiac surgery with cardiopulmonary bypass (OPTIMAL): Rationale, design, and study protocol of a multicenter randomized controlled trial. American Heart Journal. 2020; 222:147-156

108. Shim JY, Park YW, Yoon BH, Cho YK, Yang JH, Lee Y et al. Multicentre, parallel group, randomised, single-blind study of the safety and efficacy of atosiban versus ritodrine in the treatment of acute preterm labour in Korean women. BJOG: An International Journal of Obstetrics and Gynaecology. 2006; 113(11):1228-1234

109. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia. 2000; 41(9):1179-1186

110. Si Y, Xiao X, Xia C, Guo J, Hao Q, Mo Q et al. Optimising epilepsy management with a smartphone application: a randomised controlled trial. Medical Journal of Australia. 2020; 212(6):258-262

111. Simpson DM, Goldenberg J, Kasner S, Nash M, Reding MJ, Zweifler RM et al. Dalfampridine in chronic sensorimotor deficits after ischemic stroke: A proof of concept study. Journal of Rehabilitation Medicine. 2015; 47(10):924-931

112. Singhi P, Dayal D, Khandelwal N. One week versus four weeks of albendazole therapy for neurocysticercosis in children: a randomized, placebo-controlled double blind trial. Pediatric Infectious Disease Journal. 2003; 22(3):268-272

113. Singhi P, Kaushal M, Singhi S, Ray P. Seven days vs. 10 days ceftriaxone therapy in bacterial meningitis. Journal of Tropical Pediatrics. 2002; 48(5):273-279

114. Singla M, Prabhakar S, Modi M, Medhi B, Khandelwal N, Lal V. Short-course of prednisolone in solitary cysticercus granuloma: a randomized, double-blind, placebo-controlled trial. Epilepsia. 2011; 52(10):1914-1917

115. Sivenius J, Ylinen A, Kalviainen R, Riekkinen PJ, Sr. Long-term study with gabapentin in patients with drug-resistant epileptic seizures. Archives of Neurology. 1994; 51(10):1047-1050

116. Smith C, Birnbaum G, Carter JL, Greenstein J, Lublin FD. Tizanidine treatment of spasticity caused by multiple sclerosis: results of a double-blind, placebo-controlled trial. US Tizanidine Study Group. Neurology. 1994; 44(11 Suppl 9):S34-42

117. Smith D, Chadwick D, Baker G, Davis G, Dewey M. Seizure severity and the quality of life. Epilepsia. 1993; 34(Suppl 5):S31-S35

118. Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. Journal of Child Neurology. 2001; 16(2):86-92

119. Sobaniec W, Kulak W, Smigielska-Kuzia J, Bockowski L, Majkowski J, Jedrzejczak J. A multicenter, placebo-controlled, double-blind study of efficacy of a new form of carbamazepine (Carbatrol) in refractory epileptic patients. Polish Journal of Pharmacology. 2004; 56(2):195-201

120. Solanki C, Pandey P, Rao KV. Predictors of aneurysmal rebleed before definitive surgical or endovascular management. Acta Neurochirurgica. 2016; 158(6):1037-1044

121. Solomkin JS, Fant WK, Rivera JO, Alexander JW. Randomized trial of imipenem/cilastatin versus gentamicin and clindamycin in mixed flora infections. American Journal of Medicine. 1985; 78(6A):85-91

122. Sotelo J, Briceno E, Lopez-Gonzalez MA. Adding chloroquine to conventional treatment for glioblastoma multiforme: A randomized, double-blind, placebo-controlled trial. Annals of Internal Medicine. 2006; 144(5):337-343

123. Spivey WH, Roberts JR, Derlet RW. A clinical trial of escalating doses of flumazenil for reversal of suspected benzodiazepine overdose in the emergency department. Annals of Emergency Medicine. 1993; 22(12):1813-1821

124. Sprigg N, Flaherty K, Appleton JP, Salman RAS, Bereczki D, Beridze M et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. Lancet. 2018; 391(10135):2107-2115

125. Srinivasakumar P, Zempel J, Trivedi S, Wallendorf M, Rao R, Smith B et al. Treating EEG seizures in hypoxic ischemic encephalopathy: A randomized controlled trial. Pediatrics. 2015; 136(5):e1302-e1309

126. Statler VA, Albano FR, Airey J, Sawlwin DC, Graves Jones A, Matassa V et al. Immunogenicity and safety of a quadrivalent inactivated influenza vaccine in children 6-59 months of age: a phase 3, randomized, noninferiority study. Vaccine. 2019; 37(2):343-351

127. Stauffer VL, Baygani SK, Kinon BJ, Krikke-Workel JO. A short-term, multicenter, placebo-controlled, randomized withdrawal study of a metabotropic glutamate 2/3 receptor agonist using an electronic patient-reported outcome device in patients with schizophrenia. Journal of Clinical Psychopharmacology. 2014; 34(5):552-558

128. Stefan H, Wang-Tilz Y, Pauli E, Dennhofer S, Genow A, Kerling F et al. Onset of action of levetiracetam: a RCT trial using therapeutic intensive seizure analysis (TISA). Epilepsia. 2006; 47(3):516-522

129. Stefan H, Wang Y, Kerling F, Hopp P, Zhou D, Dienel A et al. Therapeutic intensive seizure analysis (TISA) in presurgical evaluation of Losigamone. Acta Neurologica Scandinavica. 2001; 104(4):195-201

130. Strengell T, Uhari M, Tarkka R, Uusimaa J, Alen R, Lautala P et al. Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. Archives of Pediatrics and Adolescent Medicine. 2009; 163(9):799-804

131. Struys MMRF, Valk BI, Eleveld DJ, Absalom AR, Meyer P, Meier S et al. A phase 1, single-center, double-blind, placebo-controlled study in healthy subjects to assess the safety, tolerability, clinical effects, and pharmacokinetics-pharmacodynamics of intravenous cyclopropyl-methoxycarbonylmetomidate (ABP-700) after a single ascending bolus dose. Anesthesiology. 2017; 127(1):20-35

132. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong YK et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncology. 2014; 15(10):1100-1108

133. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncology. 2009; 10(5):459-466

134. Stupp R, Taillibert S, Kanner A, Read W, Steinberg DM, Lhermitte B et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma a randomized clinical trial. JAMA - Journal of the American Medical Association. 2017; 318(23):2306-2316

135. Sundqvist A, Nilsson BY, Tomson T. Valproate monotherapy in juvenile myoclonic epilepsy: dose-related effects on electroencephalographic and other neurophysiologic tests. Therapeutic Drug Monitoring. 1999; 21(1):91-96

136. Sveinbjornsdottir S, Sander JW, Patsalos PN, Upton D, Thompson PJ, Duncan JS. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. Seizure. 1994; 3(1):29-35

137. Szaflarski JP, Sadek A, Greve B, Williams P, Varner JA, Moseley BD. Randomized open-label trial of intravenous brivaracetam versus lorazepam for acute treatment of increased seizure activity. Epilepsy & Behavior. 2020; 109:107127

138. Szer J, Durrant S, Schwarer AP, Bradstock KF, Gibson J, Arthur C et al. Oral versus intravenous ganciclovir for the prophylaxis of cytomegalovirus disease after allogeneic bone marrow transplantation. Internal Medicine Journal. 2004; 34(3):98-101

139. Tacke M, Rupp N, Gerstl L, Heinen F, Vill K, Bonfert M et al. Benign epilepsy with centrotemporal spikes: Correlating spike frequency and neuropsychology. Acta Neurologica Scandinavica. 2018; 138(6):475-481

140. Taghavi Ardakani A, Honarpisheh A, Fakharian E, Talebian A, Jamali M, Moosavi GA et al. Oral versus nasal vasopressin in the treatment of nocturnal enuresis in 5- to 12-year-old children. Iranian Journal of Child Neurology. 2010; 4(1):13-16

141. Taghdiri MM, Ashrafi MR, Bakhshandeh-Bali MK, Taheri-Otaghsara SM, Nasehi MM, Mohammad G. Clinical trial of vigabatrin as adjunctive therapy in children with refractory epilepsy. Iranian Journal of Pediatrics. 2013; 23(6):653-658

142. Takeuchi S, Wada K, Nagatani K, Otani N, Osada H, Nawashiro H. Sulfasalazine and temozolomide with radiation therapy for newly diagnosed glioblastoma. Neurology India. 2014; 62(1):42-47

143. Tang F, Zhu G, Jiao Z, Ma C, Chen N, Wang B. The effects of medication education and behavioral intervention on Chinese patients with epilepsy. Epilepsy & Behavior. 2014; 37:157-164

144. Tartara A, Manni R, Galimberti CA, Morini R, Mumford JP, Iudice A et al. Six-year follow-up study on the efficacy and safety of vigabatrin in patients with epilepsy. Acta Neurologica Scandinavica. 1992; 86(3):247-251

145. Tatum WOt, French JA, Faught E, Morris GL, 3rd, Liporace J, Kanner A et al. Postmarketing experience with topiramate and cognition. Epilepsia. 2001; 42(9):1134-1140

146. Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J et al. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. Lancet Neurology. 2007; 6(1):29-38

147. Temkin NR, Dikmen SS, Anderson GD, Wilensky AJ, Holmes MD, Cohen W et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. Journal of Neurosurgery. 1999; 91(4):593-600

148. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. New England Journal of Medicine. 1990; 323(8):497-502

149. Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. New England Journal of Medicine. 1994; 330(20):1407-1410

150. Terai T, Yukioka H, Fujimori M. A double-blind comparison of lidocaine and mepivacaine during epidural anaesthesia. Acta Anaesthesiologica Scandinavica. 1993; 37(6):607-610

151. Thangaratinam S MN, Newton S, Weckesser A, Bagary M, Greenhill L, et al. AntiEpileptic drug monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies. Health Technology Assessment. 2018; 22(23)

152. Thanh TN, Chiron C, Dellatolas G, Rey E, Pons G, Vincent J et al. Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome). Archives de Pédiatrie. 2002; 9(11):1120-1127

153. Thilothammal N, Banu K, Ratnam RS. Comparison of phenobarbitone, phenytoin with sodium valproate: randomized, double-blind study. Indian Pediatrics. 1996; 33(7):549-555

154. Thilothammal N, Kannan n, Krishnamurthy PV, Kamala KG, Ahamed S, Banu K. Role of phenobarbitone in preventing recurrence of febrile convulsions. Indian Pediatrics. 1993; 30(5):637-642

155. Thomas SV, Kurup JR, Kuruvilla A, Nair BN, Thomas KL, Sarma PS. An expert system for the diagnosis of epilepsy: results of a clinical trial. National Medical Journal of India. 2001; 14(5):274-276

156. Tilz C, Stefan H, Hopfengaertner R, Kerling F, Genow A, Wang-Tilz Y. Influence of levetiracetame on ictal and postictal EEG in patients with partial seizures. European Journal of Neurology. 2006; 13(12):1352-1358

157. Titre-Johnson S, Schoeler N, Eltze C, Williams R, Vezyroglou K, McCullagh H et al. Ketogenic diet in the treatment of epilepsy in children under the age of 2 years: study protocol for a randomised controlled trial. Trials. 2017; 18:195

158. Tolbert D, Cloyd J, Biton V, Bekersky I, Walzer M, Wesche D et al. Bioequivalence of oral and intravenous carbamazepine formulations in adult patients with epilepsy. Epilepsia. 2015; 56(6):915-923

159. Tolbert D, Harris SI, Bekersky I, Lee D, Isojarvi J. Withdrawal-related adverse events from clinical trials of clobazam in Lennox-Gastaut syndrome. Epilepsy & Behavior. 2014; 37:11-15

160. Tolchin B, Baslet G, Suzuki J, Martino S, Blumenfeld H, Hirsch LJ et al. Randomized controlled trial of motivational interviewing for psychogenic nonepileptic seizures. Epilepsia. 2019; 60(5):986-995

161. Trevathan E, Kerls SP, Hammer AE, Vuong A, Messenheimer JA. Lamotrigine adjunctive therapy among children and adolescents with primary generalized tonic-clonic seizures. Pediatrics. 2006; 118(2):e371-378

162. Trinka E, Ben-Menachem E, Kowacs PA, Elger C, Keller B, Loffler K et al. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: A phase III double-blind, randomized, parallel-group, multicenter study. Epilepsia. 2018; 59(2):479-491

