National Institute for Health and Care Excellence

FINAL

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

[7] Evidence reviews for monitoring

NICE guideline NG217

Evidence reviews underpinning recommendations 4.5.1 – 4.5.4 in the NICE guideline

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FINAL

Developed by the National Guideline Centre

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Contents

1 Monitoring

1.1 Review question

a) When should monitoring be carried out for people with epilepsy?

b) How should monitoring be carried out for people with epilepsy, and who should do it?

1.1.1 Introduction

Monitoring people who have a diagnosis of epilepsy involves maintaining records of seizure frequency, seizure type, prescribed medications and understanding how those medications affect the person's condition, assessing co-morbidities and, where necessary, reviewing the diagnosis. It is an ongoing exercise that considers whether the care and treatment the person has received is working, and making adjustments if there are difficulties that improves quality of life and overall well-being.

Regular monitoring is conducted for children and young people in clinical practice. Currently, adults with a new diagnosis of epilepsy will initially be provided with regular review but when regular review is no longer deemed clinically necessary for example, because their seizures are controlled using ASMs they will be discharged from epilepsy services. At the moment, people can only re-access tertiary epilepsy services through primary care referrals.

This review examines when and how monitoring should be carried out in the management of epilepsy and considers who should deliver these services.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: people with epilepsy Exclusion: new-born babies (under 28 days) with acute symptomatic seizures
Intervention(s)	Annual review Structured follow-up appointments Ad-hoc follow up appointments Any alternative methods of monitoring (e.g., drug monitoring studies)
Comparison(s)	Each other No monitoring/usual care
Outcomes	• mortality at a minimum of 1 year • seizure recurrence at a minimum of 1 year • seizure frequency at a minimum of 1 year • seizure freedom at a minimum of 1 year • drug adherence at a minimum of 1 year • quality of life at a minimum of 1 year • health care use at a minimum of 1 year • unplanned hospital admission at a minimum of 1 year • attendance at ED during a minimum of 1 year • social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at a minimum of 1 year • cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at a minimum of 1 year

	• in children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at a minimum of 1 year • educational outcome at a minimum of 1 year • placement breakup (change in care location during a minimum of 1 year)
Study design	RCTs

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

Four randomised studies were included in the review.[1, 15, 20, 45]

One randomised study[45] addressed the first part of the review question: *when should monitoring be carried out for people with epilepsy?* This study compared fixed clinical interval monitoring to clinical monitoring where timing was decided based on patient preference. Eighty per cent of the participants in the fixed clinical interval monitoring group received clinical monitoring on an annual basis, and so the comparison was deemed to be annual versus ad-hoc monitoring.

Three randomised studies[1, 15, 20] partially addressed the second part of the review question: *how should monitoring be carried out for people with epilepsy, and who should do it?* These studies involved all participants being given plasma-drug-level monitoring. In each study, one group of participants were randomly assigned to an intervention where the plasma-drug-level monitoring data were used to determine clinical management, and the remainder of the participants were assigned to an intervention where management was determined entirely on clinical grounds, without using the drug-level-monitoring data. Although these studies partially addressed the question of 'how' monitoring could be carried out, they did not address the issue of 'who' should carry out the monitoring.

The age strata involved in the studies were difficult to interpret. Although Aicua-Rapun, 2020[1] only contained adults, no information on ages was provided by Froscher, 1981.[15] Jannuzzi, 2000[20] included a wide age-range of 6-65 years but no stratification of results was provided; however, the mean age in the study was 28 and so the results are taken as relating predominantly to adults. Schougaard, 2019[45] included ages from 15 upwards without any age stratification; however, the mean age was around 47 so the results are also taken as being representative of adults.

The definition of epilepsy type was also unclear. Although Jannuzzi, 2000[20] specified the type of epilepsy – 'untreated partial or idiopathic generalised epilepsy' – the other studies did not describe the epilepsy type.

All studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 and Table 4).

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
Aicua-Rapun, 2020 [1]	Therapeutic Drug Monitoring versus clinical monitoring	Aged >18 years with diagnosis of epilepsy (no definition); exclusions: pregnancy; Median age 37; Switzerland.	Mortality Seizure recurrence	N=151; follow up at 1 year
Froscher, 1981[15]	Therapeutic Drug Monitoring versus clinical monitoring	People with minimum of 3 seizures of one seizure type in previous year; exclusions: non-compliance, alcohol addiction, pregnancy; age unclear; Germany	Seizure frequency at 1 year (frequency worse of unchanged)	N= 127; follow up at 1 year
Jannuzzi, 2000 [20]	Therapeutic Drug Monitoring versus clinical monitoring	People aged 6-65 with a diagnosis of untreated partial or idiopathic generalised epilepsy; 2 seizures in past 4 months; clinical indication to prescribe AEDs such as carbamazepine, phenytoin, valproate, phenobarbital or primidone; exclusions: benign Rolandic epilepsy, absence epilepsy or epileptic encephalopathy, any progressive disease, pregnancy, severe hepatic/renal insufficiency, history of drug or alcohol abuse, treatment with any AED; Italy	Seizure recurrence (HR and RR)	N=180; follow up at 2 years; the paper reported the number free of seizures, but this was translated to number with seizure recurrence to allow pooling of data with Aicua-Rapun, 2020.
Schougaard, 2019[45]	Annual versus ad-hoc monitoring	People aged 15 or older with an epilepsy diagnosis or suspicion of epilepsy; exclusions: paper respondents, had stopped attending standard telePRO follow-up before randomisation; Age c47; Denmark	Mortality, quality of life, seizure frequency, resource use, hospitalisations, attendances at ED, social functioning, cognitive functioning, psychological functioning	N=593; follow up at 18 months

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Annual versus ad hoc monitoring for epilepsy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Annual versus ad hoc monitoring (95% CI)
Mortality	592 (1 study) 18 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	RR 2.79 (0.52 to 15.13)	Moderate	
				6 per 1000	11 more per 1000 (from 3 fewer to 85 more)
Quality of life: WHO-5 (scale 0-100; higher better)	352 (1 study) 18 months	⨁⨁⊖⊖ LOW[c,d] due to risk of bias			The mean WHO-5 score in the intervention groups was 3.21 higher (0.05 lower to 6.38 higher)
Seizure frequency	352 (1 study) 18 months	⨁⨁⊖⊖ LOW[e,f] due to risk of bias			The mean seizure frequency in the intervention groups was 0.72 higher (1.75 lower to 3.20 higher)
Resource use - Outpatient visits	586 (1 study) 18 months	⨁⨁⨁⊖ MODERATE[a,g] due to risk of bias			The mean number of outpatient visits in the intervention groups was 0.03 lower (0.18 lower to 0.12 higher)
Resource use - telephone consultations	586 (1 study) 18 months	⨁⨁⨁⊖ MODERATE[a,h] due to risk of bias			The mean number of telephone consultations in the intervention groups was 0.31 higher (0.06 lower to 0.68 higher)
Hospitalisation	586 (1 study) 18 months	⨁⨁⨁⊖ MODERATE[a,i] due to risk of bias			The mean hospitalisation in the intervention groups was 0.04 higher (0.03 lower to 0.11 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Annual versus ad hoc monitoring (95% CI)
ED attendance	586 (1 study) 18 months	⨁⨁⊖⊖ LOW[a,j] due to risk of bias, imprecision			The mean ED attendance in the intervention groups was 0.12 higher (0.02 to 0.22 higher)
Social functioning: HLQ-4 (scale 1-4; higher better)	592 (1 study) 18 months	⨁⨁⊖⊖ LOW[c,k] due to risk of bias			The mean WHO-5 score in the intervention groups was 0.08 higher (0.02 lower to 0.17 higher)
Cognitive functioning: HLQ-9 (scale 1-5; higher better)	592 (1 study) 18 months	⨁⨁⊖⊖ LOW[c,l] due to risk of bias			The mean WHO-5 score in the intervention groups was 0.009 lower (0.15 lower to 0.13 higher)
Psychological functioning: GSE (scale 10-40; higher better)	592 (1 study) 18 months	⨁⨁⊖⊖ LOW[c,m] due to risk of bias			The mean WHO-5 score in the intervention groups was 0.22 higher (0.78 lower to 1.22 higher)

[a] *Selection bias*
[b] *Serious if the confidence intervals crossed one MID and very serious if the confidence intervals crossed both default MIDs (0.80 and 1.25)*
[c] *Selection, blinding and attrition bias*
[d] *The MID was 0.5 x the sd in control group = 9.22. The confidence intervals did not cross -9.22 or +9.22 so imprecision was deemed non-serious*
[e] *Selection and attrition bias*
[f] *The MID was 0.5 x the sd in control group = 5.94. The confidence intervals did not cross -5.94 or +5.94 so imprecision was deemed non-serious*
[g] *The MID was 0.5 x the sd in control group = 0.475. The confidence intervals did not cross -0.475 or +0.475 so imprecision was deemed non-serious*
[h] *The MID was 0.5 x the sd in control group = 0.940. The confidence intervals did not cross -0.940 or +0.940 so imprecision was deemed non-serious*
[i] *The MID was 0.5 x the sd in control group = 0.4145. The confidence intervals did not cross -0.145 or +0.145 so imprecision was deemed non-serious*
[j] *The MID was 0.5 x the sd in control group = 0.419. The upper confidence interval crossed the upper MID, so imprecision was deemed serious*
[k] *The MID was 0.5 x the sd in control group = 0.30. The upper confidence interval did not cross -0.30 or +0.30 so imprecision was deemed non-serious*
[l] *The MID was 0.5 x the sd in control group = 0.385. The upper confidence interval did not cross -0.385 or +0.385 so imprecision was deemed non-serious*
[m] *The MID was 0.5 x the sd in control group = 2.84. The upper confidence interval did not cross -2.84 or +2.84 so imprecision was deemed non-serious*

Table 4: Clinical evidence summary: therapeutic drug monitoring (TDM) versus clinical monitoring for epilepsy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with TDM versus clinical monitoring (95% CI)
Mortality	151 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b] due to risk of bias, imprecision	OR 7.29 (0.14 to 367.55)	Moderate	
				0 per 1000	10 more per 1000 (from 20 fewer to 50 more)
Seizure recurrence (RR)	267 (2 studies) 1-2 years	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	RR 1.13 (0.86 to 1.47)	Moderate	
				420 per 1000	55 more per 1000 (from 59 fewer to 197 more)
Seizure recurrence (HR)	180 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[d,c] due to risk of bias, imprecision	HR 1.05 (0.58-1.90	-	
Seizure frequency unchanged or worse	105 (1 study) 2 years	⨁⊖⊖⊖ VERY LOW[b,e] due to risk of bias, imprecision	RR 0.78 (0.46 to 1.34)	Moderate	
				385 per 1000	85 fewer per 1000 (from 208 fewer to 131 more)

[a] *Selection bias and outcome reporting bias*
[b] *Serious imprecision if the confidence intervals crossed one MID and very serious imprecision if the confidence intervals crossed both MIDs*
[c] *Selection bias and attrition bias for Jannuzzi and selection bias and outcome reporting bias for Aicua-Rapun*
[d] *Selection and attrition bias*
[e] *Very serious selection bias*

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 new cost-effectiveness analysis.

1.1.9 Committee's discussion of the evidence

Interpreting the evidence

1.1.9.1 The outcomes that matter most

The outcomes highlighted by the committee were mortality, seizure recurrence, seizure frequency, drug adherence, quality of life, healthcare resource use, social functioning, cognitive outcomes, neurodevelopmental outcomes, educational outcomes and placement breakups. These were all thought be critical because they were either 1) key patient-centred outcomes or 2) critical for evaluating health economics.