163. Trudeau V, Myers S, LaMoreaux L, Anhut H, Garofalo E, Ebersole J. Gabapentin in naive childhood absence epilepsy: results from two double-blind, placebo-controlled, multicenter studies. Journal of Child Neurology. 1996; 11(6):470-475

164. Tsounis S, Kimiskidis VK, Kazis D, Gkiatas K, Garganis K, Karageorgiou K et al. An open-label, add-on study of pregabalin in patients with partial seizures: a multicenter trial in Greece. Seizure. 2011; 20(9):701-705

165. Tungmanowutthikul S, Champawong R, Songthamwat S, Songthamwat M. Comparison of magnesium sulphate protocols by weight-adjusted versus two grams per hour for preventing convulsion in preeclampsia: A randomised controlled trial. Journal of Clinical and Diagnostic Research. 2019; 13(2):QC01-QC04

166. Turan Gurhopur FD, Isler Dalgic A. The effect of a modular education program for children with epilepsy and their parents on disease management. Epilepsy & Behavior. 2018; 78:210-218

167. Uijl SG, Uiterwaal CS, Aldenkamp AP, Carpay JA, Doelman JC, Keizer K et al. Adjustment of treatment increases quality of life in patients with epilepsy: a randomized controlled pragmatic trial. European Journal of Neurology. 2009; 16(11):1173-1177

168. Vaghadia H, Chan V, Ganapathy S, Lui A, McKenna J, Zimmer K. A multicentre trial of ropivacaine 7.5 mg x ml(-1) vs bupivacaine 5 mg x ml(-1) for supra clavicular brachial plexus anesthesia. Canadian Journal of Anaesthesia. 1999; 46(10):946-951

169. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). Stroke. 2007; 38(9):2506-2517

170. Van Der Meyden CH, Kruger AJ, Muller FO, Rabie W, Schall R. Acute oral loading of carbamazepine-CR and phenytoin in a double-blind randomized study of patients at risk of seizures. Epilepsia. 1994; 35(1):189-194

171. Van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. Epilepsia. 2013; 54(1):89-97

172. van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, Habbema JD, Moll HA. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics. 1998; 102(5):E51

173. VanLandingham KE, Crockett J, Taylor L, Morrison G. A phase 2, double-blind, placebo-controlled trial to investigate potential drug-drug interactions between cannabidiol and clobazam. Journal of Clinical Pharmacology. 2020; 60(10):1304-1313

174. Vining EP, Mellitis ED, Dorsen MM, Cataldo MF, Quaskey SA, Spielberg SP et al. Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. Pediatrics. 1987; 80(2):165-174

175. Viscusi ER, Sinatra R, Onel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. Clinical Journal of Pain. 2014; 30(2):102-110

176. Wakelee HA, Dahlberg SE, Keller SM, Tester WJ, Gandara DR, Graziano SL et al. Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncology. 2017; 18(12):1610-1623

177. Wang X, Yang D, Wang S, Zhao X, Zhang L, Chen Z et al. Effects of low-frequency repetitive transcranial magnetic stimulation on electroencephalogram and seizure frequency in 15 patients with temporal lobe epilepsy following dipole source localization. Neural Regeneration Research. 2008; 3(11):1257-1260

178. Wanigasinghe J, Arambepola C, Ranganathan SS, Sumanasena S. Randomized, single-blind, parallel clinical trial on efficacy of oral prednisolone versus intramuscular corticotropin: A 12-month assessment of spasm control in west syndrome. Pediatric Neurology. 2017; 76:14-19

179. Webster L, Chey WD, Tack J, Lappalainen J, Diva U, Sostek M. Randomised clinical trial: The long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. Alimentary Pharmacology and Therapeutics. 2014; 40(7):771-779

180. Weiden PJ, Claxton A, Kunovac J, Walling DP, Du Y, Yao B et al. Efficacy and safety of a 2-month formulation of aripiprazole lauroxil with 1-day initiation in patients hospitalized for acute schizophrenia transitioned to outpatient care: Phase 3, randomized, double-blind, active-control ALPINE study. Journal of Clinical Psychiatry. 2020; 81(3):19m13207

181. Weinbroum A, Rudick V, Sorkine P, Nevo Y, Halpern P, Geller E et al. Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients. Critical Care Medicine. 1996; 24(2):199-206

182. Welch RD, Nicholas K, Durkalski-Mauldin VL, Lowenstein DH, Conwit R, Mahajan PV et al. Intramuscular midazolam versus intravenous lorazepam for the prehospital treatment of status epilepticus in the pediatric population. Epilepsia. 2015; 56(2):254-262

183. Wheless JW, Meng TC, Van Ess PJ, Detyniecki K, Sequeira DJ, Pullman WE. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters: An open-label extension trial. Epilepsia. 2019; 60(9):1809-1819

184. Wietholtz H, Zysset T, Kreiten K, Kohl D, Buchsel R, Matern S. Effect of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. European Journal of Clinical Pharmacology. 1989; 36(4):401-406

185. Wijnen BFM, de Kinderen RJA, Lambrechts D, Postulart D, Aldenkamp AP, Majoie M et al. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. Epilepsy Research. 2017; 132:91-99

186. Wilky BA, Trucco MM, Subhawong TK, Florou V, Park W, Kwon D et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncology. 2019; 20(6):837-848

187. Wu XY, Hong Z, Wu X, Wu LW, Wang XF, Zhou D et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in Chinese patients with refractory partial-onset seizures. Epilepsia. 2009; 50(3):398-405

188. Xu F, Feng QH, Yu L, Liu J, Sun HB. Effects of topiramate versus other antiepileptic drugs on the cognitive function of patients with epilepsy. Neural Regeneration Research. 2007; 2(2):95-98

189. Xu NG, Zhu DT, Xiao B, Xie GJ. Impact of traditional antiepileptic and topiramate on the quality of life of adult epileptic patients. Chinese Journal of Clinical Rehabilitation. 2004; 8(25):5386-5388

190. Yadegary MA, Maemodan FG, Nayeri ND, Ghanjekhanlo A. The effect of self-management training on health-related quality of life in patients with epilepsy. Epilepsy & Behavior. 2015; 50:108-112

191. Yamamoto T, Kubota Y, Murayama H, Ozeki H, Numachi Y, Ikeda A. Appropriate conversion from valproate monotherapy to lamotrigine monotherapy in Japanese women with epilepsy. Epilepsy and seizure. 2016; 8(1):21-31

192. Yamamoto T, Lim SC, Ninomiya H, Kubota Y, Shin WC, Kim DW et al. Efficacy and safety of perampanel monotherapy in patients with focal-onset seizures with newly diagnosed epilepsy or recurrence of epilepsy after a period of remission: The open-label Study 342 (FREEDOM Study). Epilepsia Open. 2020; 5(2):274-284

193. Yen DJ, Yu HY, Guo YC, Chen C, Yiu CH, Su MS. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. Epilepsia. 2000; 41(9):1162-1166

194. Young AH, Geddes JR, Macritchie K, Rao SN, Vasudev A. Tiagabine in the maintenance treatment of bipolar disorders. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD005173. DOI: 10.1002/14651858.CD005173.pub2.

195. Young KD, Okada PJ, Sokolove PE, Palchak MJ, Panacek EA, Baren JM et al. A randomized, double-blinded, placebo-controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. Annals of Emergency Medicine. 2004; 43(4):435-446

196. Younus SM, Basar S, Gauri SA, Khan AA, Imran M, Abubakar S et al. Comparison of phenytoin versus levetiracetam in early seizure prophylaxis after traumatic brain

injury, at a tertiary care hospital in Karachi, Pakistan. Asian Journal of Neurosurgery. 2018; 13(4):1096-1100

197. Zamponi N, Cardinali C. Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children. Archives of Neurology. 1999; 56(5):605-607

198. Zhang PQ, Liu H, Li HJ. Influence of carbamazepine-phenobarbital combined treatment on IL-1beta, IL-6, Bcl-2 and Bax expression in children with epilepsy. Biomedical Research (India). 2017; 28(19):8501-8504

199. Zhao J, Sang Y, Zhang Y, Zhang D, Chen J, Liu X. Efficacy of levetiracetam combined with sodium valproate on pediatric epilepsy and its effect on serum miR-106b in children. Experimental and Therapeutic Medicine. 2019; 18(6):4436-4442

200. Zhong WZ, Xu ST, Yan HH, Yang XN, Zhou Q, Wu YL et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncology. 2018; 19(1):139-148

201. Zhou H, Wang N, Xu L, Huang HL, Yu CY. Clinical study on anti-epileptic drug with B vitamins for the treatment of epilepsy after stroke. European Review for Medical and Pharmacological Sciences. 2017; 21(14):3327-3331

202. Zou LP, Wang X, Dong CH, Chen CH, Zhao W, Zhao RY. Three-week combination treatment with ACTH + magnesium sulfate versus ACTH monotherapy for infantile spasms: a 24-week, randomized, open-label, follow-up study in China. Clinical Therapeutics. 2010; 32(4):692-700

Appendices

Appendix A Review protocols

A.1 Review protocol for therapeutic drug monitoring in pregnancy

ID	Field	Content
1.	Review title	What is the appropriate serial monitoring of drug levels, including timing, in girls or women who are thinking about conceiving, are pregnant or in the post-partum period?
2.	Review question	To evaluate whether therapeutic drug monitoring of girls or women on AEDs during pregnancy and post-partum reduces seizure deterioration compared with clinical features monitoring after a reduction in serum AED levels and at which time intervals should monitoring take place.
3.	Objective	The review will determine whether therapeutic drug monitoring of girls and women during and after pregnancy reduces the probability of seizure deterioration and whether particular frequencies of monitoring should be recommended.
4.	Searches	Key paper: EMPIRE study Thangaratinam S, Marlin N, Newton S, Weckesser A, Bagary M, Greenhill L, et al. AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies. Health Technol Assess. 2018;22(23):1–152. pmid:29737274 The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase

		• MEDLINE Searches will be restricted by: • English language studies • Human studies Other searches: • Reference checking of systematic reviews The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Pregnancy can affect how drugs are metabolised. In women or girls who are pregnant. Drug monitoring can help to assess what effect pregnancy may have on AEDs and what changes to prescribing AEDs might be needed to control seizures.
6.	Population	Inclusion: girls and women planning pregnancy, during pregnancy and postpartum up to 6 months Exclusion: men, non-pregnant women not planning pregnancy
7.	Intervention/Exposure/Test	Drug monitoring (measurement of drug concentration in blood or saliva) of the following AEDs: Brivaracetam Carbamazepine (for focal motor status) Chlormethiazole (clomethiazole) Clobazam

		Clonazepam (for myoclonic status) Diazepam Eslicarbazepine Ethosuximide Fosphenytoin Gabapentin Lacosamide Lamotrigine Levetiracetam Lorazepam Midazolam Oxcarbazepine Perampanel Phenobarbital (phenobarbitone) Phenytoin Pregabalin Primidone Rufinamide Steroids (methylprednisolone, prednisolone) Stiripentol Sulthiame Tiagabine Topiramate Valproate (sodium valproate/ valproic acid) Zonisamide Dose according to prescriber discretion and / or local protocols
8.	Comparator/Reference standard/Confounding factors	usual care (adjustments without level)

9.	Types of study to be included	RCTs Systematic reviews of RCTs Published NMAs and IPDs will be considered for inclusion If insufficient RCT evidence is available, prospective observational comparative studies will be considered only if they adjust for key confounders of age of epilepsy onset, classification (focal, generalised or epilepsy syndrome).
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	During pregnancy, women with epilepsy who take antiepileptic drugs may experience a reduction in serum AED levels. This has the potential to worsen seizure control with potential consequences for the mother and her unborn child. If AED doses are increased in pregnancy this may have consequences on fetal exposure to antiepileptic drugs.
12.	Primary outcomes (critical outcomes)	• Mortality of mother or baby at study follow-up • seizure freedom during pregnancy and at 6 months post-partum • Reduction in seizure frequency (50% or greater reduction in seizure frequency) • time to first seizure in pregnancy and up to up to 6 weeks post-partum • time to subsequent seizure up to 1 year • AED drug exposure (mean daily) • quality of life (any validated measures) at study follow-up • adverse events – AED related (toxicity)

		– Pregnancy complications in mother and baby (admission to HDU/ICU for mother, admission to NICU for baby) – Seizures during labour – Attendance at ED – Congenital anomalies (neural tube defects (spina bifida), limb defects (club foot), cleft lip and palette etc) – Neurodevelopmental outcomes (Griffith Mental Development Scales and the Bayley Scales of Infant and Toddler Development scale)
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. EviBASE will be used for data extraction.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Nonrandomised study, including cohort studies: Cochrane ROBINS-I 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions

		• correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects. Consider groups identified in the equality impact assessment. Indicate any modifiers of treatment effect/confounders that will be used to try to explain heterogeneity.] Please see example protocols for relevant text: N:\TECHNICAL TEAMS\Research Fellows\Methodology RF\Current processes\Processes same in all types of review\Protocols\Example protocols

17.	Analysis of sub-groups	Groups to be considered from the equality impact assessment: women with learning disabilities Statistically heterogeneity will be assessed by visually examining the forest plots and by calculating the I^2 inconsistency statistic (with an I^2 value of more than 50% indicating considerable heterogeneity). In the event of heterogeneity, subgroup analysis will be undertaken based on the following possible modifiers of treatment effect:			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact. Angela Cooper National Guideline Centre Angela.cooper@rcplondon.ac.uk 5b Named contact e-mail epilepsies@nice.org.uk 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: From the National Guideline Centre: Gill Ritchie, Guideline Lead Angela Cooper, Senior Research Fellow Rafina Yarde, Systematic reviewer Margaret Constanti, Senior Health economist Joseph Runicles, Information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112.	
29.	Other registration details		
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords		
33.	Details of existing review of same topic by same authors		
34.	Current review status	☐	Ongoing
		☒	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information		
36.	Details of final publication	www.nice.org.uk	

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A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[25] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B Literature search strategies

This literature search strategy was used for the following review:

- To evaluate whether therapeutic drug monitoring of girls or women on AEDs during pregnancy and post-partum reduces seizure deterioration compared with clinical features monitoring after a reduction in serum AED levels and at which time intervals should monitoring take place.

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[25]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 10 August 2020	Randomised controlled trials Systematic review studies Observational studies Exclusions
Embase (OVID)	1974 – 10 August 2020	Randomised controlled trials Systematic review studies Observational studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 8 of 12 CENTRAL to 2020 Issue 8 of 12	None

Medline (Ovid) search terms

1.	exp female/
2.	exp pregnancy/
3.	pregnancy outcome/
4.	exp pregnancy complications/
5.	exp prenatal exposure delayed effects/
6.	postnatal care/
7.	postpartum period/
8.	exp Breast Feeding/
9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre-natal or postnatal or post-natal or postpartum or post-partum or conceiv* or breast feed* or breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum).ti,ab.

10.	or/1-9
11.	exp epilepsy/
12.	seizures/
13.	exp status epilepticus/
14.	seizures, febrile/
15.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
16.	or/11-15
17.	10 and 16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	randomized controlled trial.pt.
38.	controlled clinical trial.pt.
39.	randomi#ed.ti,ab.
40.	placebo.ab.
41.	randomly.ti,ab.
42.	Clinical Trials as topic.sh.
43.	trial.ti.
44.	or/37-43
45.	Meta-Analysis/
46.	exp Meta-Analysis as Topic/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	exp case control studies/
67.	case control*.ti,ab.
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/56-69
71.	Monitoring, Physiologic/ or Monitoring, Ambulatory/ or Neurophysiological Monitoring/
72.	monitor*.ti,ab.
73.	Patient compliance/ or Medication Adherence/ or Drug Monitoring/
74.	exp Patient Outcome Assessment/
75.	("patient reported outcome measures" or PROM).ti,ab.
76.	"Continuity of Patient Care"/
77.	patient care/
78.	"Delivery of Health Care, Integrated"/
79.	critical pathways/
80.	((care or clinical or critical or patient*) adj2 manag*).ti,ab.
81.	Telemetry/ or Telemedicine/
82.	(telemonitor* or telemedicine or telehealth or tele medicine or tele health or smartphone* or smart phone or ipad* or iphone* or device* or virtual or remote or wireless or internet or wifi or wi fi).ti,ab.
83.	exp "Appointments and Schedules"/
84.	Self-Care/
85.	(self adj (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)).ti,ab.
86.	((survellian* or review* or assess* or test* or evaluat* or program* or observed or observation* or provision or strateg* or clinic or clinics or pattern* or followup* or follow up* or checkup or check up* or appointment*) adj3 (timing* or timed or time point* or times or duration or interval* or year* or annual* or biannual or month* or period* or frequen* or infrequent* or continu* or intermittent or irregular or routine* or regular* or schedul* or longterm or long term or short-term or short term or early or earliest * or proactiv* or special* or nurse* or general practi* or GP or family practi* or doctor* or medical or physician* or patient* or outpatient* or out-patient*)).ti,ab.
87.	((drug* or medication* or pharm*) adj (compliance or complying or adher*)).ti,ab.
88.	or/71-87
89.	36 and 88
90.	89 and (44 or 55 or 70)

91.	limit 90 to English language

1 **Embase (Ovid) search terms**

1.	exp female/
2.	exp pregnancy/
3.	pregnancy outcome/
4.	pregnancy complication/
5.	prenatal exposure/
6.	postnatal care/
7.	puerperium/
8.	breast feeding/
9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre natal or postnatal or post natal or postpartum or post-partum or conceiv* or breast feed* or breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum).ti,ab.
10.	or/1-9
11.	exp epilepsy/
12.	seizure/
13.	epileptic state/
14.	febrile convulsion/
15.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
16.	or/11-15
17.	letter.pt. or letter/
18.	note.pt.
19.	editorial.pt.
20.	case report/ or case study/
21.	(letter or comment*).ti.
22.	or/17-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animal/ not human/
26.	nonhuman/
27.	exp Animal Experiment/
28.	exp Experimental Animal/
29.	animal model/
30.	exp Rodent/
31.	(rat or rats or mouse or mice).ti.
32.	or/24-31
33.	*physiologic monitoring/
34.	*ambulatory monitoring/
35.	*neurophysiological monitoring/
36.	monitor*.ti,ab.
37.	*patient compliance/
38.	*medication compliance/
39.	*drug monitoring/
40.	*outcome assessment/
41.	("patient reported outcome measures" or PROM).ti,ab.

42.	*patient care/
43.	*integrated health care system/
44.	*clinical pathway/
45.	((care or clinical or critical or patient*) adj2 manag*).ti,ab.
46.	*telemetry/
47.	*telemedicine/
48.	(telemonitor* or telemedicine or telehealth or tele medicine or tele health or smartphone* or smart phone or ipad* or iphone* or device* or virtual or remote or wireless or internet or wifi or wi fi).ti,ab.
49.	*hospital management/
50.	*self care/
51.	(self adj (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)).ti,ab.
52.	((survellian* or review* or assess* or test* or evaluat* or program* or observed or observation* or provision or strateg* or clinic or clinics or pattern* or followup* or follow up* or checkup or check up* or appointment*) adj3 (timing* or timed or time point* or times or duration or interval* or year* or annual* or biannual or month* or period* or frequen* or infrequent* or continu* or intermittent or irregular or routine* or regular* or schedul* or longterm or long term or short-term or short term or early or earliest * or proactiv* or special* or nurse* or general practi* or GP or family practi* or doctor* or medical or physician* or patient* or outpatient* or out-patient*)).ti,ab.
53.	((drug* or medication* or pharm*) adj (compliance or complying or adher*)).ti,ab.
54.	or/33-53
55.	random*.ti,ab.
56.	factorial*.ti,ab.
57.	(crossover* or cross over*).ti,ab.
58.	((doubl* or singl*) adj blind*).ti,ab.
59.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
60.	crossover procedure/
61.	single blind procedure/
62.	randomized controlled trial/
63.	double blind procedure/
64.	or/55-63
65.	systematic review/
66.	meta-analysis/
67.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
68.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
69.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71.	(search* adj4 literature).ab.
72.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
73.	cochrane.jw.
74.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
75.	or/65-74
76.	Clinical study/
77.	Observational study/
78.	family study/

79.	longitudinal study/
80.	retrospective study/
81.	prospective study/
82.	cohort analysis/
83.	follow-up/
84.	cohort*.ti,ab.
85.	83 and 84
86.	(cohort adj (study or studies or analys* or data)).ti,ab.
87.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
88.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	(before adj2 after adj2 (study or studies or data)).ti,ab.
90.	exp case control study/
91.	case control*.ti,ab.
92.	cross-sectional study/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/76-82,85-93
95.	10 and 16
96.	95 not 32
97.	54 and 96
98.	97 and (64 or 75 or 94)
99.	limit 98 to English language

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Female] explode all trees
#2.	MeSH descriptor: [Pregnancy] explode all trees
#3.	MeSH descriptor: [Pregnancy Outcome] explode all trees
#4.	MeSH descriptor: [Pregnancy Complications] explode all trees
#5.	MeSH descriptor: [Prenatal Exposure Delayed Effects] explode all trees
#6.	MeSH descriptor: [Postnatal Care] explode all trees
#7.	MeSH descriptor: [Postpartum Period] explode all trees
#8.	MeSH descriptor: [Breast Feeding] explode all trees
#9.	(female* or wom?n or girl or pregnan* or conception or prenatal or pre natal or postnatal or post natal or postpartum or post partum or conceiv* or breast feed* or breastfeed* or breastfed or breast fed or breast milk or breastmilk or mother* milk or human milk or colostrum):ti,ab
#10.	(or #1-#9)
#11.	MeSH descriptor: [Epilepsy] explode all trees
#12.	MeSH descriptor: [Seizures] this term only
#13.	MeSH descriptor: [Status Epilepticus] explode all trees
#14.	MeSH descriptor: [Seizures, Febrile] this term only
#15.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#16.	(or #11-#15)
#17.	#10 and #16
#18.	MeSH descriptor: [Monitoring, Physiologic] this term only
#19.	MeSH descriptor: [Monitoring, Ambulatory] this term only

#20.	MeSH descriptor: [Neurophysiological Monitoring] this term only
#21.	monitor*:ti,ab
#22.	MeSH descriptor: [Patient Compliance] this term only
#23.	MeSH descriptor: [Medication Adherence] this term only
#24.	MeSH descriptor: [Drug Monitoring] this term only
#25.	MeSH descriptor: [Patient Outcome Assessment] explode all trees
#26.	("patient reported outcome measures" or PROM):ti,ab
#27.	MeSH descriptor: [Continuity of Patient Care] this term only
#28.	MeSH descriptor: [Patient Care] this term only
#29.	MeSH descriptor: [Delivery of Health Care, Integrated] this term only
#30.	MeSH descriptor: [Critical Pathways] this term only
#31.	((care or clinical or critical or patient*) near/2 manag*):ti,ab
#32.	MeSH descriptor: [Telemetry] this term only
#33.	MeSH descriptor: [Telemedicine] this term only
#34.	(telemonitor* or telemedicine or telehealth or tele medicine or tele health or smartphone* or smart phone or ipad* or iphone* or device* or virtual or remote or wireless or internet or wifi or wi fi):ti,ab
#35.	MeSH descriptor: [Appointments and Schedules] explode all trees
#36.	MeSH descriptor: [Self Care] this term only
#37.	(self near (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)):ti,ab
#38.	((survellian* or review* or assess* or test* or evaluat* or program* or observed or observation* or provision or strateg* or clinic or clinics or pattern* or followup* or follow up* or checkup or check up* or appointment*) near/3 (timing* or timed or time point* or times or duration or interval* or year* or annual* or biannual or month* or period* or frequen* or infrequent* or continu* or intermittent or irregular or routine* or regular* or schedul* or longterm or long term or short-term or short term or early or earliest* or proactiv* or special* or nurse* or general practi* or GP or family practi* or doctor* or medical or physician* or patient* or outpatient* or out-patient*)):ti,ab
#39.	((drug* or medication* or pharm*) near (compliance or complying or adher*)):ti,ab
#40.	(or #18-#39)
#41.	#17 and #40

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to an Epilepsies population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics and quality of life studies.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	Health Economics 1 January 2014 – 13 May 2021 Quality of Life 1946 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Embase	Health Economics 1 January 2014 – 13 May 2021	Health economics studies Quality of life studies

Database	Dates searched	Search filter used
	Quality of Life 1974 – 13 May 2021	Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

1 **Medline (Ovid) search terms**

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/44-61
63.	26 and (43 or 62)

1 **Embase (Ovid) search terms**

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/

17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Seizures EXPLODE ALL TREES

#3.	MeSH DESCRIPTOR Status Epilepticus EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Seizures, Febrile EXPLODE ALL TREES
#5.	((dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome))
#6.	#1 OR #2 OR #3 OR #4 OR #5