1.1.9.2 The quality of the evidence

Quality of the evidence for the outcomes varied from very low to moderate. Any downgrades in quality rating were due to risk of bias and/or imprecision. Risk of bias was largely due to selection bias secondary to unclear allocation concealment, performance bias due to the impossibility of blinding patients and health care professionals, and attrition bias resulting from high levels of drop-out.

1.1.9.3 Benefits and harms

The evidence only covered two comparisons: 1) regular versus ad-hoc monitoring, and 2) therapeutic drug monitoring versus clinical monitoring.

Regular versus ad-hoc monitoring

The evidence showed no clinically important differences in benefits and harm between annual monitoring and ad-hoc monitoring. Using informal consensus, the committee agreed that both approaches to monitoring probably had benefits, but that the dominance of one over the other depended on the context.

Advantages of ad-hoc monitoring were discussed, and included its propensity to allow patients to develop a sense of control and ownership of the management of their condition, which might foster a shared approach to patient-centred treatment planning. In particular, ad-hoc monitoring might help to ensure that concerns and problems would be dealt with in a

timely fashion, rather than at a later point in time when therapeutic responses or advice might be less effective.

The main disadvantages of an ad-hoc approach were also discussed, and included the risk that certain groups of patients might not take the initiative to contact services when required, which could have consequences such as serious adverse events, or deterioration in a patient's condition. In addition, a patient's failure to contact services might lead to inappropriate discharge from services, and subsequent loss of contact with care. The point was also raised that epilepsy may not have the signs that can pre-emptively alert a patient to the need to contact services; for example, a patient with asthma may note that breathing is worse and contact services, but in epilepsy there is no such warning. Thus ad-hoc follow up may often be too late to manage a problem, whereas a regular monitoring approach would at least ensure that the patient is maintained on the list and known to services. This was agreed to be a particular problem for patients with a more serious or complex condition. A further disadvantage was highlighted as the burden on staffing, with an ad-hoc approach requiring extra personnel (such as epilepsy nurses) to answer phone calls and co-ordinate care.

The committee agreed that to reduce the extent of missed follow-ups, ad-hoc methods should not be used in groups with the potential for reduced independence or difficulty in making decisions, such as people with learning difficulties or children and young people. Furthermore, ad-hoc methods should not be used for very high-risk patients, regardless of capacity for decision-making, because the consequences of missed follow-ups would be potentially more serious. High-risk patients were identified as people at risk of SUDEP, people with frequent uncontrolled seizures, or those at risk from adverse treatment events (because of the intrinsic risk from their treatment regimen, or because of the interaction between co-morbidities and their treatment). In addition, the committee agreed that ad-hoc methods should not be used in more complex situations where the burden on ad-hoc services might be higher, and where a planned and regular approach might be logistically easier.

Therefore, the committee recommended that ad-hoc monitoring methods, through providing people with the contact information to directly access services in primary, secondary and tertiary care when required, should be provided. However, the committee also agreed, the caveat that, regular reviews on at least a 12-month basis should be provided to certain groups who might not benefit from an ad-hoc approach. The committee agreed that regular monitoring should be on at least a 12-month schedule because this guaranteed a minimum of one follow up per year (reflecting usual practice) but also allowed for more frequent follow-ups if need dictated.

The people identified as appropriate for a regular monitoring approach included people with learning disabilities, children, people with drug-resistant epilepsy, people at high risk of SUDEP, people with difficult relevant comorbidities (i.e., complex psychosocial situations /cognitive/mental health problems), people on high-risk anti-seizure medication, and girls/women of child-bearing potential on high-risk teratogenic medication. The committee commented that regular monitoring reviews was current practice for children and young people with two reviews per year being typical. The frequency should be discussed with them and their families and carers, but should be at least every 12 months . People with learning disabilities already have an annual general health review as standard practice, often provided in a GP practice by a GP or nurse, which has made an impact on reducing premature mortality. However, the committee thought that a person with epilepsy may require specialist input.

There was some residual concern within the committee that ad-hoc monitoring, despite being limited to some extent by the caveats described above, would still place a high demand on the health services, particularly in terms of the personnel required to co-ordinate such an approach. However, the consensus was that because ad-hoc monitoring would only be

instituted for those requiring less resources, demand on services would not be unduly affected.

Therapeutic drug monitoring versus clinical monitoring

The evidence also showed there were no clinically important differences in benefits and harms between therapeutic drug monitoring (involving measurement of plasma drug levels) and clinical monitoring.

The committee agreed that therapeutic drug monitoring offered few benefits for the majority of patients, but that there might be some advantages if patients are having side-effects because adverse events to medication might be reduced by precise downward drug titration resulting from more accurate knowledge of plasma drug levels. In people with uncontrolled seizures, there might also be an advantage through precise upward titration resulting from more accurate knowledge of plasma drug levels. There might also be advantages in situations where drug levels were critical because the drug itself was particularly high risk, where drug compliance might be poor, or where the patient had conditions such as renal failure or pregnancy that increased risk from normally lower-risk drugs (lamotrigine during pregnancy).

The committee, therefore, recommended that anti-seizure drug monitoring should be considered if seizures are uncontrolled, patients are having side effects, or unless the patient has poor drug compliance, is pregnant or planning pregnancy (especially on lamotrigine), or has renal failure.

1.1.9.4 Cost effectiveness and resource use

The committee discussed the benefits associated with ad-hoc monitoring versus regular monitoring and noted that in current practice, patients receive regular monitoring if deemed clinically necessary (for example, people with drug-resistant epilepsy, learning disabilities, or people at high risk of SUDEP). The committee also noted that people with a new diagnosis of epilepsy would initially be provided with a regular review, but when regular review is no longer deemed clinically necessary (for example, because their seizures are controlled using ASMs), these patients will be discharged from epilepsy services. Therefore, currently, people can only re-access tertiary epilepsy services through primary care referrals.

It was discussed that many people with epilepsy feel anxious about the prospect of being discharged from epilepsy services which could potentially impact their quality of life (QoL). It was also noted that, in some instances, people may receive regular reviews for longer than needed due to the associated anxieties of being discharged from the service and not being able to easily re-access services. The committee acknowledged that providing an ad-hoc monitoring service for people who do not require regular review, where patients are provided appropriate contact details to access care, would reduce anxiety and potentially result in cost savings for the NHS.

Additional resources may be needed to facilitate a service where people with epilepsy receive contact details and information on how to access epilepsy services (for example, specialist nurse services). These costs will likely be offset because people with epilepsy will not necessarily need to go through primary care to obtain a referral to secondary and tertiary care. This is also likely to result in time-saving efficiencies in the long-run as people may not require face-to-face appointments to obtain advice from a health care professional. Subsequently, the committee made a recommendation to make people aware they can ask for a review if they have any concerns related to their epilepsy, need advice, or their health care needs change. The committee also noted people with epilepsy, and their family or careers if appropriate, should be provided with contact details and information on how to access epilepsy services.

The committee acknowledged that for those groups of people who would benefit from regular monitoring (for example, people with drug-resistant epilepsy, learning disabilities, and people at high risk of SUDEP), this should be provided. This recommendation is not expected to result in a substantial resource impact as regular monitoring of these people should already be provided in current practice.

The committee also acknowledged regular monitoring reviews for children and young people should be conducted at least every 12 months and made a recommendation to reflect this. The committee noted that regular monitoring is conducted for children and young people in clinical practice therefore, this recommendation is not expected to result in a substantial resource impact.

No clinical benefit was found for therapeutic drug monitoring. The committee noted that drug monitoring is not routinely conducted in clinical practice. However, current practice can vary, and some centres may provide therapeutic drug monitoring for a number of people. More commonly in clinical practice, therapeutic drug monitoring is provided in specific instances such as for people whose seizures are uncontrolled or experiencing side effects from their medication. Therefore, the committee made a recommendation largely reflective of current practice to consider drug monitoring only in people with uncontrolled seizures, experiencing side effects from their medication, not adhering to medication, or require more supervision based on clinical need (for example, people with renal failure). As this recommendation is largely reflective of current practice it is not expected to result in a substantial resource impact. The committee also noted the recommendation may result in cost savings for the NHS by restricting therapeutic drug monitoring to select groups of people.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 4.5.1 – 4.5.4 in the NICE guideline.

References

1. Aicua-Rapun I, Andre P, Rossetti AO, Ryvlin P, Hottinger AF, Decosterd LA et al. Therapeutic drug monitoring of newer antiepileptic drugs: A randomized trial for dosage adjustment. Annals of Neurology. 2020; 87(1):22-29

2. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. Archives of Disease in Childhood. 2010; 95(9):731-738

3. Arfman IJ, Wammes-van der Heijden EA, Ter Horst PGJ, Lambrechts DA, Wegner I, Touw DJ. Therapeutic drug monitoring of antiepileptic drugs in women with epilepsy before, during, and after pregnancy. Clinical Pharmacokinetics. 2020; 59(4):427-445

4. Bahrani K, Singh MB, Bhatia R, Prasad K, Vibha D, Shukla G et al. Telephonic review for outpatients with epilepsy-A prospective randomized, parallel group study. Seizure. 2017; 53:55-61

5. Bergmann M, Prieschl M, Walser G, Luef G, Rumpold G, Unterberger I. Computer-based monitoring and evaluation of epilepsy-related health variables and their impact on treatment decision. Epilepsy & Behavior. 2018; 84:173-178

6. Block VA, Pitsch E, Tahir P, Cree BA, Allen DD, Gelfand JM. Remote physical activity monitoring in neurological disease: A systematic review. PloS One. 2016; 11(4):e0154335

7. Borusiak P, Bast T, Kluger G, Weidenfeld A, Langer T, Jenke ACW et al. A longitudinal, randomized, and prospective study of nocturnal monitoring in children and adolescents with epilepsy: Effects on quality of life and sleep. Epilepsy & Behavior. 2016; 61:192-198

8. Bottacchi E, Carenini E, Boati E, Porazzi D, Grampa G, Guerrini R et al. A prospective randomized study on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy: interim evaluation. Bollettino - Lega Italiana contro l'Epilessia. 1996; (95-96):171-173

9. Busch RM, Love TE, Jehi LE, Ferguson L, Yardi R, Najm I et al. Effect of invasive EEG monitoring on cognitive outcome after left temporal lobe epilepsy surgery. Neurology. 2015; 85(17):1475-1481

10. Camfield P, Camfield C. Monitoring for adverse effects of antiepileptic drugs. Epilepsia. 2006; 47(Suppl 1):31-34

11. Chong E, Dupuis LL. Therapeutic drug monitoring of lamotrigine. Annals of Pharmacotherapy. 2002; 36(5):917-920

12. Contin M, Riva R, Albani F, Avoni P, Baruzzi A. Topiramate therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. Therapeutic Drug Monitoring. 2002; 24(3):332-337

13. Demir M, Akarsu EO, Dede HO, Bebek N, Yildiz SO, Baykan B et al. Investigation of the roles of new antiepileptic drugs and serum bdnf levels in efficacy and safety monitoring and quality of life: A clinical research. Current Clinical Pharmacology. 2020; 15(1):49-63

14. Faught E. Measure for measure: Measuring the usefulness of measuring antiseizure medication levels. Epilepsy Currents. 2020; 20(3):132-133

15. Froscher W, Eichelbaum M, Gugler R, Hildenbrand G, Penin H. A prospective randomised trial on the effect of monitoring plasma anticonvulsant levels in epilepsy. Journal of Neurology. 1981; 224(3):193-201

16. Gatti G, Bartoli A, Cian P, Monaco F, Perucca E. The impact of therapeuthic drug monitoring (TDM) on clinical outcome in patients with epilepsy: a randomized, multicentre prospective study. Fundamental and Clinical Pharmacology. 1996; 10(2):191

17. Gram L, Wulff K, Rasmussen KE, Flachs H, Wurtz-Jorgensen A, Sommerbeck KW et al. Valproate sodium: a controlled clinical trial including monitoring of drug levels. Epilepsia. 1977; 18(2):141-148

18. 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

19. Hu M, Zhang C, Xiao X, Guo J, Sun H. Effect of intensive self-management education on seizure frequency and quality of life in epilepsy patients with prodromes or precipitating factors. Seizure. 2020; 78:38-42

20. 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

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

22. Johannessen SI, Battino D, Berry DJ, Bialer M, Kramer G, Tomson T et al. Therapeutic drug monitoring of the newer antiepileptic drugs. Therapeutic Drug Monitoring. 2003; 25(3):347-363

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

24. Kamali F, Thomas SH. Effect of saliva flow rate on saliva phenytoin concentrations: implications for therapeutic monitoring. European Journal of Clinical Pharmacology. 1994; 46(6):565-567

25. Khachian A, Seyedoshohadaee M, Hosseini AF, Bahiraei N, Shamsi M. Effectiveness of an educational program with family-centered approach on self-management behaviors of people with epilepsy. Annals of Tropical Medicine and Public Health. 2018; 3(Special Issue):S4-S9

26. Knott C, Hamshaw-Thomas A, Reynolds F. Phenytoin-valproate interaction: Importance of saliva monitoring in epilepsy. British Medical Journal. 1982; 284(6308):13-16

27. Modi AC, Guilfoyle SM, Mann KA, Rausch JR. A pilot randomized controlled clinical trial to improve antiepileptic drug adherence in young children with epilepsy. Epilepsia. 2016; 57(3):e69-75

28. Morrow JI, Harvey I, Richens A. A randomised controlled trial of routine neurology care versus specialised epilepsy clinic care for patients with epilepsy - short term results. 18th International Epilepsy Congress. 1989:25

29. 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

30. Pakpour AH, Gholami M, Esmaeili R, Naghibi SA, Updegraff JA, Molloy GJ et al. A randomized controlled multimodal behavioral intervention trial for improving antiepileptic drug adherence. Epilepsy & Behavior. 2015; 52(Pt A):133-142

31. Patsalos PN, Berry DJ, Bourgeois BFD, 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

32. 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

33. Pennington M, Ring H, Howlett J, Smith C, Redley M, Murphy C et al. The impact of an epilepsy nurse competency framework on the costs of supporting adults with epilepsy and intellectual disability: findings from the EpAID study. Journal of Intellectual Disability Research. 2019; 63(12):1391-1400

34. Peterson GM, McLean S, Millingen KS. A randomised trial of strategies to improve patient compliance with anticonvulsant therapy. Epilepsia. 1984; 25(4):412-417

35. 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

36. Remick M, Ibrahim GM, Mansouri A, Abel TJ. Patient phenotypes and clinical outcomes in invasive monitoring for epilepsy: An individual patient data meta-analysis. Epilepsy & Behavior. 2020; 102:106652

37. Remington G, Agid O, Foussias G, Ferguson L, McDonald K, Powell V. Clozapine and therapeutic drug monitoring: is there sufficient evidence for an upper threshold? Psychopharmacology. 2013; 225(3):505-518

38. 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

39. 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

40. 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

41. Rossetti AO, Schindler K, Alvarez V, Sutter R, Novy J, Oddo M et al. Does continuous video-EEG in patients with altered consciousness improve patient outcome? Current evidence and randomized controlled trial design. Journal of Clinical Neurophysiology. 2018; 35(5):359-364

42. Sahlroot JT, Pledger GW, Privitera M, Bell WE. Electronic compliance monitoring in a clinical trial of dezinamide. Epilepsia. 1993; 34(Suppl 6):40-41

43. Sarkissian S, Wennberg R. Effects of the acute care nurse practitioner role on epilepsy monitoring outcomes. Outcomes Management for Nursing Practice. 1999; 3(4):161-166

44. 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

45. Schougaard LMV, Mejdahl CT, Christensen J, Lomborg K, Maindal HT, de Thurah A et al. Patient-initiated versus fixed-interval patient-reported outcome-based follow-up in outpatients with epilepsy: a pragmatic randomized controlled trial. Journal of Patient-Reported Outcomes. 2019; 3(1):61

46. Schultz L, Mahmoud SH. Is therapeutic drug monitoring of lacosamide needed in patients with seizures and epilepsy? European Journal of Drug Metabolism and Pharmacokinetics. 2020; 45(3):315-349

47. 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

48. Sivasankari V, Tharani CB, Gobinathan S. A clinical evaluation of therapeutic drug monitoring of phenytoin in epileptic patients in a tertiary care teaching hospital, Chennai, Tamilnadu: A randomized, open label comparative study. International Journal of Pharma and Bio Sciences. 2012; 3(2):271-280

49. Striano S, Striano P, Capone D, Pisani F. Limited place for plasma monitoring of new antiepileptic drugs in clinical practice. Medical Science Monitor. 2008; 14(10):RA173-178

50. Tan J, Paquette V, Levine M, Ensom MHH. Levetiracetam clinical pharmacokinetic monitoring in pediatric patients with epilepsy. Clinical Pharmacokinetics. 2017; 56(11):1267-1285

51. 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)

52. Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD002216. DOI: 10.1002/14651858.CD002216.pub2.

53. Toth M, Papp KS, Gede N, Farkas K, Kovacs S, Isnard J et al. Surgical outcomes related to invasive EEG monitoring with subdural grids or depth electrodes in adults: A systematic review and meta-analysis. Seizure. 2019; 70:12-19

54. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: A systematic review. Therapeutic Drug Monitoring. 2005; 27(1):10-17

55. 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

56. Venz S, Cordes M, Straub HB, Hierholzer J, Schröder R, Richter W et al. Preoperative evaluation of drug resistant focal epilepsies with 123I-iomazenil SPECT. Comparison with vidio/EEG monitoring and postoperative results. Nuklearmedizin. 1994; 33(5):189-193

57. Vieluf S, El Atrache R, Hammond S, Touserkani FM, Loddenkemper T, Reinsberger C. Peripheral multimodal monitoring of ANS changes related to epilepsy. Epilepsy & Behavior. 2019; 96:69-79

58. Warren E, Hart G, Winterbottom J, Baker G, Jacoby A, Luker K et al. An evaluation of a nurse specialist/case manager intervention in the management of epilepsy. Epilepsia. 1999; 40(Suppl 2):107

59. Willems LM, Reif PS, Spyrantis A, Cattani A, Freiman TM, Seifert V et al. Invasive EEG-electrodes in presurgical evaluation of epilepsies: Systematic analysis of implantation-, video-EEG-monitoring- and explantation-related complications, and review of literature. Epilepsy & Behavior. 2019; 91:30-37

60. Woo E, Chan YM, Yu YL, Chan YW, Huang CY. If a well-stabilized epileptic patient has a subtherapeutic antiepileptic drug level, should the dose be increased? A randomized prospective study. Epilepsia. 1988; 29(2):129-139

61. World Health Organisation. In-home EEG monitoring in suspected epilepsy. 2011. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01862796/full

62. Zheng Y, Ding X, Guo Y, Chen Q, Wang W, Zheng Y et al. Multidisciplinary management improves anxiety, depression, medication adherence, and quality of life among patients with epilepsy in eastern China: A prospective study. Epilepsy & Behavior. 2019; 100(Pt A):106400

Appendices

Appendix A Review protocols

A.1 Review protocol for monitoring of people with epilepsy

ID	Field	Content
0.	PROSPERO registration number	CRD4020180301
1.	Review title	Ongoing monitoring of people with epilepsy
2.	Review question	6.1 When should monitoring be carried out for people with epilepsy? 6.2 How should monitoring be carried out for people with epilepsy, and who should do it?
3.	Objective	The objective of the review is to determine how often people with epilepsy should be monitored and how it should be carried out by health care professionals.
4.	Searches	The following databases (from inception) will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Other searches: Inclusion lists 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	Epilepsy is a disease characterized by an enduring predisposition in which brain activity becomes abnormal, causing seizures or periods of unusual behaviour, sensations, and sometimes loss of awareness. At least two unprovoked seizures are generally required for an epilepsy diagnosis.
6.	Population	Inclusion: people with epilepsy Exclusion: new-born babies (under 28 days) with acute symptomatic seizures
7.	Intervention/Exposure/Test	(a) Annual monitoring review (b) Structured follow-up monitoring appointments
8.	Comparator/Reference standard/Confounding factors	(a) No monitoring (b) Ad-hoc follow-up monitoring appointments (c) Any alternative pattern of monitoring
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. If insufficient RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders (age), including both prospective cohort studies and retrospective cohort studies that had been adjusted for age and gender Published NMAs and IPDs will be considered for inclusion. For a systematic review to be included it must be conducted to the same methodological standard as NICE guideline reviews. If sufficient details are not provided to include a relevant systematic review, the review will only be used for citation searching. Follow-up will be a minimum of one year
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	It is important people with epilepsy are reviewed at regular intervals to ensure that they are not maintained for long periods on treatment that is ineffective or poorly tolerated. Monitoring is also important to assess any adverse events associated with treatment.
12.	Primary outcomes (critical outcomes)	• mortality • seizure recurrence • seizure frequency • seizure freedom • drug adherence • quality of life (measured with a validated scale) • health care resource use • unplanned hospital admission • attendance at ED outcomes will be reported at a minimum of 1 year Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as “time to 12 months seizure freedom”, (i.e., time to event: HR or mean time) followed by “achievement of 12 months seizure freedom” (RR).
13.	Secondary outcomes (important outcomes)	• social functioning (measures of adaptive functioning or adaptive behaviour using a validated scale) at a minimum of 1 year • cognitive outcomes (including neuropsychological measures of global cognitive functioning, executive functioning and memory using a validated scale) at a minimum of 1 year • in children and young people: neurodevelopmental outcomes (behavioural and emotional outcomes measured with a validated scale) at a minimum of 1 year • educational outcome at a minimum of 1 year • placement breakup (change in care location during a minimum of 1 year) • Contact with mental health services • Anxiety/depression/emotional distress HADS, PHQ-9, BDI/BAI and Core10, SDQ and PI-ED, BAI-Y and BDI-Y and YPCore, CBCL
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. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised studies, 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.	
17.	Analysis of sub-groups	Groups to be considered from the equality impact assessment: • children and young people • girls and women of who are able to get pregnant (including those who are pregnant and breastfeeding) • older people • people with learning disabilities Subgroups that will be investigated if heterogeneity is present: • according to the risk of bias of individual studies • by age (children, young people and adults) • type of epilepsy (generalised, focal, epilepsy syndrome) • country of study (UK, US, Europe and rest of the world	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	March 2020	
22.	Anticipated completion date	tbc	
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 National Guideline Centre Angela Cooper angela.cooper@rcplondon.ac.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: 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	[Give the citation and link for the published protocol if there is one.]	
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	[Give words or phrases that best describe the review.]	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2004 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[29] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with "Minor limitations" then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with "Very serious limitations" then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

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

Appendix B Literature search strategies

This literature search strategy was used for the following review:

- When should monitoring be carried out for people with epilepsy? How should monitoring be carried out for people with epilepsy, and who should do it?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[29]

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 – 07 May 2020	Randomised controlled trials Systematic review studies Exclusions
Embase (OVID)	1974 – 07 May 2020	Randomised controlled trials Systematic review studies Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 5 of 12 CENTRAL to 2020 Issue 5 of 12	None
Epistemonikos (The Epistemonikos Foundation)	Inception to 07 May 2020	Systematic review studies

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/

10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Monitoring, Physiologic/ or Monitoring, Ambulatory/ or Neurophysiological Monitoring/
28.	monitor*.ti,ab.
29.	Patient compliance/ or Medication Adherence/ or Drug Monitoring/
30.	exp Patient Outcome Assessment/
31.	("patient reported outcome measures" or PROM).ti,ab.
32.	"Continuity of Patient Care"/
33.	patient care/
34.	"Delivery of Health Care, Integrated"/
35.	critical pathways/
36.	((care or clinical or critical or patient*) adj2 manag*).ti,ab.
37.	Telemetry/ or Telemedicine/
38.	(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.
39.	exp "Appointments and Schedules"/
40.	Self Care/
41.	(self adj (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)).ti,ab.
42.	((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.
43.	((drug* or medication* or pharm*) adj (compliance or complying or adher*)).ti,ab.
44.	or/27-43
45.	26 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ti,ab.