1

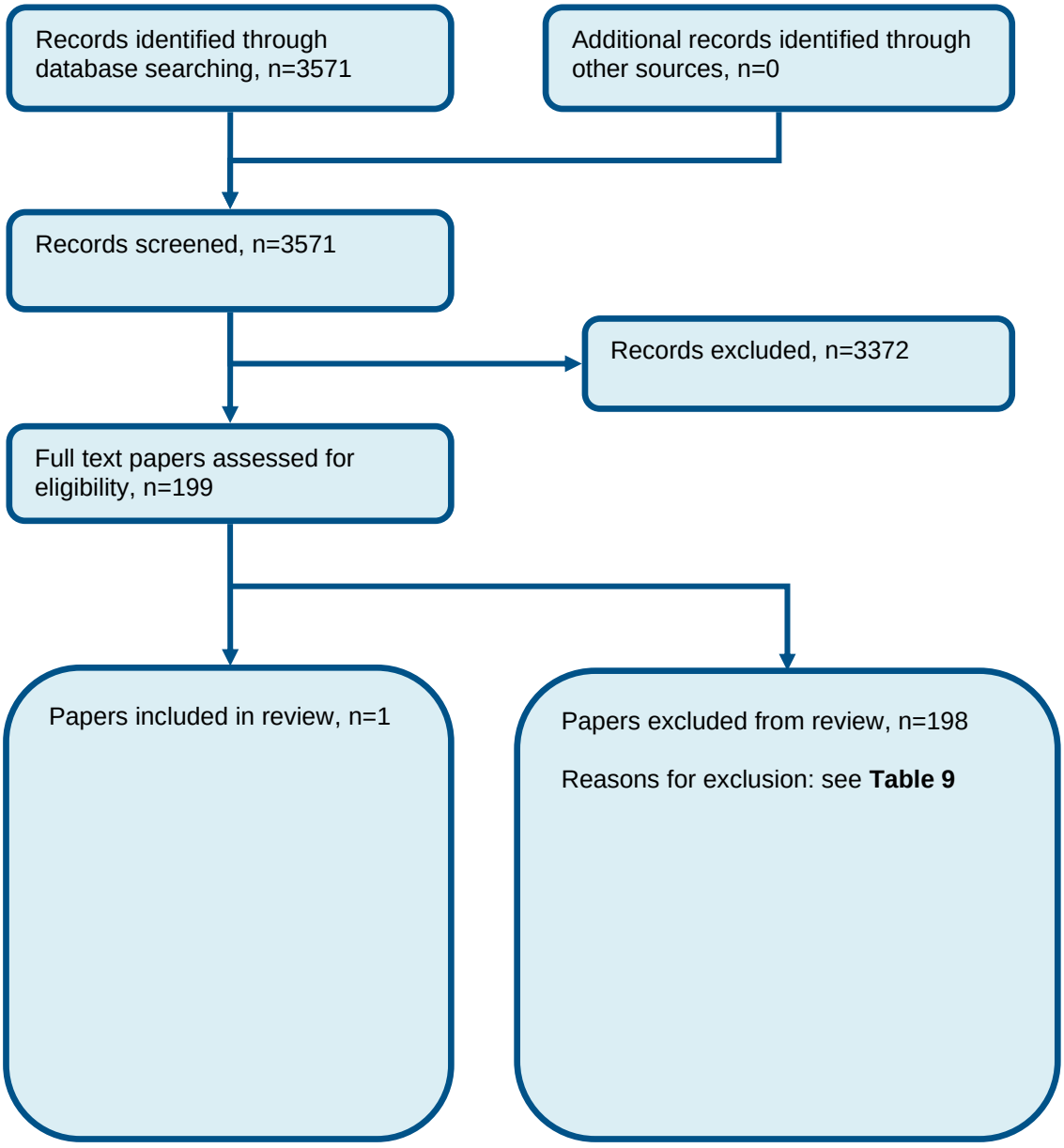
2

3

4

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of therapeutic drug monitoring in pregnancy



Appendix D Effectiveness evidence

Study	**THANGARATINAM 2018 trial: Thangaratinam s 2018[151]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=263)
Countries and setting	Conducted in United Kingdom; Setting: Obstetric and/or epilepsy clinics in secondary and tertiary care units.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: From antenatal booking until 6 weeks post-partum
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Inclusion criteria specified a 'confirmed diagnosis of epilepsy including primary, localised or unclassified.'
Stratum	Overall
Subgroup analysis within study	Not applicable: Subgroup analyses were undertaken only to check for effect modification and to assess statistical assumptions.
Inclusion criteria	Viable pregnancy of < 24 weeks' gestation; confirmed diagnosis of epilepsy (including primary, localised or unclassified); lamotrigine monotherapy/polytherapy (with carbamazepine, phenytoin or levetiracetam) or carbamazepine monotherapy or phenytoin monotherapy or levetiracetam monotherapy; capable of understanding the information provided; and ≥25% reduction in serum AED level at any time in pregnancy, compared with baseline or pre-pregnancy levels
Exclusion criteria	Aged < 16 years; documented status epilepticus in the last year or non-epileptic seizures in the last 2 years; non-lamotrigine polytherapy or sodium valproate monotherapy or polytherapy; participation in any blinded, placebo-controlled trials of investigational medicinal products in pregnancy; significant learning disability; unable to complete seizure diaries or recall frequency of seizures accurately; history of alcohol or substance abuse or dependence in the last 2 years; or an expressed intention not to take anti-epileptic drugs in pregnancy.

Recruitment/selection of patients	No details.
Age, gender and ethnicity	Age: Not stated. Gender: All females. Ethnicity: White, Black, Asian, Mixed, Other
Further population details	
Extra comments	.
Indirectness of population	No indirectness: The study population comprised pregnant women with a confirmed diagnosis of epilepsy, during pregnancy and up to 6 weeks post-partum.
Interventions	(n=133) Intervention 1: Usual care. As for the intervention group, participants in the Clinical Features Monitoring (CFM) control group participated in the RCT only if serum AED levels reduced by ≥25% compared with pre-pregnancy or initial antenatal visit. A decision to change AED dosage was made without either the clinician or mother having knowledge of monthly serum AED levels, unless an unblinding procedure was requested. The conditions for unblinding were: (i) deterioration of seizures despite treatment (in which case the serum AED level was revealed at the request of the clinician), (ii) clinical suspicion of toxicity, (iii) if levels were above the therapeutic range with risks of toxicity, or (iv) if results were requested by the clinician or mother for any other reason. Duration From randomisation until 6 to 8 weeks post-partum. Concurrent medication/care: Obstetric care. Indirectness: No indirectness; Indirectness comment: Although serum AED levels were measured for the control group, the protocol condition of 'usual care (adjustments without level)' was fulfilled. Comments: 2 women from the original randomised CFM arm (n=135) were randomised in error after the end of pregnancy. They were analysed with a non-randomised group (for which data were not extracted). (n=130) Intervention 2: Monitoring of AEDs - Combination of drugs. As for the control (CFM) group, all women in the intervention (TDM) group participated in the RCT only if serum AED levels reduced by ≥25% compared with pre-pregnancy or initial antenatal visit. Monthly serum AED levels were communicated to the responsible clinicians. The clinician discussed with the mother the potential risk of reduced serum levels and the risks and benefits to both mother and baby of increasing the doses. Shared decisions were made on the basis of the following options: (i) more frequent TDM, (ii) immediate dose increase, or (iii) delayed increase pending early testing. Duration From randomisation until 6 to 8 weeks post-partum. Concurrent medication/care: Obstetric care. Indirectness: No indirectness; Indirectness comment: The AEDs monitored were all among those specified in the protocol. Comments: 2 women from the original randomised TDM arm (n=132) were randomised in error after the end of pregnancy. They were analysed with a non-randomised group (for which data were not extracted).

Funding	Academic or government funding (National Institute for Health Research)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC DRUG MONITORING versus USUAL CARE

Protocol outcome 1: Quality of life at As stated
- Actual outcome: Maternal quality of life (QOLIE-31) at From randomisation to 36 weeks gestation.; Group 1: mean 71 (SD 16); n=114, Group 2: mean 73.7 (SD 13.5); n=110; QOLIE-31 0 to 100 Top=--; Comments: Adjusted MD (95%CI): –2.5 (–5.1 to 0.0)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome. Lack of clinician blinding was unlikely to risk performance bias. ; Indirectness of outcome: No indirectness ; Baseline details: N (%) for TDM versus CFM: Maternal congenital abnormalities 5(4) versus 5(4); Diabetes 3(2) versus 1(1); Chronic hypertension 2(2) versus 2(2); Renal disease 3(2) versus 2(2); HIV infection 0(0) versus 0(0); Learning difficulties 3(2) versus 1(1); Mental illness 19(15) versus 15(11). ; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 16; Group 2 Number missing: 23
- Actual outcome: Maternal quality of life (QOLIE-31 overall health) at From randomisation to 36 weeks gestation.; Group 1: mean 6.9 (SD 1.8); n=115, Group 2: mean 7.3 (SD 1.6); n=110; QOLIE-31 (overall health) Maximum score 10 Top=High is good outcome; Comments: Adjusted MD (95%CI): –0.35 (–0.72 to 0.02)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome. Lack of clinician blinding was unlikely to risk performance bias. ; Indirectness of outcome: No indirectness ; Baseline details: N (%) for TDM versus CFM: Maternal congenital abnormalities 5(4) versus 5(4); Diabetes 3(2) versus 1(1); Chronic hypertension 2(2) versus 2(2); Renal disease 3(2) versus 2(2); HIV infection 0(0) versus 0(0); Learning difficulties 3(2) versus 1(1); Mental illness 19(15) versus 15(11). ; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 15; Group 2 Number missing: 23
- Actual outcome: Maternal quality of life (EQ-5D) at From randomisation to 6 weeks post-partum.; Group 1: mean 0.9 (SD 0.2); n=99, Group 2: mean 0.9 (SD 0.18); n=102; EQ-5D Maximum score 1 Top=High is good outcome; Comments: Adjusted MD (95%CI): 0.00 (–0.05 to 0.05)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome. Lack of clinician blinding was unlikely to risk performance bias. ; Indirectness of outcome: No indirectness ; Baseline details: N (%) for TDM versus CFM: Maternal congenital abnormalities 5(4) versus 5(4); Diabetes 3(2) versus 1(1); Chronic hypertension 2(2) versus 2(2); Renal disease 3(2) versus 2(2); HIV infection 0(0) versus 0(0); Learning difficulties 3(2) versus 1(1); Mental illness 19(15) versus 15(11). ; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 31; Group 2 Number missing: 31

Protocol outcome 2: Seizure freedom during pregnancy and at 6 months post-partum as stated
- Actual outcome: Proportion of women who experienced no seizures. From randomisation to 6 weeks post-partum.; Group 1: 79/127, Group 2: 80/130
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors, self-completing a seizure diary that was designed for the trial. Bias could arise through differential reporting of what is sometimes a subjective outcome. Lack of clinician blinding was unlikely to risk performance bias; Indirectness of outcome: No indirectness, Comments: Period of observation in study (up to 6 weeks post-partum) is shorter than that specified in the review protocol (up to 6 months post-partum) but is still clinically useful.; Baseline details: Age 1st seizure, years since 1st seizure, seizures 3 months prior, seizure class, AED dose at baseline and randomisation and medical history (7 variables). All comparable except complex seizures (TDM 28% v CFM 14%) and mean dose CBZ at rand (TDM 581.3mg v CFM 695mg).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 3: Mortality of mother or baby at study follow-up
- Actual outcome: Maternal mortality rate. From randomisation to 6 weeks post-partum.; Group 1: 0/130, Group 2: 0/133
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias; Indirectness of outcome: No indirectness; Baseline details: Smoking status, alcohol intake and medical history (7 variables). All comparable.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Rate of stillbirth. From randomisation to end of pregnancy.; Group 1: 0/125, Group 2: 2/134; Comments: Unclear why CFM number analysed exceeds number randomised to that group.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Unclear why CFM number analysed exceeds number randomised to that group. Data available for 134 women (133 randomised); Indirectness of outcome: No indirectness; Baseline details: Smoking status, alcohol intake, medical history (7 variables), previous neonatal death or stillbirth, at least 1 previous child with congenital abnormality, AED intake at baseline and randomisation. All comparable except CBZ intake at randomisation.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 5; Group 2 Number missing: 0
- Actual outcome: Neonatal mortality rate. at Not stated.; Group 1: 0/126, Group 2: 0/134; Comments: Unclear why CFM number analysed exceeds number randomised to that group.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -

There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Unclear why CFM number analysed exceeds number randomised to that group. Data available for 134 women (133 randomised); Indirectness of outcome: No indirectness, Comments: The time-period is assumed to be within 28 days of a live birth. • The review protocol stipulates 'mortality of mother or baby at study follow-up.' The study outcome is judged to be consistent with the review protocol stipulation and is judged not to constitute indirectness; Baseline details: Smoking status, alcohol intake, medical history (7 variables), previous neonatal death or stillbirth, at least 1 previous child with congenital abnormality, AED intake at baseline and randomisation. All comparable except CBZ intake at randomisation.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 4; Group 2 Number missing: 0

Protocol outcome 4: Time to first seizure in pregnancy and up to up to 6 weeks post-partum and time to subsequent seizure up to 1 year
- Actual outcome: Time to first seizure. Cumulative analysis time of 25,001 days from randomisation to first seizure; Group 1: n=127; Group 2: n=130; HR 0.82; Lower CI 0.55 to Upper CI 1.2; Test statistic: Cox proportional hazards model; Comments: The authors stated: 'There was a 20% reduction in the time to first seizure with therapeutic drug monitoring compared with clinical features monitoring, a difference that was not significant (HR 0.8, 95% CI 0.55 to 1.2). However, the point estimate HR would correspond to an increase in time (rather than the stated 'reduction in time') to first seizure (TDM versus CFM).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors, self-completing a seizure diary that was designed for the trial. Bias could arise through differential reporting of what is sometimes a subjective outcome. Lack of clinician blinding was unlikely to risk performance bias; Indirectness of outcome: No indirectness; Baseline details: Covariates: AED type, seizures 3 months prior to consent, mat age (not reported), age at 1st seizure, seizure classification. Additional possible confounders: smoking, alcohol intake, med history (7 variables), AED dose and years since 1st seizure. Comparable except CBZ dose and % with complex seizures.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 3; Group 2 Number missing: 3
- Actual outcome: Overall time to first and subsequent seizures. Cumulative analysis time of 35,859 days from randomisation to censoring; Group 1: n=127 ; Group 2: n=130; HR 1.34; Lower CI 0.7 to Upper CI 2.6; Test statistic: Andersen-Gill modification of Cox proportional hazards model for analysis of events that recur within a single subject.; Comments: The authors stated: 'The analysis of overall time to first seizure and subsequent seizures showed a larger increase with therapeutic drug monitoring than clinical features monitoring, but this was not significant (HR 1.3, 95% CI 0.7 to 2.6). However, the point estimate HR would correspond to a decrease (rather than the reported increase) in time to first and subsequent seizures (TDM versus CFM).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors, self-completing a seizure diary that was designed for the trial. Bias could arise through differential reporting of what is sometimes a subjective outcome. Lack of clinician blinding was unlikely to risk performance bias; Indirectness of outcome: No indirectness, Comments: Follow-up time for subsequent seizures (6 weeks) was shorter than specified in the review protocol (1 year) but is still clinically useful.; Baseline details: Covariates: AED type, seizures 3 months prior to consent, mat age (not reported), age at 1st seizure, seizure classification. Additional possible confounders: smoking, alcohol intake, med history (7 variables), AED dose and years since 1st seizure. Comparable except CBZ dose and % with complex seizures.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 3; Group 2 Number missing: 3

Protocol outcome 5: AED exposure as stated
- Actual outcome: Mean daily dose of AED prescribed: CBZ monotherapy. From randomisation to 6 weeks post-partum.; Group 1: mean 616.7 mg (SD 355.8); n=16, Group 2: mean 695 mg (SD 336.4); n=20; Comments: MD (95%CI) for TDM effect: –12.1 (–226.7 to 202.4)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias.; Indirectness of outcome: No indirectness; Baseline details: Possible confounders: alcohol intake (comparable across groups) and other medications used (not reported).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean daily dose of AED prescribed: LTG monotherapy. From randomisation to 6 weeks post-partum.; Group 1: mean 290.9 mg (SD 137.5); n=68, Group 2: mean 252.6 mg (SD 148); n=70; Comments: MD (95%CI) for TDM effect: 32.3 (–14.4 to 79.0)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias.; Indirectness of outcome: No indirectness; Baseline details: Possible confounders: alcohol intake (comparable across groups) and other medications used (not reported).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean daily dose of AED prescribed: LEV monotherapy. From randomisation to 6 weeks post-partum.; Group 1: mean 1735.6 mg (SD 701.9); n=31, Group 2: mean 1628.5 mg (SD 926.5); n=31; Comments: MD(95%CI) for TDM effect: 166.5 (–229.8 to 562.7)

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias.; Indirectness of outcome: No indirectness; Baseline details: Possible confounders: alcohol intake (comparable across groups) and other medications used (not reported).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean daily dose of AED prescribed: LTG and LEV polytherapy - LTG component. From randomisation to 6 weeks post-partum.; Group 1: mean 487.5 mg (SD 206.7); n=11, Group 2: mean 413.8 mg (SD 91.1); n=14; Comments: MD (95%CI) for TDM effect: 97.4 (–28.7 to 223.4). NOTE: REPORTED NUMBER ANALYSED IN EACH GROUP MAY HAVE BEEN REVERSED IN ERROR.

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Reported number observed in each group for this outcome appears to have been swapped in error. Note that reversed numbers tally in Table 3.; Indirectness of outcome: No indirectness; Baseline details: Possible confounders: alcohol intake (comparable across groups) and other medications used (not reported).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-

randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean daily dose of AED prescribed: LTG and LEV polytherapy - LEV component. From randomisation to 6 weeks post-partum.; Group 1: mean 1920.1 mg (SD 858.9); n=11, Group 2: mean 2122.2 mg (SD 1077.5); n=14; Comments: MD (95%CI) for TDM effect: –137.3 (–945.9 to 671.4). NOTE: REPORTED NUMBER ANALYSED IN EACH GROUP MAY HAVE BEEN REVERSED IN ERROR.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Reported number observed in each group for this outcome appears to have been swapped in error. Note reversed numbers tally with Table 3.; Indirectness of outcome: No indirectness; Baseline details: Possible confounders: alcohol intake (comparable across groups) and other medications used (not reported).; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Adverse events as stated
- Actual outcome: Maternal admission to HDU/ICU. From randomisation to 6 weeks post-partum.; Group 1: 5/127, Group 2: 3/130; Comments: OR (95%CI): 1.8 (0.41 to 7.8)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias.; Indirectness of outcome: No indirectness; Baseline details: Smoking status, alcohol intake and medical history (7 variables). All comparable.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 3; Group 2 Number missing: 3
- Actual outcome: Rate of major congenital malformation. From randomisation to 6 weeks post-partum.; Group 1: 7/125, Group 2: 10/134; Comments: OR (95%CI) 0.66 (0.23 to 1.8)
Unclear why the number analysed in the CFM arm exceeded the number randomised.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Unclear why CFM number analysed exceeds number randomised to that group. Data available for 134 women (133 randomised); Indirectness of outcome: No indirectness, Comments: Major congenital malformations were defined in the study as 'structural abnormalities with surgical, medical or cosmetic importance diagnosed either antenatally or postnatally.' The review protocol stipulates 'congenital anomalies (neural tube defects (spina bifida), limb defects (club foot), cleft lip and palette etc).' The study outcome is consistent with the review protocol stipulation and is judged not to constitute indirectness; Baseline details: Smoking status, alcohol intake, previous neonatal death or stillbirth, at least 1 previous child with congenital abnormality, AED intake at baseline and randomisation. All comparable except CBZ intake at randomisation.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 5; Group 2 Number missing: 0
- Actual outcome: Rate of admission to neonatal unit. Time period of observation not stated. Assumed to be from randomisation to 4 weeks post-partum.; Group 1: 16/125, Group 2: 18/134; Comments: OR (95%CI) 1.6 (0.29 to 9.5)

Unclear why the number analysed in the CFM arm exceeded the number randomised.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments -

There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. Lack of clinician blinding was unlikely to risk performance bias. Unclear why CFM number analysed exceeds number randomised to that group. Data available for 134 women (133 randomised); Indirectness of outcome: No indirectness; Baseline details: Smoking status, alcohol intake, medical history (7 variables), previous neonatal death or stillbirth, at least 1 previous child with congenital abnormality, AED intake at baseline and randomisation. All comparable except CBZ intake at randomisation.; Blinding details: Described as 'double blind' but this refers to clinicians and women in the CFM arm being blind to serum AED levels, and to whether allocated to CFM or non-randomised cohort. CFM decisions were made in knowledge that unblinding was possible.; Group 1 Number missing: 5; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	

Appendix E Forest plots

E.1 Therapeutic drug monitoring (TDM) versus clinical features monitoring (CFM)

Figure 2: Risk of first seizure

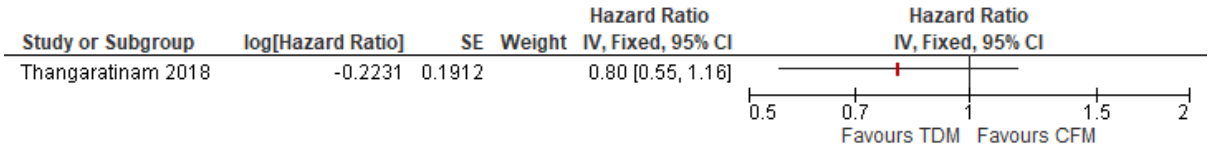


Figure 3: Risk of multiple seizures

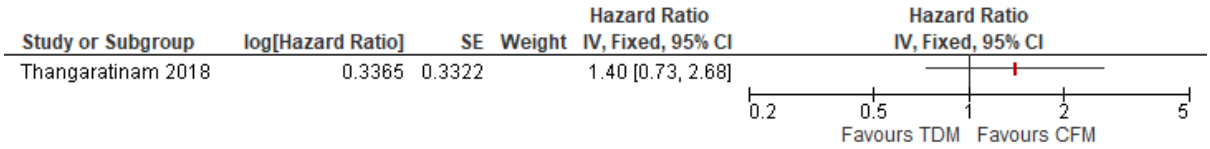
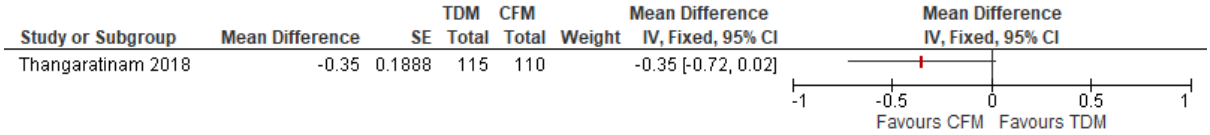
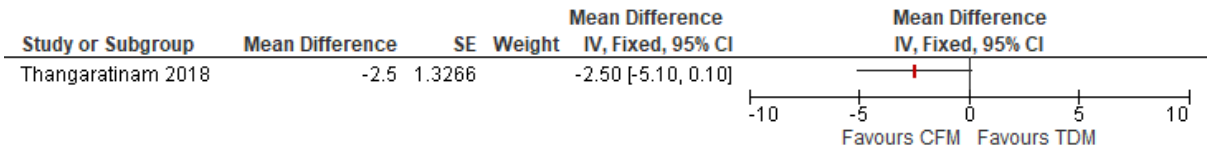


Figure 4: Quality of life (QOLIE-31 overall health)



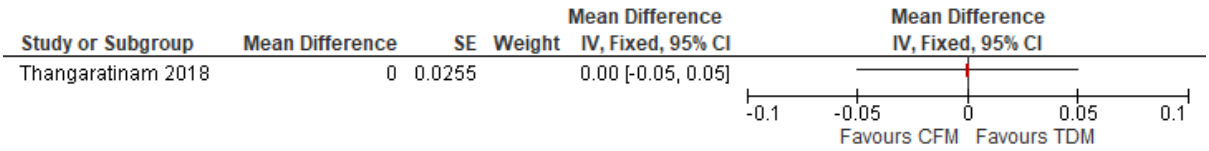
Range of scores 0 to 10; better indicated by higher values.

Figure 5: Quality of life (QOLIE-31)



Range of scores 0 to 100; better indicated by higher values.

Figure 6: Quality of life (EQ-5D)



Range of scores 0 to 1; better indicated by higher values.