49.	placebo.ab.
50.	randomly.ti,ab.
51.	Clinical Trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	exp Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(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.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	45 and (53 or 64)

Embase (Ovid) search terms

1.	exp epilepsy/
2.	seizure/
3.	epileptic state/
4.	febrile convulsion/
5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	*physiologic monitoring/

26.	*ambulatory monitoring/
27.	*neurophysiological monitoring/
28.	monitor*.ti,ab.
29.	*patient compliance/
30.	*medication compliance/
31.	*drug monitoring/
32.	*outcome assessment/
33.	("patient reported outcome measures" or PROM).ti,ab.
34.	*patient care/
35.	*integrated health care system/
36.	*clinical pathway/
37.	((care or clinical or critical or patient*) adj2 manag*).ti,ab.
38.	*telemetry/
39.	*telemedicine/
40.	(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.
41.	*hospital management/
42.	*self care/
43.	(self adj (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)).ti,ab.
44.	((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.
45.	((drug* or medication* or pharm*) adj (compliance or complying or adher*)).ti,ab.
46.	or/25-45
47.	24 and 46
48.	random*.ti,ab.
49.	factorial*.ti,ab.
50.	(crossover* or cross over*).ti,ab.
51.	((doubl* or singl*) adj blind*).ti,ab.
52.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
53.	crossover procedure/
54.	single blind procedure/
55.	randomized controlled trial/
56.	double blind procedure/
57.	or/48-56
58.	systematic review/
59.	meta-analysis/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.

64.	(search* adj4 literature).ab.
65.	(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.
66.	cochrane.jw.
67.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
68.	or/58-67
69.	47 and (57 or 68)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Epilepsy] explode all trees
#2.	MeSH descriptor: [Seizures] this term only
#3.	MeSH descriptor: [Status Epilepticus] explode all trees
#4.	MeSH descriptor: [Seizures, Febrile] this term only
#5.	(dravet syndrome or epilep* or convuls* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome):ti,ab
#6.	(or #4-#5)
#7.	MeSH descriptor: [Monitoring, Physiologic] this term only
#8.	MeSH descriptor: [Monitoring, Ambulatory] this term only
#9.	MeSH descriptor: [Neurophysiological Monitoring] this term only
#10.	monitor*:ti,ab
#11.	MeSH descriptor: [Patient Compliance] this term only
#12.	MeSH descriptor: [Medication Adherence] this term only
#13.	MeSH descriptor: [Drug Monitoring] this term only
#14.	MeSH descriptor: [Patient Outcome Assessment] explode all trees
#15.	("patient reported outcome measures" or PROM):ti,ab
#16.	MeSH descriptor: [Continuity of Patient Care] this term only
#17.	MeSH descriptor: [Patient Care] this term only
#18.	MeSH descriptor: [Delivery of Health Care, Integrated] this term only
#19.	MeSH descriptor: [Critical Pathways] this term only
#20.	((care or clinical or critical or patient*) near/2 manag*):ti,ab
#21.	MeSH descriptor: [Telemetry] this term only
#22.	MeSH descriptor: [Telemedicine] this term only
#23.	(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
#24.	MeSH descriptor: [Appointments and Schedules] explode all trees
#25.	MeSH descriptor: [Self Care] this term only
#26.	(self near (care or caring or manag* or checkup or check* up or assess* or test* or evaluat*)):ti,ab
#27.	((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
#28.	((drug* or medication* or pharm*) near (compliance or complying or adher*)):ti,ab
#29.	(or #7-#27)

#30.	#6 and #29

Epistemonikos search terms

1.	(title:(monitor*) OR abstract:(monitor*)) AND (title:((title:((epilepsies OR epilepsy)) OR abstract:((epilepsies OR epilepsy)))) OR abstract:((title:((epilepsies OR epilepsy)) OR abstract:((epilepsies OR epilepsy)))))

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 Quality of Life 1974 – 13 May 2021	Health economics studies Quality of life studies Exclusions
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 May 2021 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp epilepsy/
2.	seizures/
3.	exp status epilepticus/
4.	seizures, febrile/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	quality-adjusted life years/
45.	sickness impact profile/
46.	(quality adj2 (wellbeing or well being)).ti,ab.
47.	sickness impact profile.ti,ab.
48.	disability adjusted life.ti,ab.
49.	(qal* or qtime* or qwb* or daly*).ti,ab.
50.	(euroqol* or eq5d* or eq 5*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.

62.	or/44-61
63.	26 and (43 or 62)

Embase (Ovid) search terms

1.	exp *epilepsy/
2.	*landau kleffner syndrome/
3.	exp *seizure/
4.	"seizure, epilepsy and convulsion"/
5.	(dravet syndrome or epilep* or continuous spike wave or slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	quality adjusted life year/
40.	sickness impact profile/

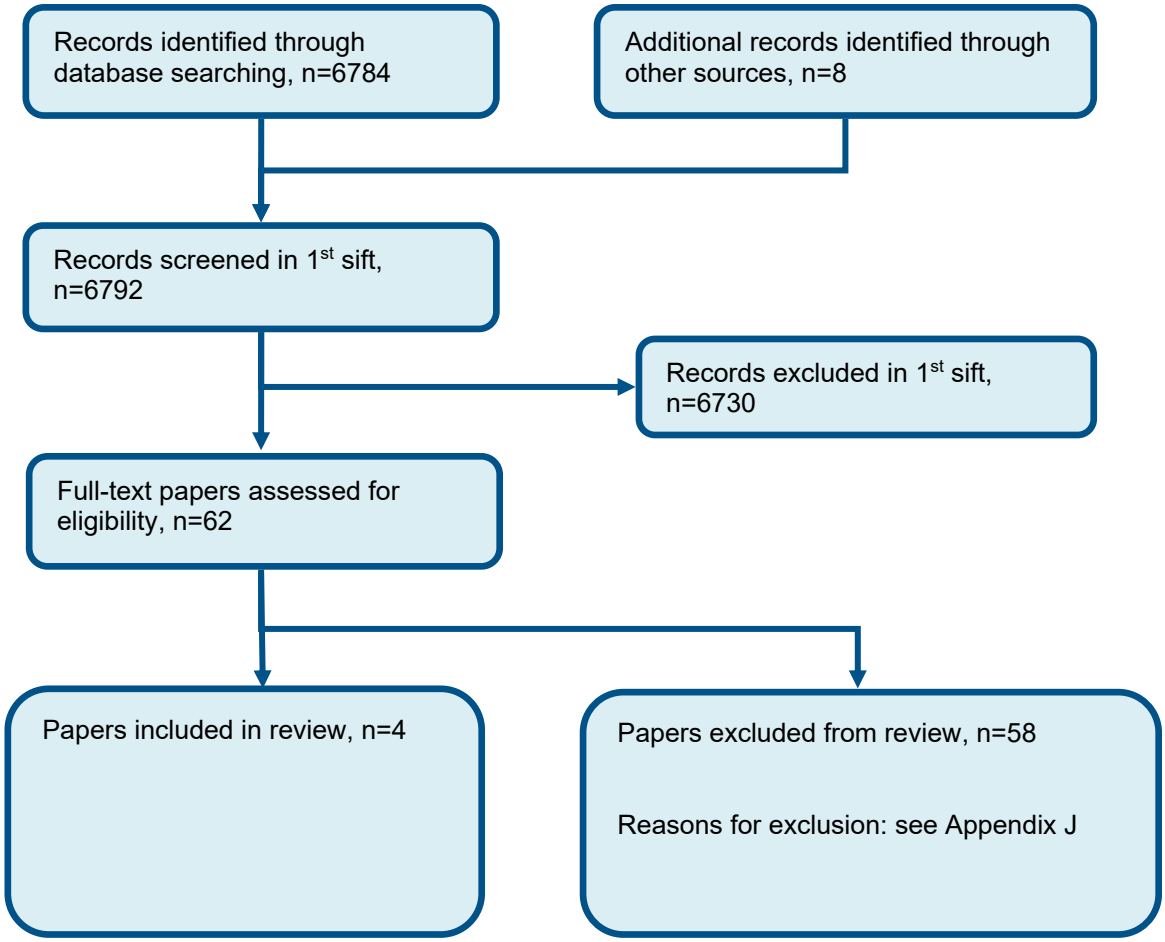
41.	(quality adj2 (wellbeing or well being)).ti,ab.
42.	sickness impact profile.ti,ab.
43.	disability adjusted life.ti,ab.
44.	(qal* or qtime* or qwb* or daly*).ti,ab.
45.	(euroqol* or eq5d* or eq 5*).ti,ab.
46.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
47.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
48.	(hui or hui1 or hui2 or hui3).ti,ab.
49.	(health* year* equivalent* or hye or hyes).ti,ab.
50.	discrete choice*.ti,ab.
51.	rosser.ti,ab.
52.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
53.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
54.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
55.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
56.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
57.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
58.	or/39-57
59.	24 and (38 or 58)

NHS EED and HTA (CRD) search terms

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

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of monitoring



Appendix D Effectiveness evidence

Study	**AICUA-RAPUN, 2020 trial: Aicua-rapun 2020[1]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Switzerland; Setting: Outpatient department
Line of therapy	1st line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: 'diagnosed with epilepsy'
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged >18 yrs; diagnosis of epilepsy
Exclusion criteria	Pregnancy
Recruitment/selection of patients	Unclear, but almost certainly recruited in the outpatient department
Age, gender and ethnicity	Age - Median (range): 37(18-82). Gender (M:F): 44.4:56.6. Ethnicity: unclear
Further population details	1. Age: Adults (>18 inclusion criterion). 2. Country of study: Europe not including UK (Switzerland). 3. Type of epilepsy: focal (>75% focal).