Figure 7: Seizure freedom

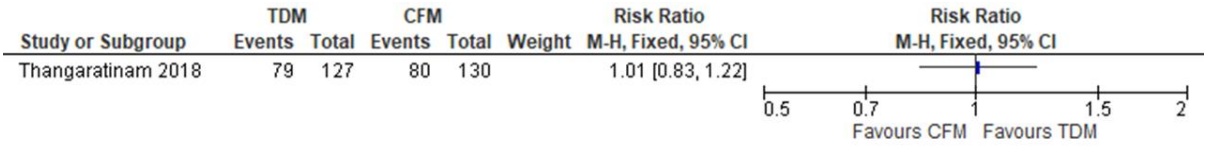


Figure 8: Maternal mortality

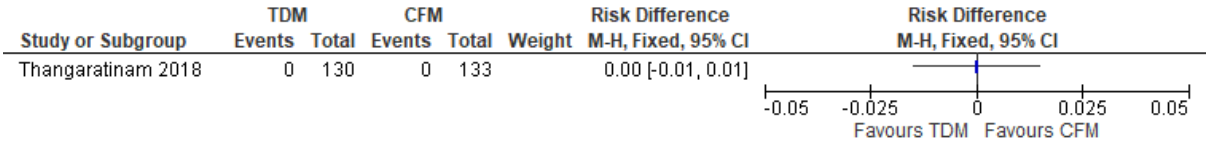


Figure 9: Maternal admission to HDU/ICU

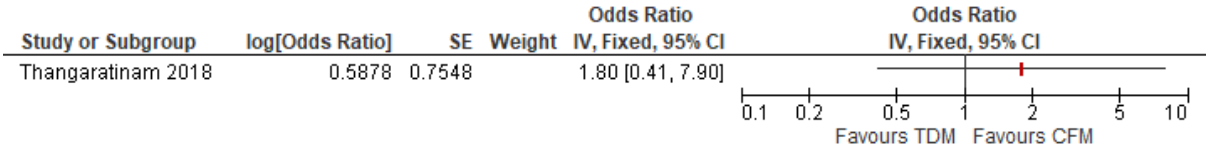


Figure 10: Mean daily carbamazepine exposure (monotherapy)

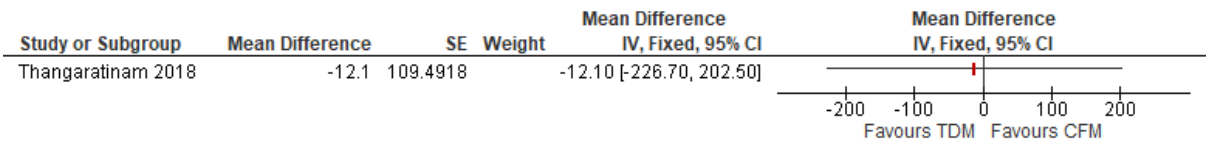


Figure 11: Mean daily lamotrigine exposure (monotherapy)

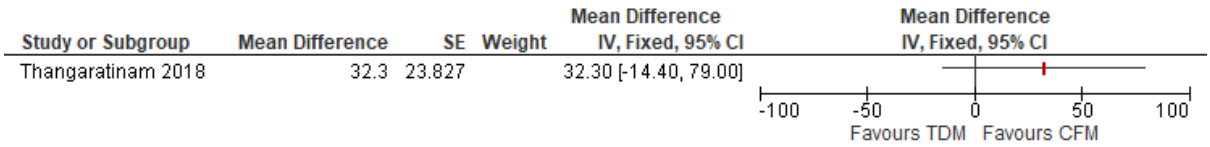


Figure 12: Mean daily levetiracetam exposure (monotherapy)

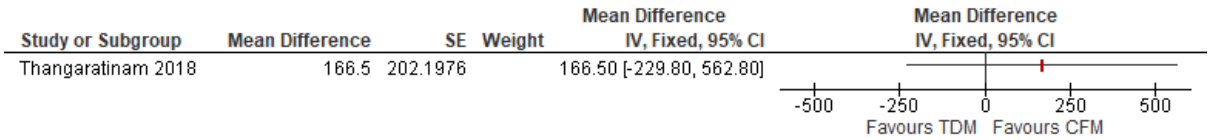


Figure 13: Mean daily levetiracetam exposure (in women on levetiracetam plus lamotrigine polytherapy)

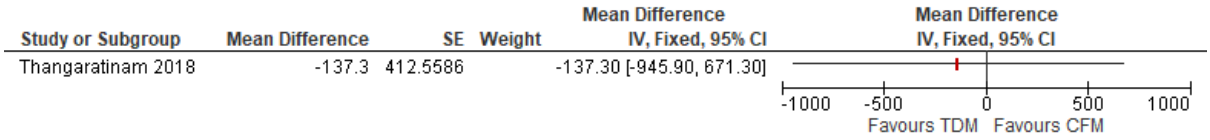


Figure 14: Mean daily lamotrigine exposure (in women on levetiracetam plus lamotrigine polytherapy)

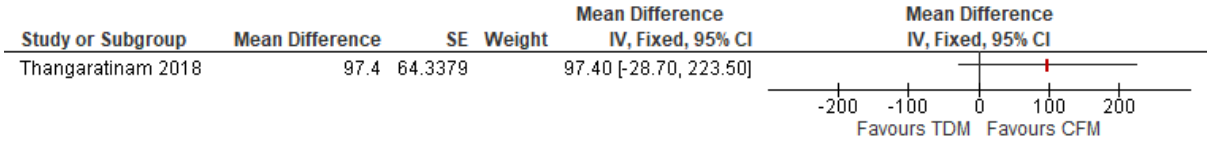


Figure 15: Stillbirth

Figure 16: Neonatal mortality

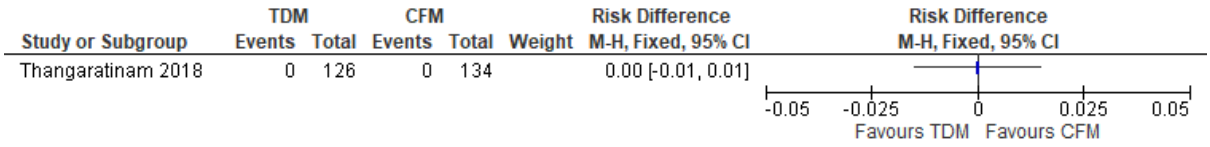


Figure 17: Major congenital malformation

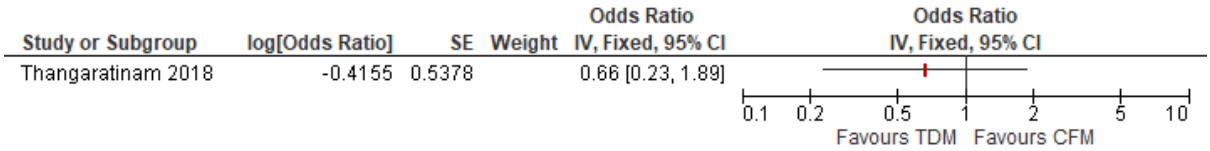
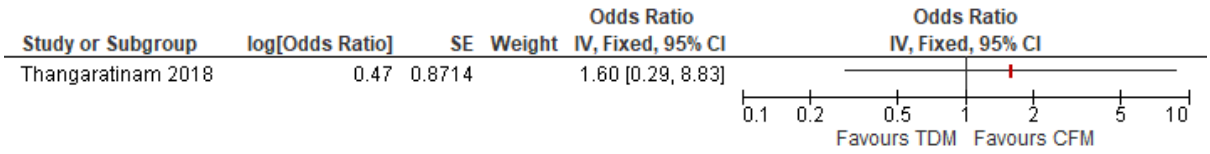


Figure 18: Admission to Neonatal Intensive Care Unit



Appendix F GRADE table

Table 7: Clinical evidence profile: therapeutic drug monitoring versus clinical features monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Therapeutic drug monitoring versus clinical features monitoring	Control	Relative (95% CI)	Absolute		
Quality of life (QOLIE-31 Overall Health) (follow-up from randomisation to 36 weeks gestation; range of scores: 0-10; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	115	110	-	MD 0.35 lower (0.72 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (QOLIE-31) (range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	114	110	-	MD 2.5 lower (5.1 lower to 0.1 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (EQ-5D) (range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision[5]	none	99	102	-	MD 0 higher (0.05 lower to 0.05 higher)	⊕⊕OO LOW	CRITICAL
Time to first seizure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	127	130	HR 0.8 (0.55 to 1.16)	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Time to first and subsequent seizures												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	127	130	HR 1.4 (0.73 to 2.68)	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Proportion of women who experienced no seizures												

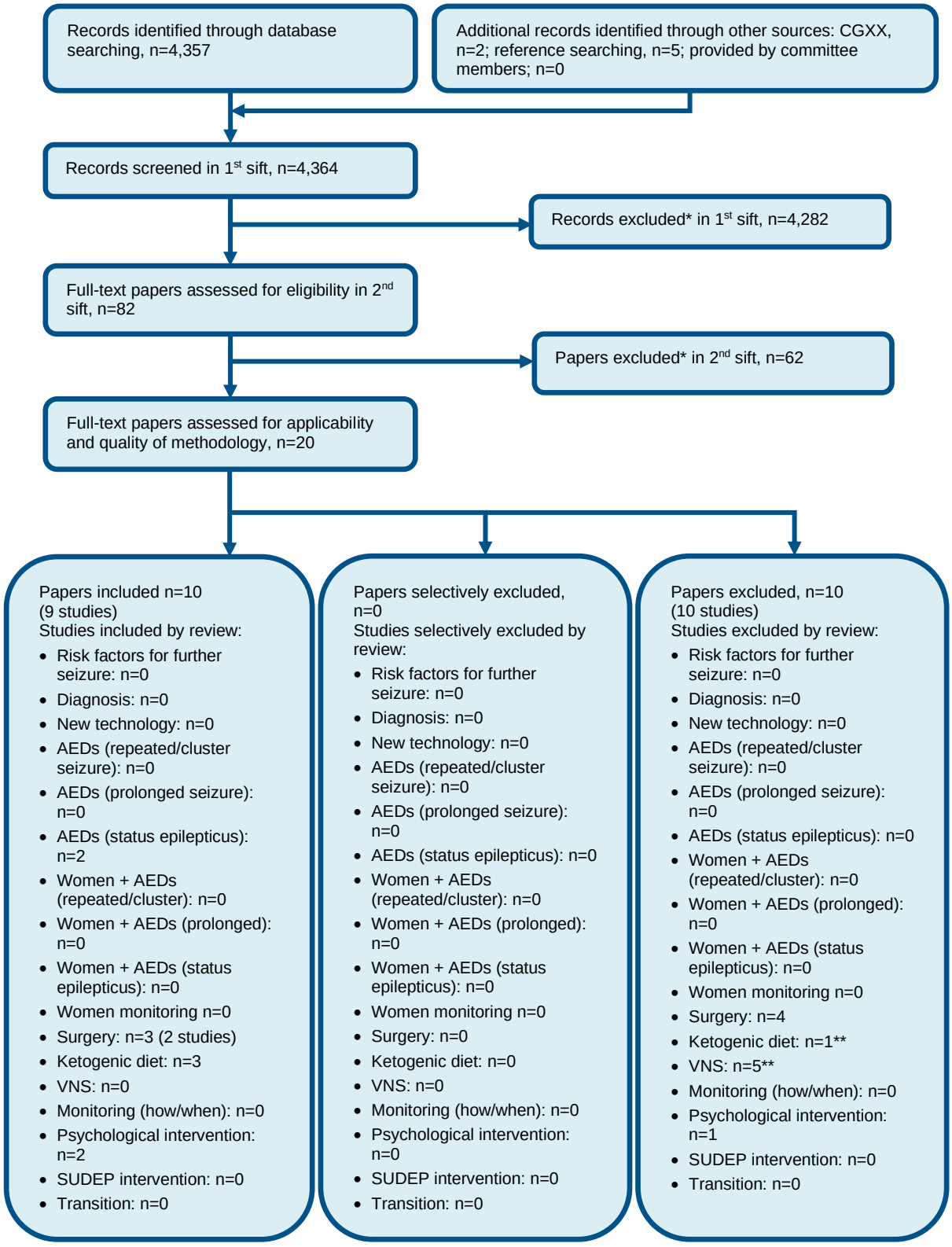
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	79/127 (62.2%)	80/130	RR 1.01 (0.83 to 1.22)	6 more per 1000 (from 105 fewer to 135 more)	⊕⊕OO LOW	CRITICAL
								61.5%				
Maternal mortality												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	0/130 (0%)	0/133	RD 0 (-0.01 to 0.01)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Maternal admission to HDU/ICU												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[7]	none	5/127 (3.9%)	3/130	OR 1.8 (0.41 to 7.9)		⊕OOO VERY LOW	CRITICAL
								2.3%				
Mean daily AED exposure (mg) CBZ monotherapy (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[11]	none	16	20	-	MD 12.1 lower (226.7 lower to 202.5 higher)	⊕OOO VERY LOW	CRITICAL
Mean daily AED exposure (mg) LTG monotherapy (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[12]	none	68	70	-	MD 32.3 higher (14.4 lower to 79 higher)	⊕⊕OO LOW	CRITICAL
Mean daily AED exposure (mg) LEV monotherapy (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[13]	none	31	31	-	MD 166.5 higher (229.8 lower to 562.8 higher)	⊕⊕OO LOW	CRITICAL
Mean daily AED exposure (mg) LEV + LTG (focus on LEV) (Better indicated by lower values)												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[14]	none	11	14	-	MD 137.3 lower (945.9 lower to 671.3 higher)	⊕OOO VERY LOW	CRITICAL
Mean daily exposure (mg): LEV + LTG (focus on LTG) (Better indicated by lower values)												