Extra comments	Focal epilepsy 75.5%; drug-resistant epilepsy 48.7%; epilepsy duration 7 ys, median of 1 previous AEDs tried (range 0-9); All being given a newer AED (Brivaracetam, Lacosamide, Lamotrigine, Levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, zonisamide) at standard doses
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Therapeutic Drug Monitoring. A pharmacist specializing in TDM assessed all plasma levels of the study drugs. Results were systematically relayed to the clinician within 24 hours. The clinician was not given target levels but was free to adjust medication using these results. Duration 1 year. Concurrent medication/care: Three to four monitoring visits were given per year, based on clinical need. Patients had to take medication at least 6 hours before or after the blood sampling. Indirectness: No indirectness Further details: 1. risk of bias: Very low (n=75) Intervention 2: Clinical monitoring (no access to TDM results). TDM was carried out by the pharmacist as before but results were not relayed to the clinician (unless the patient reached a clinical endpoint, or until the end of follow up). Duration 1 year. Concurrent medication/care: Three to four monitoring visits were given per year, based on clinical need. Patients had to take medication at least 6 hours before or after the blood sampling. Indirectness: No indirectness Further details: 1. risk of bias: Very low
Funding	Academic or government funding (Swiss National Scientific Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC DRUG MONITORING versus CLINICAL MONITORING (NO ACCESS TO TDM RESULTS)

Protocol outcome 1: Mortality at 1 yr. or more
- Actual outcome: Death at 1 year; Group 1: 1/76, Group 2: 0/75
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness; Baseline details: Similar for past history of seizures; Group 1 Number missing: 18, Reason: 11 premature end with no endpoint, 4 no plasma levels, 3 prescribed change not allowed; Group 2 Number missing: 16, Reason: 7 premature end with no endpoint, 3 no plasma levels, 4 prescribed change not allowed, 2 pregnant

Protocol outcome 2: Seizure recurrence at 1 year or more
- Actual outcome: All inefficacy endpoints: combination of at least 2 seizures with lack of awareness, or status epilepticus, or need to add a treatment because of loss of efficacy at 1 year; Group 1: 24/76, Group 2: 19/75

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Departure from protocol outcome - the outcome comprises the need to add a treatment because of loss of efficacy, which may not necessarily relate to seizures; Baseline details: Similar for past history of seizures; Group 1 Number missing: 18, Reason: 11 premature end with no endpoint, 4 no plasma levels, 3 prescribed change not allowed; Group 2 Number missing: 16, Reason: 7 premature end with no endpoint, 3 no plasma levels, 4 prescribed change not allowed, 2 pregnant	
Protocol outcomes not reported by the study	Quality of life at 1 year or more; Seizure freedom at 1 year or more); Seizure frequency at 1 year or more; Drug adherence at 1 year or more; health care resource use at Define; Hospitalisation - unplanned at 1 year or more; Attendance at ED at 1 year or more; contact with mental health services at Define; Length of stay at Define; Social functioning at Define; Neurodevelopmental outcomes at Define; Cognitive outcomes at Define; educational outcome at Define; placement breakup (change in care location) at Define; Psychological outcomes at Define

Study	**FROSCHER, 1981 trial: Froscher 1981[15]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=127)
Countries and setting	Conducted in Germany; Setting: Outpatients department in Germany
Line of therapy	1st line
Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Minimum of 3 seizures of one seizure type during preceding year
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Minimum of 3 seizures of one seizure type during preceding year

Exclusion criteria	non-compliance; alcohol addiction; pregnancy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): Not reported. Ethnicity: Unclear
Further population details	1. Age: Not stated / Unclear 2. Country of study: Europe not including UK (Germany). 3. Type of epilepsy: generalised ('Grand mal').
Extra comments	'Grand mal' 21/105; 'grand mal and psychomotor seizures' 53/105; 'grand mal and absences' 31/105
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Therapeutic Drug Monitoring. Plasma drug levels were measured and reported to the treating physician who attempted to keep the plasma levels within the 'therapeutic range'. Duration 1 year. Concurrent medication/care: The antiepileptic drugs that were monitored included carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid. Indirectness: No indirectness Further details: 1. risk of bias: Very low Comments: n is unclear. (n=64) Intervention 2: Clinical monitoring (no access to TDM results). Duration 1 year. Concurrent medication/care: The antiepileptic drugs that were monitored included carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone and valproic acid. Indirectness: No indirectness Further details: 1. risk of bias: Very low Comments: n unclear
Funding	Academic or government funding (Bundesministerium fur Jugend, Famillie und Gesundheit)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC DRUG MONITORING versus CLINICAL MONITORING (NO ACCESS TO TDM RESULTS)

Protocol outcome 1: Seizure frequency at 1 year or more
- Actual outcome: seizure frequency unchanged or worse at 1 year; Group 1: 16/53, Group 2: 20/52; Comments: All seizure types summated

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 10, Reason: not reported; Group 2 Number missing: 12, Reason: not reported	
Protocol outcomes not reported by the study	Quality of life at 1 year or more; Mortality at 1 yr. or more; Seizure recurrence at 1 year or more; Seizure freedom at 1 year or more); Drug adherence at 1 year or more; health care resource use at Define; Hospitalisation - unplanned at 1 year or more; Attendance at ED at 1 year or more; contact with mental health services at Define; Length of stay at Define; Social functioning at Define; Neurodevelopmental outcomes at Define; Cognitive outcomes at Define; educational outcome at Define; placement breakup (change in care location) at Define; Psychological outcomes at Define

Study	**JANNUZZI, 2000 trial: Jannuzzi 2000[20]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=180)
Countries and setting	Conducted in Italy; Setting: Multicentre setting in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of untreated partial or idiopathic generalised epilepsy, based on clinical, electrophysiologic and imaging investigations
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	age 6-65; diagnosis of untreated partial or idiopathic generalised epilepsy; a history of at least 2 seizures in previous 4 months; clinical indication to prescribe carbamazepine, phenytoin, valproate, phenobarbital or primidone; ability to comply with procedures;
Exclusion criteria	benign Rolandic epilepsy, absence epilepsy or epileptic encephalopathy; any progressive disease; pregnancy; severe hepatic/renal insufficiency; history of drug/alcohol abuse; treatment with any AED
Recruitment/selection of patients	Unclear
Age, gender and ethnicity	Age - Range: 6-65 years; mean of 27 in TDM group and 29 in control group. Gender (M:F): 94: 86. Ethnicity: unclear
Further population details	1. Age: Adults (Included children but average age around 28). 2. Country of study: Europe not including UK (Italy). 3. Type of epilepsy: focal (115/180 had partial epilepsy, though 65/180 had generalised).
Extra comments	median number of seizures in the 4 months before treatment 3; patients with partial epilepsy 115/180; number of patients with generalised epilepsy 65/180; simple partial seizures 42/180; complex partial 75/180; secondarily generalised tonic-clonic 66/180; primarily generalised tonic-clonic 56/180; absence 7/180; carbamazepine 111/180; phenobarbital 40/180; phenytoin 8/180; sodium valproate 40/180
Indirectness of population	No indirectness
Interventions	(n=93) Intervention 1: Therapeutic Drug Monitoring. In one group (TDM group), the dosage of the selected AED was adjusted based on serum drug level monitoring to achieve within a period 53 months steady-state concentrations within the target range. The target ranges used were 10-20 pg/ml (40-80 pM) for PHT, 15-40 pg/ml(64-172 pM) for PB, 4-1 1 ~g/ml(l7-46pM) for CBZ, and 40-100 pg/ml (280-700 phf) for VPA. For PRM-treated patients, only metabolically derived PB was used for TDM purposes. All blood samples were collected at steady state. For patients treated with PHT, PB, PRM, and controlled-release CBZ, samples had to be collected before the morning dose, 5 12 h (PHT, CBZ) or 515 h (PB, PRM) after the last administration. For VPA and immediate-release CBZ, two samples had to be obtained, one before the morning dose (512 h after the last administration) and one 3 h later, and the physicians were instructed to aim at serum drug concentrations within the target range in both samples. For patients taking VPA, food intake was delayed until the second sample was taken. If seizures persisted despite serum levels in the lower part of the target range, the protocol required that physicians adjust the dosage further to produce AED levels in the upper part of the range. Levels below the target range were allowed only if the patient was unable to tolerate higher concentrations. Levels above target were allowed at the discretion of the treating physician only when there were no significant side effects and seizures persisted at target concentrations. At all study sites, physicians had to be able to use TDM

	results within 7 days of sampling. Duration 2 years. Concurrent medication/care: Seizures were recorded daily on appropriate cards by the patients or their guardians. All patients were seen in the clinic approximately every month during the first 3 months, every 3 months in the subsequent 9 months, and at least twice during the second year of follow up. Investigations also included a medical examination and generic questioning for possible side effects. Other investigations were carried out if clinically indicated. Indirectness: No indirectness Further details: 1. risk of bias: Very low (n=87) Intervention 2: Clinical monitoring (no access to TDM results). In the second group (control group), blood samples for the determination of AED levels were collected in a similar way, but TDM results were not made available to the treating physician. In this group, dosage was adjusted on purely clinical grounds, aiming at achieving optimal seizure control over the shortest reasonable period. If no satisfactory response was achieved after 6-1 2 months and the physician thought that continuation of treatment without knowledge of serum drug concentration was no longer ethically acceptable, the patient could be crossed over to the TDM group and managed subsequently according to the protocol described for that group. Except for the feedback (or lack of feedback) derived from TDM data, precise modalities of dosage adjustments within each group were left to the clinicians' judgment, and patients were followed up as in routine clinical care. Duration of follow-up was 2 years unless exit criteria were met. The latter were (a) need to switch the patient to another drug, (b) need to add a second drug, or (c) for the control group only, unsatisfactory response after 6-12 months, requiring evaluation of TDM data collected up to that time (in the latter case, patients were still followed up for 52 years according to the procedures outlined for the TDM group). Duration 2 years. Concurrent medication/care: Seizures were recorded daily on appropriate cards by the patients or their guardians. All patients were seen in the clinic approximately every month during the first 3 months, every 3 months in the subsequent 9 months, and at least twice during the second year of follow up. Investigations also included a medical examination and generic questioning for possible side effects. Other investigations were carried out if clinically indicated. Indirectness: No indirectness Further details: 1. risk of bias: Very low
Funding	Academic or government funding (European Commission)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: THERAPEUTIC DRUG MONITORING versus CLINICAL MONITORING (NO ACCESS TO TDM RESULTS)

Protocol outcome 1: Seizure recurrence at 1 year or more
- Actual outcome: Recurrence of any seizure at 2 years;
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Median of 3 seizures in each group in 4 months before treatment; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Seizure freedom at 1 year or more)

- Actual outcome: Number remaining seizure free at the end of the study at 2 years; Group 1: 22/58, Group 2: 24/58; Comments: The paper reported that overall 38% of TDM patients remained seizure free and that 41% of the control patients remained seizure free. However, the denominator for each group is unclear. It may be the original numbers randomised (93 and 87 respectively), but it could be the final number after attrition (58 in each group). The paper does not make this clear. I have opted for the denominator being the numbers after attrition as this gives the most conservative result (lower power). Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Median of 3 seizures in each group in 4 months before treatment; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 1 year or more; Mortality at 1 yr. or more; Seizure frequency at 1 year or more; Drug adherence at 1 year or more; health care resource use at Define; Hospitalisation - unplanned at 1 year or more; Attendance at ED at 1 year or more; contact with mental health services at Define; Length of stay at Define; Social functioning at Define; Neurodevelopmental outcomes at Define; Cognitive outcomes at Define; educational outcome at Define; placement breakup (change in care location) at Define; Psychological outcomes at Define