1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[15]	none	11	14	-	MD 97.4 higher (28.7 lower to 223.5 higher)	⊕⊕OO LOW	CRITICAL
Stillbirth												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/125 (0%)	2/134	OR 0.14 (0.01 to 2.31)	**13 fewer per 1000** (from 15 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
								1.5%				
Neonatal mortality												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[10]	none	0/126 (0%)	0/134	RD 0 (-0.01 to 0.01)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Major congenital malformation												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[7]	none	7/125 (5.6%)	10/134	OR 0.66 (0.23 to 1.89)		⊕OOO VERY LOW	CRITICAL
								7.5%				
Admission to Neonatal Intensive Care Unit												
1	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[7]	none	16/125 (12.8%)	18/134	OR 1.6 (0.29 to 8.83)		⊕OOO VERY LOW	CRITICAL
								13.4%				

[1] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome.
[2] MID for this outcome was calculated as -/+ 0.8.
[3] The MID for this outcome was -/+6.75
[4] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias. The RCT component of the study was not blinded and for this outcome participants were outcome assessors. Bias could arise through differential reporting of the outcome. There was a high but similar rate of attrition in both groups.
[5] The MID for this outcome was -/+ 0.09.
[6] The MID for this outcome was 0.8 and 1.25. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[7] The MID for this outcome was 0.8 and 1.25. The outcome was downgraded by 2 increments as the confidence interval crossed both MIDs.
[8] MID for this outcome was 0.8 and 1.25.
[9] There is no clear statement that the allocation sequence was kept concealed from recruiters. This risks selection bias.
[10] Downgraded by 1 increment as the outcome is from a single study with zero events in both arms, and sample size >70 and <350
[11] The MID for this outcome was -/+168.2. The outcome was downgraded by 2 increments as the confidence interval crossed both MIDs.

[12] The MID for this outcome was -/+74.0. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[13] The MID for this outcome was -/+463.25. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.
[14] The MID for this outcome was -/+538.75. The outcome was downgraded by 2 increments as the confidence interval crossed both MIDs.
[15] The MID for this outcome was -/+45.55. The outcome was downgraded by 1 increment as the confidence interval crossed one MID.

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

None

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 8: Studies excluded from the clinical review

Study	Exclusion reason
Helde 2005[2]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Islamiyah 2019[3]	Incorrect study design. Men. Non-pregnant women not planning pregnancy. Incorrect interventions
Jacob 2016[4]	Incorrect study design. (narrative review)
Jacob 2019[5]	Incorrect study design. (narrative review
Jannuzzi 2000[6]	Non-pregnant women not planning pregnancy. Men
Jarvie 2018[7]	Systematic review: study designs inappropriate. (included studies relating to pregnancy were either case reports or observational studies).
Jimenez 2020[8]	Not English language. (only abstract is in English language)
Johannessen 2008[9]	Incorrect study design. (narrative review)
Kelly 1984[10]	Incorrect study design. (narrative review)
Kim 2018[11]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Koch 1983[12]	Not English language
Kusznir vitturi 2019[13]	TDM was not explored as an exposure
Larkin 1988[14]	Incorrect study design. (conference abstract)
Leenen 2018[15]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Lhatoo 2001[16]	Men. Non-pregnant women not planning pregnancy. Children. TDM not explored as an exposure
Longo 2009[17]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Losada-camacho 2014[18]	Non-pregnant women not planning pregnancy
Maguire 2016[19]	Systematic review is not relevant to review question or unclear PICO. Non-pregnant women not planning pregnancy
Mauri llerda 2015[20]	Incorrect study design. (clinical practice guideline)
Mcauley 2002[21]	Incorrect study design. (narrative review)
Mehrotra 1990[22]	Incorrect study design. Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Mikov 2010[23]	Incorrect study design. (conference abstract)

Study	Exclusion reason
Miskov 2009[24]	Inappropriate comparison. (mean percentage AED dose adjustment (during pregnancy TDM and during postnatal TDM) was compared for women with favourable versus adverse pregnancy outcomes. This was not considered to justify inclusion as there was no comparison of outcomes for TDM versus usual care).
Nilsson 2001[26]	Incorrect study design. Non-pregnant women not planning pregnancy. Men
Nonoda 2014[27]	Population was children aged 2.4 to 18. There was no subgroup analysis of women planning/in/post pregnancy)
Otani 1985[28]	Inappropriate comparison. (The association of altered serum levels of AED with changes in seizure frequency was explored. This was not considered to justify inclusion as there was no comparison of outcomes for TDM versus usual care).
Pack 2006[29]	Incorrect study design. (narrative review)
Patsalos 2008[30]	Incorrect study design. (narrative review)
Patsalos 2018[31]	Incorrect study design. (narrative review)
Pennell 2004[34]	Incorrect study design. (narrative review)
Pennell 2006[32]	Incorrect study design. (narrative review)
Pennell 2008[33]	Incorrect study design. (narrative review)
Pennell 2008[37]	Inappropriate comparison. Prospective, observational comparison of seizure frequency before pregnancy without TDM, and during the study period with TDM. Seizure frequency stratified by seizure classification (all, or generalised tonic-clonic), but no adjustment for age at onset of epilepsy.
Pennell 2016[35]	Incorrect study design. (narrative review)
Pennell 2018[36]	TDM was not explored as an exposure in this prospective observational study. The exposure variable was epilepsy versus no epilepsy. The primary outcome was proportion achieving pregnancy in 12 months.
Perucca 2003[38]	Incorrect study design. (narrative review)
Pirie 2014[39]	Systematic review: study designs inappropriate
Plumpton 2015[40]	Economic analysis. Measurement of drug level was not the intervention. Rather, it was a self-administered questionnaire (implementation intention intervention).
Pulliam 1996[41]	Retrospective patient record review. Non-pregnant women not planning pregnancy. Men
Rahmathullah 1990[42]	Incorrect interventions. Incorrect population (preschool children)
Rajadhyaksha 1999[43]	Incorrect interventions. Incorrect population (children aged 2 to 14 with intracranial granuloma and seizures)
Raju 1994[44]	Incorrect interventions. Non-pregnant women not planning pregnancy. Men. Children aged 12 or over
Ramsay 1994[45]	Incorrect population (patients with refractory epilepsy receiving VNS). Incorrect interventions
Rashid 2017[46]	Incorrect interventions. Inappropriate comparison
Rath 2009[47]	Incorrect study design. (narrative review). Incorrect interventions. Inappropriate comparison
Reardon 2017[48]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions. Inappropriate comparison
Reid 2008[49]	Incorrect population (children with cerebral palsy). Incorrect interventions
Rektor 2020[50]	Incorrect interventions. Non-pregnant women not planning pregnancy. Men

Study	Exclusion reason
Remy 1989[51]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Rentmeester 1991[53]	Incorrect population. Incorrect interventions
Rentmeester 1991[52]	Incorrect population. Incorrect interventions
Rezaei 2012[54]	Incorrect population. Incorrect interventions
Riaz 2013[55]	Incorrect population. Incorrect interventions
Rich 2016[56]	Incorrect population. Incorrect interventions
Richardson 1998[57]	Incorrect population. Incorrect interventions
Richens 1994[58]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Ridsdale 1997[61]	Men. Non-pregnant women not planning pregnancy
Ridsdale 2000[59]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Ridsdale 2018[62]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Ridsdale 2018[60]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions
Rieckmann 2012[63]	Incorrect population. Incorrect interventions
Ring 2018[64]	Incorrect population. Incorrect interventions
Riveau 2018[65]	Incorrect population. Incorrect interventions
Rivera-castano 2012[66]	Incorrect population. Incorrect interventions
Robinson 1989[67]	Incorrect population. Incorrect interventions
Rogin 2014[68]	Incorrect population. Incorrect interventions
Romo 2015[69]	Incorrect population. Incorrect interventions
Rosati 2016[70]	Incorrect population. Incorrect interventions
Rosenfeld 2015[71]	Incorrect population. Incorrect interventions
Rosman 1993[72]	Incorrect population. Incorrect interventions
Rosman 2001[73]	Incorrect population. Incorrect interventions
Rossetti 2014[74]	Incorrect population. Incorrect interventions
Rts 2011[76]	Incorrect population. Incorrect interventions
Rts 2015[75]	Incorrect population. Incorrect interventions
Ryvlin 2014[77]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions. Inappropriate comparison
Sabers 1995[78]	Incorrect population. Incorrect interventions
Sabna 2018[79]	Incorrect population. Incorrect interventions
Saccone 2016[80]	Systematic review is not relevant to review question or unclear PICO. Incorrect interventions
Sacevich 2018[81]	Incorrect population. Incorrect interventions
Sachdeo 1992[82]	Incorrect population. Incorrect interventions
Sachdeo 1997[83]	Incorrect population. Incorrect interventions
Sackeim 1993[84]	Incorrect population. Incorrect interventions
Sackellares 2004[85]	Incorrect population. Incorrect interventions
Sáez-llorens 2002[86]	Incorrect population. Incorrect interventions
Sahjpaul 2003[87]	Incorrect population. Incorrect interventions
Saida 2017[88]	Incorrect population. Incorrect interventions
Salinsky 1995[90]	Incorrect population. Incorrect interventions
Salinsky 1996[91]	Incorrect population. Incorrect interventions

Study	Exclusion reason
Salinsky 2010[89]	Incorrect interventions
Salloway 2018[92]	Incorrect population. Incorrect interventions
Saposnik 2016[93]	Incorrect population. Incorrect interventions
Saygin 2002[94]	Incorrect population. Incorrect interventions
Schachter 1995[95]	Incorrect population. Incorrect interventions
Schechtmann 2010[96]	Incorrect population. Incorrect interventions
Schonenberg 2017[97]	Incorrect population. Incorrect interventions
Schougaard 2017[98]	Incorrect population. Incorrect interventions
Scott 1999[99]	Non-pregnant women not planning pregnancy. Incorrect interventions. Inappropriate comparison
Sedman 1990[100]	Incorrect population. Incorrect interventions
Seo 2007[101]	Incorrect population. Incorrect interventions
Sethi 2002[102]	Incorrect population. Incorrect interventions
Seynaeve 2016[103]	Incorrect population. Incorrect interventions
Shaw 2006[105]	Non-pregnant women not planning pregnancy. Incorrect interventions. Inappropriate comparison
Shaw 2010[104]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions. Inappropriate comparison
Shefner 2009[106]	Incorrect population. Incorrect interventions
Shi 2020[107]	Incorrect population. Incorrect interventions
Shim 2006[108]	Incorrect population. Incorrect interventions
Shorvon 2000[109]	Incorrect population. Incorrect interventions
Si 2020[110]	Incorrect population. Incorrect interventions
Simpson 2015[111]	Incorrect population. Incorrect interventions
Singhi 2002[113]	Incorrect population. Incorrect interventions
Singhi 2003[112]	Incorrect population. Incorrect interventions
Singla 2011[114]	Incorrect population. Incorrect interventions
Sivenius 1994[115]	Incorrect population. Incorrect interventions
Smith 1993[117]	Incorrect population. Incorrect interventions
Smith 1994[116]	Incorrect population. Incorrect interventions
Smits 2001[118]	Incorrect population. Incorrect interventions
Sobaniec 2004[119]	Incorrect population. Incorrect interventions
Solanki 2016[120]	Incorrect population. Incorrect study design
Solomkin 1985[121]	Incorrect population. Incorrect interventions
Sotelo 2006[122]	Non-pregnant women not planning pregnancy. Men. Incorrect interventions. Inappropriate comparison
Spivey 1993[123]	Incorrect population. Incorrect interventions
Sprigg 2018[124]	Incorrect population. Incorrect interventions
Srinivasakumar 2015[125]	Incorrect population. Incorrect interventions
Statler 2019[126]	Incorrect population. Incorrect interventions
Stauffer 2014[127]	Incorrect population. Incorrect interventions
Stefan 2001[129]	Incorrect population. Incorrect interventions
Stefan 2006[128]	Incorrect population. Incorrect interventions
Strengell 2009[130]	Non-pregnant women not planning pregnancy. Incorrect interventions. Inappropriate comparison
Struys 2017[131]	Incorrect population. Incorrect interventions
Stupp 2009[133]	Incorrect population. Incorrect interventions