Study	**SCHOUGAARD, 2019 trial: Schougaard 2019[45]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=593)
Countries and setting	Conducted in Denmark
Line of therapy	1st line
Duration of study	Follow up (post intervention): 18 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: 'diagnosis of epilepsy or suspicion of epilepsy'

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	15 yrs or older; epilepsy diagnosis or suspicion of epilepsy; attending standard telePRO follow up; filled in last questionnaire on the internet
Exclusion criteria	paper respondents; had stopped attending standard telePRO follow-up before randomisation
Recruitment/selection of patients	After randomisation, patients in open access telePRO given option to continue with standard care (standard telePRO)
Age, gender and ethnicity	Age - Range of means: 46.3 to 47.2. Gender (M:F): 297:296. Ethnicity: unclear
Further population details	1. Age: Adults (mean age around 46). 2. Country of study: Europe not including UK (Denmark). 3. Type of epilepsy: Not stated / Unclear
Extra comments	Open access telePRO/standard telePRO: No or low education: 27%/25%; duration of epilepsy 16.1yrs/16.9yrs; 1 or more seizures in last year: 28%/28%; living alone 22%/25%
Indirectness of population	No indirectness
Interventions	(n=247) Intervention 1: Monitoring at a defined interval - annually. In standard telePRO, patients filled in fixed-interval disease-specific questionnaires every 3, 6, or 12 months (80% every 12 months), which were used as a partly automatic tool to support the decision regarding whether the patient needed clinical attention at the present time. In the questionnaire, all patients could request a telephone consultation or an appointment in the outpatient clinic, regardless of their response to the other questions in the questionnaire. The patient's response to the questionnaires was given a green, yellow, or red colour by using a pre-defined automated algorithm. Green indicated no need of clinical attention, red indicated need of attention, whereas yellow indicated that the patient might need attention. Green responses were handled automatically by the server software, and a new questionnaire was automatically scheduled to be sent to the patient at the pre-defined fixed interval, for example, after 12months. All yellow and red responses were shown on an alert list, available to the clinicians, who accessed the list daily. A red response indicated need of clinical attention, and the clinician contacted the patient as quickly as possible. Patients were either contacted by telephone or they received a face-to-face appointment. For yellow responses, patients were only contacted if the clinicians judged that it was necessary. The patient's questionnaire response was graphically presented to the clinicians, who accessed all the yellow and red responses through the Electronic Health Record system

	together with other relevant data from the record (laboratory tests, medication, etc.) Duration 18 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. risk of bias: Very low Comments: 80% had fixed monitoring every 12 months, and not at 3,6 or 9 months. So, it was effectively annual monitoring. (n=346) Intervention 2: Ad hoc follow up monitoring - Ad hoc monitoring. For patients randomized to open access telePRO, patient contact with the outpatient clinic was based on the patient's preferences. Patients were asked to contact the outpatient clinic by themselves when they felt it necessary. Thus, at any time during the follow-up period, these patients could indicate a need for contact with the outpatient clinic by filling in the disease-specific questionnaire. For this purpose, an open access website 'My Epilepsy' was developed. The website contains four core elements to allow patients to: 1) answer a questionnaire when they needed to get in contact with the clinic, 2) view their previously questionnaire responses, 3) view information about the questionnaire, and 4) view contact information (e.g., telephone number) to the outpatient clinic. Patients had access to the open access website via a secure login to the Danish ehealth Portal Sundhed.dk". In addition, the patients could also phone the outpatient clinic if needed. All questionnaire responses in the open access arm turned red (definite need of attention) on the alert list to the clinicians, since these patients were instructed to only fill in the questionnaire if they needed to talk to a clinician. The clinician checked the alert list daily and assessed the red open access responses as quickly as possible in the same web-system as in standard telePRO [8, 22]. The patients were contacted by telephone, and a face-to-face appointment was scheduled if necessary. If the patient did not fill in a questionnaire to the outpatient clinic within a priori defined timespan, the web system automatically sent a reminder to the patients with instructions to fill in the questionnaire. For example, a reminder was sent after 12 months if the patient prior to randomization was originally referred to a 6-month fixed questionnaire interval in standard telePRO. The clinicians also received information on the alert list about patients who did not respond to these reminders, and they were subsequently contacted by a clinician. Duration 18 months. Concurrent medication/care: None. Indirectness: No indirectness Further details: 1. risk of bias: Very low
Funding	Academic or government funding (Aarhus University, Central Denmark Regions Health Research Foundation, and TrygFonden. TrygFonden appears to be a computer security company, so there may be industrial, as well as governmental/academic, interests. Paper states no conflicts of interest relating to study funding.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANNUALLY versus AD HOC MONITORING

Protocol outcome 1: Quality of life at 1 year or more
- Actual outcome: Well-being WHO-5 at 18 months; MD; 3.21 (95%CI 0.05 to 6.38) 0 worst 0-100 Top=High is good outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: 68 vs 68.9 for WHO-5; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Mortality at 1 yr. or more

- Actual outcome: mortality at 18 months; Group 1: 4/247, Group 2: 2/345
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: NA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Seizure frequency at 1 year or more
- Actual outcome: Number of seizures in previous 12 months at 18 months; MD; 0.72 (95%CI -1.75 to 3.2);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: 28% vs 28% for 1 or more seizures; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: health care resource use at Define
- Actual outcome: Outpatient visits at 18 months; Group 1: mean 0.42 visits (SD 0.86); n=243, Group 2: mean 0.45 visits (SD 0.95); n=343
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: NA; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Telephone consultations at 18 months; Group 1: mean 1.3 number of calls (SD 2.46); n=243, Group 2: mean 0.99 number of calls (SD 1.88); n=343
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: NA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Hospitalisation - unplanned at 1 year or more
- Actual outcome: Hospitalisations at 18 months; Group 1: mean 0.09 number of admissions (SD 0.49); n=243, Group 2: mean 0.05 number of admissions (SD 0.29); n=343
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: NA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Attendance at ED at 1 year or more
- Actual outcome: Emergency room visits at 18 months; Group 1: mean 0.19 ED visits (SD 0.72); n=243, Group 2: mean 0.07 ED visits (SD 0.38); n=343
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: NA; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Social functioning at Define
- Actual outcome: Social support for health (HLQ 4) at 18 months; MD; 0.08 (95%CI -0.02 to 0.17);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: 68 vs 68.9 for WHO-5; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 8: Cognitive outcomes at Define
- Actual outcome: Understanding health information well enough to know what to do (HLQ 9) at 18 months; MD; -0.009 (95%CI -0.15 to 0.13);
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: 68 vs 68.9 for WHO-5; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Psychological outcomes at Define - Actual outcome: Self-efficacy (GSE) at 18 months; MD; 0.22 (95%CI -0.78 to 1.22); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 68 vs 68.9 for WHO-5; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Seizure recurrence at 1 year or more; Seizure freedom at 1 year or more); Drug adherence at 1 year or more; Length of stay at Define; Neurodevelopmental outcomes at Define; educational outcome at Define; placement breakup (change in care location) at Define; contact with mental health services at Define

Appendix E Forest plots

E.1 Annual versus ad-hoc monitoring

Figure 2: Mortality

Study or Subgroup	Annual Events	Annual Total	Ad-hoc Events	Ad-hoc Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Schougaard, 2019	4	247	2	345	100.0%	2.79 [0.52, 15.13]
Total (95% CI)		**247**		**345**	**100.0%**	**2.79 [0.52, 15.13]**
Total events	4		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.19 (P = 0.23)

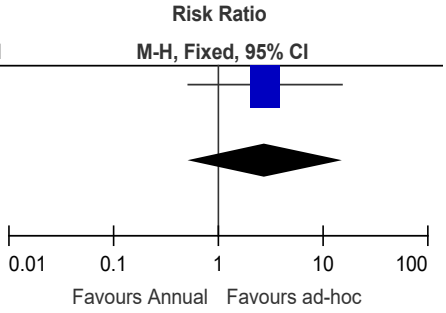


Figure 3: Quality of life: WHO-5

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Schougaard, 2019	3.21	1.6123	100.0%	3.21 [0.05, 6.37]
Total (95% CI)			**100.0%**	**3.21 [0.05, 6.37]**

Heterogeneity: Not applicable

Test for overall effect: Z = 1.99 (P = 0.05)

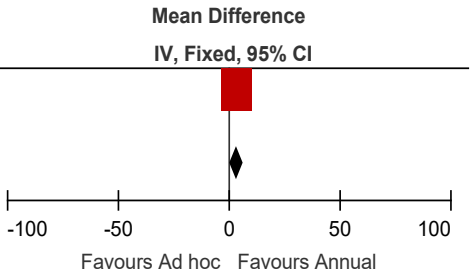


Figure 4: Seizure frequency

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Schougaard, 2019	0.72	1.2602	100.0%	0.72 [-1.75, 3.19]
Total (95% CI)			**100.0%**	**0.72 [-1.75, 3.19]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.57 (P = 0.57)

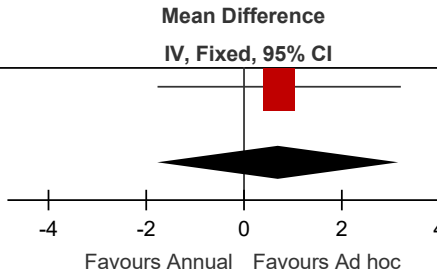


Figure 5: Resource use – outpatient visits

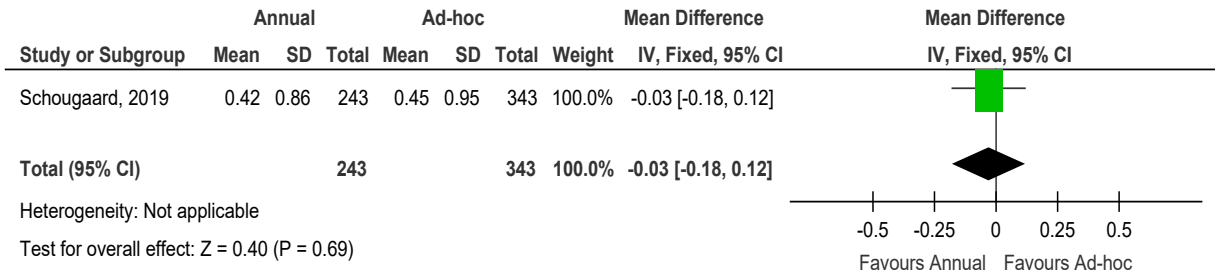


Figure 6: Resource use – telephone consultations

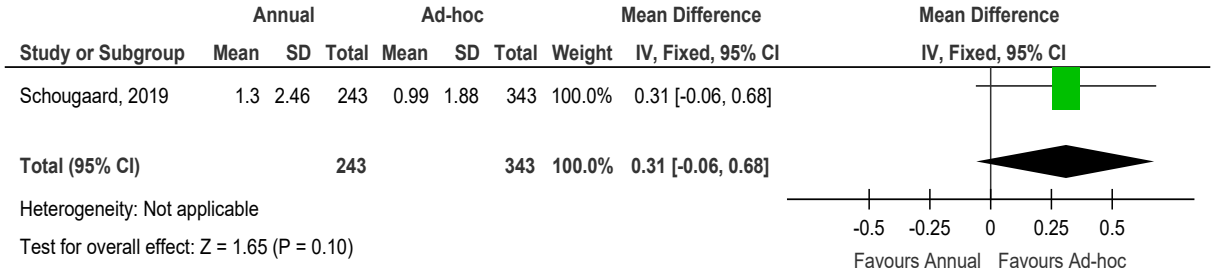


Figure 7: Hospitalisation

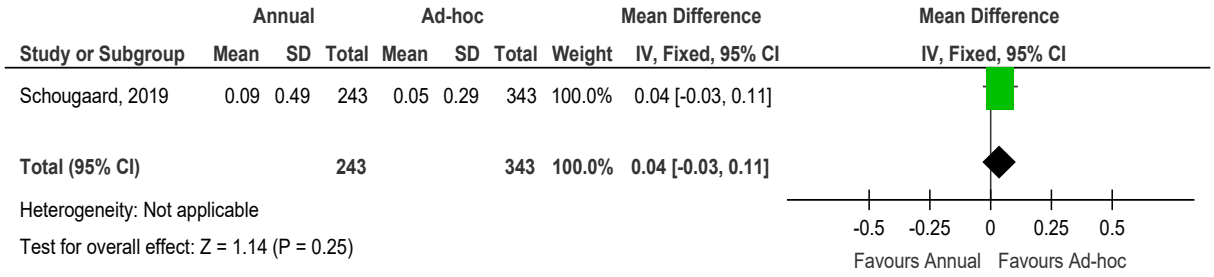


Figure 8: ED attendance

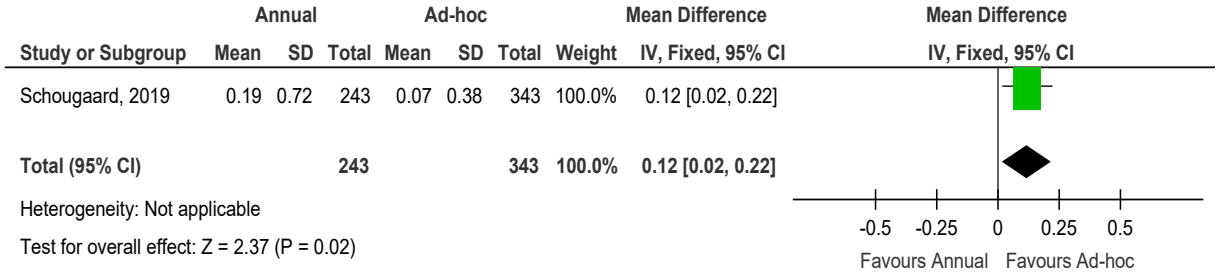


Figure 9: Social functioning HLQ-4

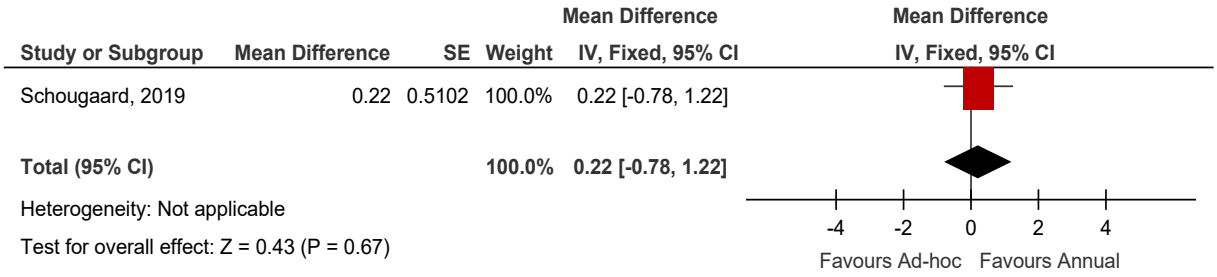


Figure 10: Cognitive functioning HLQ-9

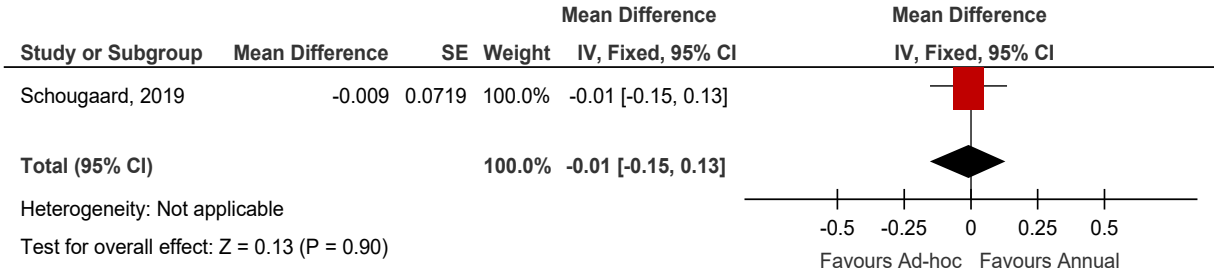
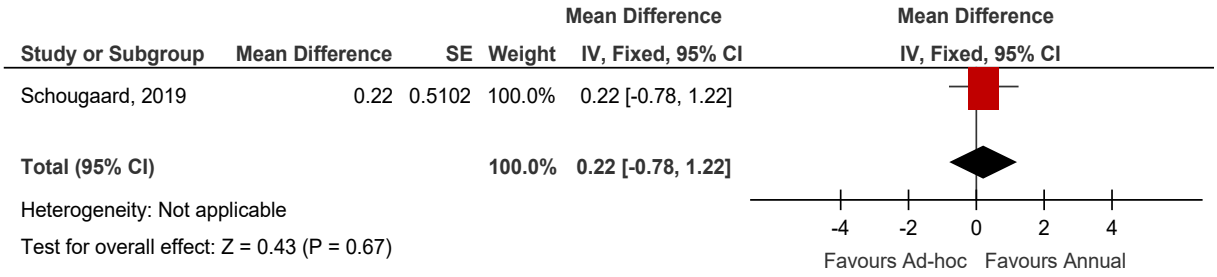


Figure 11: Psychological functioning GSE



E.2 Therapeutic drug monitoring (TDM) versus clinical monitoring

Figure 12: Mortality

Study or Subgroup	TDM Events	TDM Total	Clinical Events	Clinical Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aicua-Rapun, 2020	1	76	0	75	100.0%	7.29 [0.14, 367.55]
Total (95% CI)		**76**		**75**	**100.0%**	**7.29 [0.14, 367.55]**
Total events	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

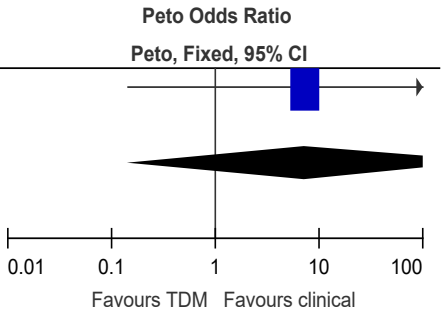


Figure 13: Seizure recurrence (RR)

Study or Subgroup	TDM Events	TDM Total	Clinical Events	Clinical Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aicua-Rapun, 2020	24	76	19	75	36.0%	1.25 [0.75, 2.08]
Jannuzzi, 2000	36	58	34	58	64.0%	1.06 [0.79, 1.42]
Total (95% CI)		**134**		**133**	**100.0%**	**1.13 [0.86, 1.47]**
Total events	60		53			

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%

Test for overall effect: Z = 0.88 (P = 0.38)

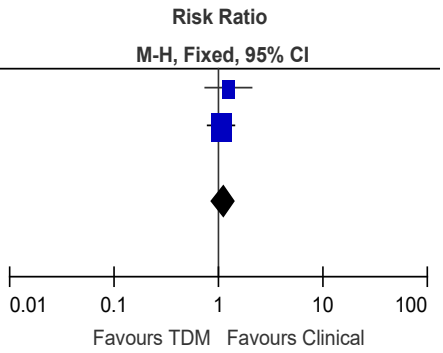


Figure 14: Seizure recurrence (HR)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Jannuzzi, 2000	0.0488	0.3028	100.0%	1.05 [0.58, 1.90]
Total (95% CI)			**100.0%**	**1.05 [0.58, 1.90]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.16 (P = 0.87)

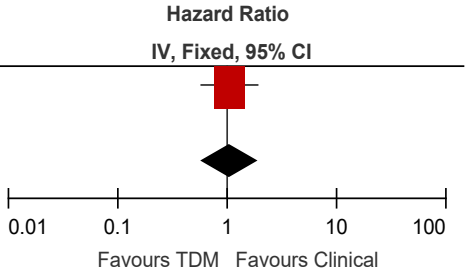
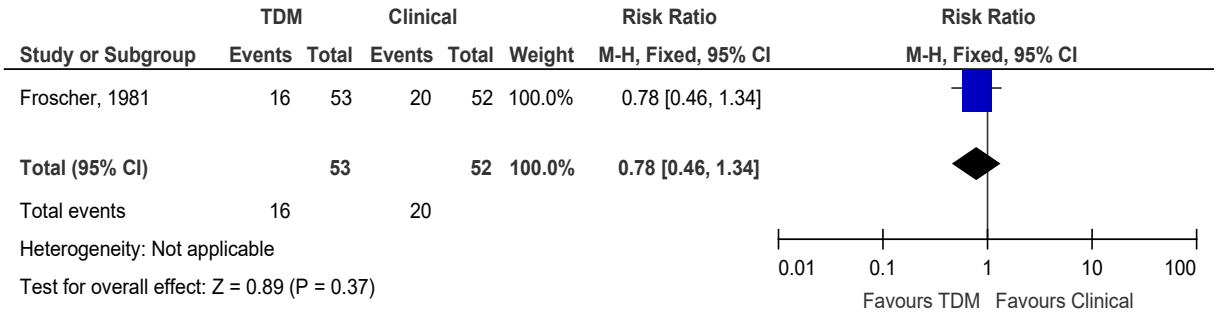


Figure 15: Seizure frequency – unchanged or worse



Appendix F GRADE tables

Table 7: Clinical evidence profile: Annual versus ad-hoc monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Annual monitoring	Ad-hoc monitoring	Relative (95% CI)	Absolute		
Mortality (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/247 (1.6%)	0.6%	RR 2.79 (0.52 to 15.13)	11 more per 1000 (from 3 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL
Quality of life – WHO 5 (follow up mean 18 months; Scale from 0 to 100; Better indicated by higher values)												
1	randomised trials	Very serious[3]	no serious inconsistency	no serious indirectness	No serious imprecision[4]	none	150	202	MD 3.21 (0.05 to 6.38)	MD 3.21 higher (0.05 higher to 6.38 higher)	⊕⊕OO LOW	CRITICAL
Seizure frequency												
1	randomised trials	Very serious[5]	no serious inconsistency	no serious indirectness	No serious imprecision[6]	none	150	202	MD 0.72 (-1.75 to 3.20)	MD 0.72 higher (1.75 lower to 3.20 higher)	⊕⊕OO LOW	CRITICAL
Resource use - outpatient visits (follow-up mean 18 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision[7]	none	243	343	-	MD 0.03 lower (0.18 lower to 0.12 higher)	⊕⊕⊕O MODERATE	CRITICAL
Resource use - telephone consultations (follow up mean 18 months; Better indicated by lower values)												