Study	Exclusion reason
Stupp 2014[132]	Incorrect population. Incorrect interventions
Stupp 2017[134]	Incorrect population. Incorrect interventions
Sundqvist 1999[135]	Incorrect population. Incorrect interventions
Sveinbjornsdottir 1994[136]	Incorrect population. Incorrect interventions
Szaflarski 2020[137]	Incorrect population. Incorrect interventions
Szer 2004[138]	Incorrect population. Incorrect interventions
Tacke 2018[139]	Incorrect population
Taghavi ardakani 2010[140]	Incorrect population. Incorrect interventions
Taghdiri 2013[141]	Incorrect population. Incorrect interventions
Takeuchi 2014[142]	Incorrect population. Incorrect interventions
Tang 2014[143]	Incorrect population. Incorrect interventions
Tartara 1992[144]	Incorrect population. Incorrect interventions
Tatum 2001[145]	Incorrect population. Incorrect study design
Temkin 1990[148]	Incorrect population. Incorrect interventions
Temkin 1999[147]	incorrect population. Incorrect interventions
Temkin 2007[146]	Incorrect population. Incorrect interventions
Tennison 1994[149]	Incorrect population. Incorrect interventions
Terai 1993[150]	Incorrect population. Incorrect interventions
Thanh 2002[152]	Incorrect population. Incorrect interventions
Thilothammal 1993[154]	Incorrect population. Incorrect interventions
Thilothammal 1996[153]	Incorrect population. Incorrect interventions
Thomas 2001[155]	Incorrect population. Incorrect interventions
Tilz 2006[156]	Incorrect population. Incorrect interventions
Titre-johnson 2017[157]	Incorrect population. Incorrect interventions
Tolbert 2014[159]	Incorrect population. Incorrect interventions
Tolbert 2015[158]	Incorrect population. Incorrect interventions
Tolchin 2019[160]	Incorrect population. Incorrect interventions
Trevathan 2006[161]	Incorrect population. Incorrect interventions
Trinka 2018[162]	Incorrect population. Incorrect interventions
Trudeau 1996[163]	Incorrect population. Incorrect interventions
Tsounis 2011[164]	Incorrect population. Incorrect interventions
Tungmanowutthikul 2019[165]	Incorrect population. Incorrect interventions
Turan gurhopur 2018[166]	Incorrect population. Incorrect interventions
Uijl 2009[167]	Incorrect population. Incorrect interventions
Vaghadia 1999[168]	Incorrect population. Incorrect interventions
Vahedi 2007[169]	Incorrect population. Incorrect interventions
Van der meyden 1994[170]	Incorrect population. Incorrect interventions
Van paesschen 2013[171]	Incorrect population. Incorrect interventions
Van stuijvenberg 1998[172]	Incorrect population. Incorrect interventions
Vanlandingham 2020[173]	Incorrect population. Incorrect interventions
Vining 1987[174]	Incorrect population. Incorrect interventions
Viscusi 2014[175]	Incorrect population. Incorrect interventions
Wakelee 2017[176]	Incorrect population. Incorrect interventions
Wang 2008[177]	Incorrect population. Incorrect interventions
Wanigasinghe 2017[178]	Incorrect population. Incorrect interventions

Study	Exclusion reason
Webster 2014[179]	Incorrect population. Incorrect interventions
Weiden 2020[180]	Incorrect population. Incorrect interventions
Weinbroum 1996[181]	Incorrect population. Incorrect interventions
Welch 2015[182]	Incorrect population. Incorrect interventions
Wheless 2019[183]	Incorrect population. Incorrect interventions
Wietholtz 1989[184]	Incorrect population. Incorrect interventions
Wijnen 2017[185]	Incorrect population. Incorrect interventions
Wilky 2019[186]	Incorrect population. Incorrect interventions
Wu 2009[187]	Incorrect population. Incorrect interventions
Xu 2004[189]	Incorrect population. Incorrect interventions
Xu 2007[188]	Incorrect population. Incorrect interventions
Yadegary 2015[190]	Incorrect population. Incorrect interventions
Yamamoto 2016[191]	Incorrect study design. Inappropriate comparison
Yamamoto 2020[192]	Incorrect population. Incorrect interventions
Yen 2000[193]	Incorrect population. Incorrect interventions
Young 2004[195]	Incorrect population. Incorrect interventions
Young 2006[194]	Incorrect population. Incorrect interventions
Younus 2018[196]	Incorrect population. Incorrect interventions
Zamponi 1999[197]	Incorrect population. Incorrect interventions
Zhang 2017[198]	Incorrect population. Incorrect interventions
Zhao 2019[199]	Incorrect population. Incorrect interventions
Zhong 2018[200]	Incorrect population. Incorrect interventions
Zhou 2017[201]	Incorrect population. Incorrect interventions
Zou 2010[202]	Incorrect population. Incorrect interventions

J.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 9: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

Appendix K Research recommendations – full details

What is the clinical and cost effectiveness of decisions about therapeutic drug monitoring (TDM) in girls, young women, and women with epilepsy? Particular focus should be on anti-seizure medications where concentrations are known to potentially change during pregnancy.

Research recommendation

What is the clinical and cost effectiveness of decisions about therapeutic drug monitoring (TDM) in girls, young women, and women with epilepsy?

Why this is important

There is evidence of increased risks for women with epilepsy in pregnancy, including ten-fold increased risk of maternal mortality, and risks of worsening seizure control.

Maternal tonic clonic seizures especially if occurring in sleep are associated risks of sudden unexpected death in epilepsy (SUDEP), and status epilepticus.

In addition to major risks to the mother, uncontrolled epilepsy with generalised tonic clonic convulsions is associated with risks of harm to the fetus including miscarriage, fetal hypoxia and acidosis, and fetal loss. The effect of seizures can impact daily living, resulting in loss of driving licence, negative impact on employment and relationships and reduced quality of life (QoL), all of which are heightened in pregnancy.

The potential for ASM (antiseizure medication) serum concentrations changing in pregnancy has become a focus of clinical management in pregnancy, with variable implementation in the UK for epilepsy monitoring before, during and after pregnancy. The focus on maintaining a stable ASM concentration during and after pregnancy is difficult owing to the alteration of ASM pharmacokinetics including increased volume of distribution, elevated renal clearance, and induction of hepatic metabolism. There is evidence lamotrigine, levetiracetam, oxcarbazepine and phenytoin serum concentrations potentially change during pregnancy.

There is uncertainty of how best to manage the changes in ASM concentration, to influence improvement in pregnancy and post-pregnancy seizure control, while mitigating ASM toxicity for mother and baby.

In the face of uncertainty of how best to manage the risks of changes ASM serum concentrations pregnancy, it is important to investigate the effectiveness of therapeutic drug monitoring (TDM) in girls, young women, and women with epilepsy, especially focusing on anti-seizure medications where concentrations are known to potentially change during pregnancy.

Rationale for research recommendation

Importance to 'patients' or the population	Little is known of the best approach to managing ASM serum concentrations before, during and after pregnancy, and the potential benefits and harms of different management strategies. There are significant risks associated with maternal seizures in pregnancy and risks of SUDEP and maternal death has been linked to finding sub-therapeutic drug levels. This has raised concern of the potential to reduce avoidable maternal death, and there is significant public and political concern about this.
Relevance to NICE guidance	Therapeutic drug monitoring (TDM) before, during and after pregnancy has been considered in this guideline due to the uncertainty of effective management and variable implementation

	in practice. There is need for focused attention on the effective management strategies for TDM, particularly for lamotrigine, levetiracetam, oxcarbazepine and phenytoin as evidence of potential serum levels changing in pregnancy exists.
Relevance to the NHS	The outcome would affect the management of ASM in pregnancy, particular the routine uses of TDM before, during and after pregnancy provided by the NHS. This may also predict future healthcare needs for women with epilepsy before, during and after pregnancy. The outcome may have potential cost and resource implication as this is not routine practice in the NHS. The work offers clear benefit with the potential outcome of influencing ASM prescribing in pregnancy; the opportunity to reduce fetal ASM exposure (for example by preventing erroneous increases in ASMs during pregnancy) and ensuring that risks for post-partum risks of ASM toxicity are minimised
National priorities	High
Current evidence base	Evidence was provided by a single randomised controlled trial of TDM versus clinical features monitoring (CFM) among women under 24 weeks gestation in whom ASM concentrations had fallen by 25% or more. It was agreed that this trial was inconclusive, neither providing straightforward evidence in favour of TDM in pregnancy, nor providing clear evidence against it. This research recommendation was therefore made for further study to address the clinical and cost effectiveness of decisions about TDM in girls, young women, and women with epilepsy.
Equality considerations	The variable implementation of TDM in current practice has uncertain impact on equitable care provision. This research recommendation will focus on women with epilepsy of all ethnicities who have potential for pregnancy, without age restriction including girls under the age of 16 years, and including women with intellectual disabilities, and those within following vulnerable groups.

1 **Modified PICO table**

Population	Girls, young women, and women with epilepsy who are of childbearing potential
Intervention	Anti-seizure medication therapeutic drug monitoring
Comparator	Different TDM strategies; clinical features monitoring; different ASM
Outcome	Mortality of mother or baby at study follow-up, seizure freedom during pregnancy and at six months post-partum, reduction in seizure frequency (50% or more), time to first seizure in pregnancy and up to up to six weeks post-partum, time to subsequent seizures (within an observation period of up to one year), ASM exposure (mean daily), and quality of life (using any validated measures) at study follow-up. Adverse events: ASM toxicity, pregnancy complications in the mother or baby (maternal admission to a high dependency or intensive care unit or admission of the baby to a neonatal intensive care unit), seizures during labour, attendance at an emergency department, congenital anomalies, and neurodevelopmental outcomes.

Study design	RCT; Prospective study design
Timeframe	From pre-pregnancy, pregnancy and up to 12m post-partum. Long term.
Additional information	None

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Appendix L Additional information

Algahtani, H., et al. (2019). "Antiepileptic Drugs Usage in Pregnant Women with Epilepsy in Saudi Arabia." Journal of Epilepsy Research **9**(2): 134-138.

Background and Purpose: Epilepsy is one of the most common neurological disorders requiring continuous treatment during pregnancy. In Saudi Arabia, there is only one publication that studied the outcome of pregnancies in women with epilepsy, published in 1999. The aim of the study is to determine the major congenital malformations in infants resulting from exposure to antiepileptic drugs in pregnant women with epilepsy.

Methods: This is a retrospective observational study that was conducted at King Abdulaziz Medical City, Jeddah, Saudi Arabia, involving pregnant women with epilepsy using antiepileptic drugs during pregnancy. We also studied babies born to those mothers. The study period was 5 years from 2014 to 2018.

Results: Six hundred babies were included in the study, born to 154 mothers with epilepsy using antiepileptic drugs during pregnancy. In addition, there were 111 losses of fetuses before 20 weeks of gestation. The only malformation detected was a ventricular septal defect in one child, whose mother was using polytherapy (valproic acid and levetiracetam). Three babies were born with epilepsy, and four babies had other associated disorders (Down syndrome, osteoporosis, esotropia, and hearing impairment).

Conclusions: The results of this small study are an urgent call for the establishment of congenital malformations registry in Saudi Arabia. In addition, specialized epilepsy clinics utilizing multidisciplinary care are highly recommended. A specific group of interest for such clinics are married women, who have epilepsy and are using antiepileptic drugs since planning of pregnancy is not part of the culture in Saudi Arabia.