1	no methodology chosen	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision[8]	none	243	343	-	MD 0.31 higher (0.06 lower to 0.68 higher)	⊕⊕⊕O MODERATE	CRITICAL
Hospitalisation (follow up mean 18 months; Better indicated by lower values)												
1	no methodology chosen	serious[1]	no serious inconsistency	no serious indirectness	No serious imprecision[9]	none	243	343	-	MD 0.04 higher (0.03 lower to 0.11 higher)	⊕⊕⊕O MODERATE	CRITICAL
ED attendance (follow up mean 18 months; Better indicated by lower values)												
1	no methodology chosen	serious[1]	no serious inconsistency	no serious indirectness	Serious imprecision[10]	none	243	343	-	MD 0.12 higher (0.02 to 0.22 higher)	⊕⊕OO LOW	CRITICAL
Social functioning: HLQ-4 (follow up mean 18 months; Scale from 1 to 4; Better indicated by higher values)												
1	no methodology chosen	Very serious[3]	no serious inconsistency	no serious indirectness	No serious imprecision[11]	none	150	202	-	MD 0.08 higher (0.02 lower to 0.17 higher)	⊕⊕OO LOW	CRITICAL
Cognitive functioning: HLQ-9 (follow up mean 18 months; Scale from 1 to 5; Better indicated by higher values)												
1	no methodology chosen	Very serious[3]	no serious inconsistency	no serious indirectness	No serious imprecision[12]	none	150	202	-	MD 0.009 lower (0.15 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
Psychological functioning: GSE (follow up mean 18 months; Scale from 10 to 40; Better indicated by higher values)												
1	no methodology chosen	Very serious[3]	no serious inconsistency	no serious indirectness	No serious imprecision[13]	none	150	202	-	MD 0.22 higher (0.78 lower to 1.22 higher)	⊕⊕OO LOW	CRITICAL

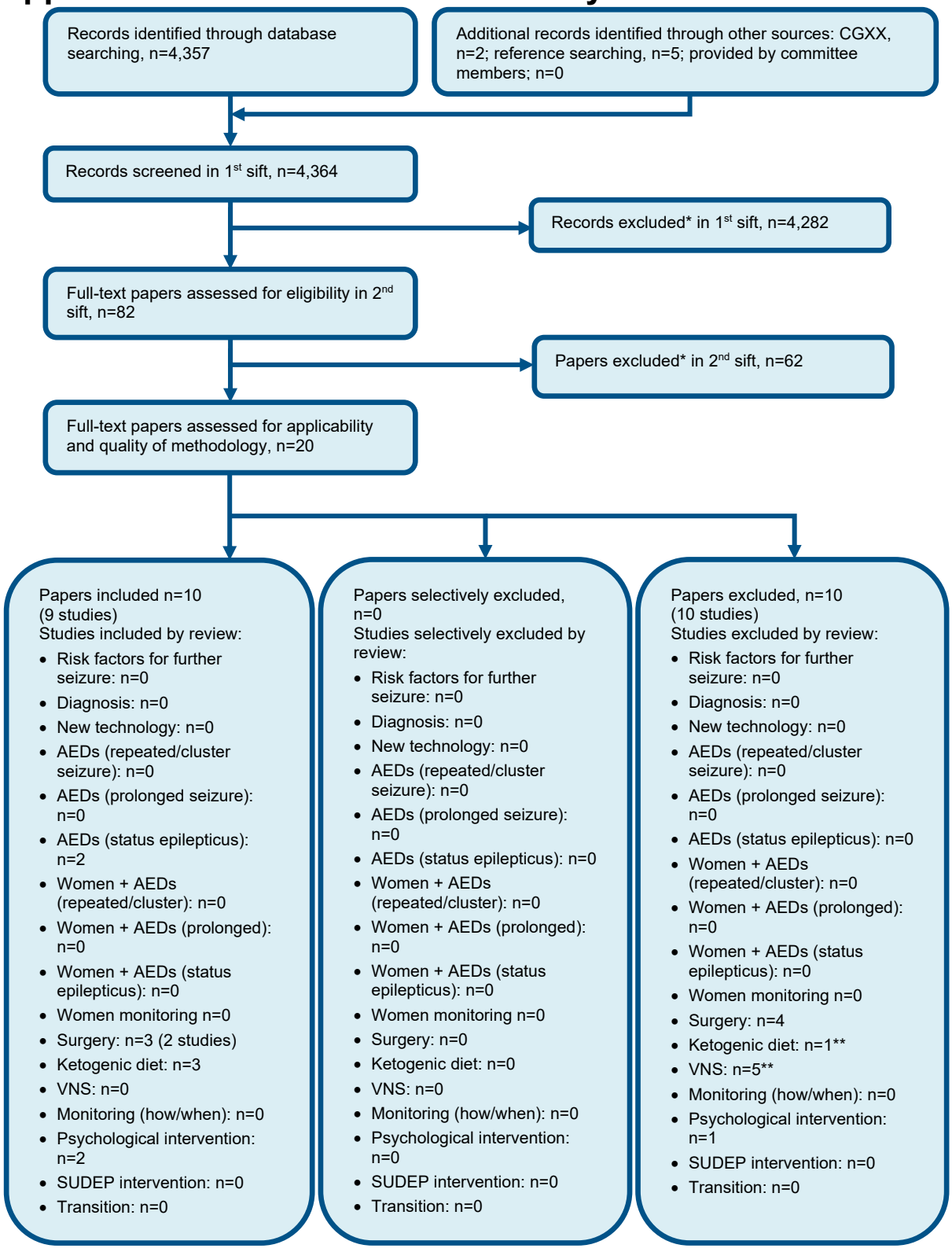
[1] Selection bias
[2] Serious if the confidence intervals crossed one MID and very serious if the confidence intervals crossed both default MIDs (0.80 and 1.25)
[3] selection bias, performance bias and attrition bias
[4] The MID was 0.5 x the sd in control group = 9.22. The confidence intervals did not cross -9.22 or +9.22 so imprecision was deemed non-serious
[5] Selection and attrition bias
[6] The MID was 0.5 x the sd in control group = 5.94. The confidence intervals did not cross -5.94 or +5.94 so imprecision was deemed non-serious
[7] The MID was 0.5 x the sd in control group = 0.475. The confidence intervals did not cross -0.475 or +0.475 so imprecision was deemed non-serious
[8] The MID was 0.5 x the sd in control group = 0.94. The confidence intervals did not cross -0.940 or +0.940 so imprecision was deemed non-serious
[9] The MID was 0.5 x the sd in control group = 0.4145. The confidence intervals did not cross -0.145 or +0.145 so imprecision was deemed non-serious
[10] The MID was 0.5 x the sd in control group = 0.419. The upper confidence interval crossed the upper MID of +0.419, so imprecision was deemed serious
[11] The MID was 0.5 x the sd in control group = 0.30. The upper confidence interval did not cross -0.30 or +0.30 so imprecision was deemed non-serious
[12] The MID was 0.5 x the sd in control group = 0.385. The upper confidence interval did not cross -0.385 or +0.385 so imprecision was deemed non-serious
[13] The MID was 0.5 x the sd in control group = 2.84. The upper confidence interval did not cross -2.84 or +2.84 so imprecision was deemed non-serious

Table 8: Clinical evidence profile: therapeutic drug monitoring (TDM) versus clinical monitoring

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TDM	Clinical monitoring	Relative (95% CI)	Absolute		
Mortality (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/76 (1.3%)	0%	OR 7.29 (0.14 to 367.55)	-	⊕OOO VERY LOW	CRITICAL
seizure recurrence RR (follow-up 1-2 years)												
2	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	60/134 (44.8%)	42%	RR 1.13 (0.86 to 1.47)	55 more per 1000 (from 59 fewer to 197 more)	⊕OOO VERY LOW	CRITICAL
seizure recurrence HR (follow-up 2 years)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 1.05 (0.58 to 1.90)	-	⊕OOO VERY LOW	CRITICAL
Seizure frequency unchanged or worse (follow-up mean 2 years)												
1	randomised trials	very serious5	no serious inconsistency	no serious indirectness	very serious[2]	none	16/53 (30.2%)	38.5%	RR 0.78 (0.46 to 1.34)	85 fewer per 1000 (from 208 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL

[1] Selection bias and outcome reporting bias
[2] Serious imprecision if the confidence intervals crossed one MID and very serious imprecision if the confidence intervals crossed both MIDs
[3] Selection bias and attrition bias for Jannuzzi and selection bias and outcome reporting bias for Aicua-Rapun
[4] selection and attrition bias
[5] Very serious selection bias

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 health economic modelling was undertaken for this review.

Appendix J Excluded studies

J.1 Clinical studies

Table 9: Studies excluded from the clinical review

Study	Exclusion reason
Anderson 2010[2]	SR - references checked
Arfman 2020[3]	SR - references checked
Bahrani 2017[4]	less than 1 year follow up
Bergmann 2018[5]	Inpatient monitoring only at baseline and discharge
Block 2016[6]	SR - references checked
Borusiak 2016[7]	Sleep monitoring, not monitoring of response to treatment; follow up < 1year
Bottacchi 1996[8]	Not in English
Busch 2015[9]	Cohort study
Camfield 2006[10]	SR - references checked
Chong 2002[11]	SR - references checked
Contin 2002[12]	Non-randomised. On drug interaction effects on plasma drug concentrations
Demir 2020[13]	Wrong interventions; cross-sectional
Faught 2020[14]	Commentary on Aicua-Rapun, 2020
Gatti 1996[16]	Conference abstract
Gram 1977[17]	Wrong interventions - drug comparison study
Helde 2005[18]	Contains multiple interventions versus an inactive control
Hu 2020[19]	Examines effects of patient education
Jarvie 2018[21]	SR - references checked
Johannessen 2003[22]	SR - refs checked
Johannessen 2008[23]	SR - refs checked
Kamali 1994[24]	No protocol outcomes
Khachian 2018[25]	educational intervention

Knott 1982[26]	non-randomised study
Modi 2016[27]	No monitoring intervention
Morrow 1989[28]	Citation only found - no paper available
Ntr 2011[61]	Citation only found - no paper available
Pakpour 2015[30]	incorrect intervention
Patsalos 2008[31]	SR - refs checked
Patsalos 2018[32]	SR - references checked
Pennington 2019[33]	Incorrect intervention; multiple interventions
Peterson 1984[34]	Incorrect intervention; multiple interventions
Pirie 2014[35]	SR - references checked
Remick 2020[36]	SR - references checked
Remington 2013[37]	Review
Ridsdale 1997[39]	no usable outcomes
Ridsdale 2000[38]	Incorrect intervention
Ring 2018[40]	non RCT
Rossetti 2018[41]	non RCT
Sahlroot 1993[42]	conference abstract
Sarkissian 1999[43]	non RCT
Schougaard 2017[44]	non RCT ; protocol only
Schultz 2020[46]	SR - references checked
Si 2020[47]	<1 year
Sivasankari 2012[48]	Not available
Striano 2008[49]	review
Tan 2017[50]	SR - references checked
Thangaratinam s 2018[51]	<1 yr. follow up
Tomson 2007[52]	SR - references checked
Toth 2019[53]	SR - references checked

Touw 2005[54]	SR - references checked
Uijl 2009[55]	<1 year follow up
Venz 1994[56]	Not in English
Vieluf 2019[57]	SR - references checked
Warren 1999[58]	conference abstract
Willems 2019[59]	non RCT
Woo 1988[60]	Study comparing stable dose versus increased dose: monitoring was common between both groups
Zheng 2019[62]	Incorrect intervention; multiple 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 10: Studies excluded from the health economic review

Reference	Reason for exclusion
None	