



National Institute for Health and Clinical Excellence

Epilepsy
Guideline Consultation Comments Table
12.01.11 – 26.01.11

Type	Stakeholder	Order No	Document	Page No	Line No	Comments	Developer's Response
SH	British Nuclear Medicine Society	4.00		general		Please insert each new comment in a new row. No comments	Please respond to each comment Thank you for your comment.
SH	Cyberonics Inc.	13.00	Full	422	15	  <p>NICE VNS Therapy P 01-25-11 NATL INST pediatric_Studies.pdf FOR HEAL AND CLIN</p> <p>Since the original guidelines were introduced there have been a number of studies published or presented demonstrating the health economic benefits of VNS in refractory epilepsy including the following;</p> <p><u>Cost Effectiveness - Healthcare Utilization Reduced With VNS Therapy</u></p> <p>Although no formal cost-effectiveness study has been conducted for VNS Therapy, many studies describing savings and reduced utilization have been published. Relevant excerpts from these papers are provided below.</p> <ul style="list-style-type: none"> ○ This study was conducted in Belgium in the late 1990s and American dollars were reported. Reductions in costs were statistically significant. <p>Boon p Vonck K, Vandekerckhove T et al. Vagus Nerve Stimulation for Medically Refractory Epilepsy; Efficacy and Cost-Benefit Analysis. Acta Neurochir (Wie) 1999;141:447-453</p> <p>Before the implantation, the mean yearly epilepsy-related direct medical costs per patient were estimated to be 8830 US\$ (n=13); range: 1879-31129 US\$; sd=7667); the average number of hospital admission days per year was 21 (range:4-100; sd=25.7). In the 12 months after implantation, ERDMC had decreased to 4215 US\$ (range: 615-11794 US\$: sd=3558 (Wilcoxon signed rank test n=13; p=0.018) and the average number of admission days to 8 (range: 0-35) (Wilcoxon signed rank test n=13: p=0.023)</p> <ul style="list-style-type: none"> ○ This study was also conducted in Belgium during the late 1990s and used 	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.

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						<p>Please insert each new comment in a new row.</p> <p>American dollars; n=20, average follow-up was 36 months. Again, savings were statistically significant.</p> <p>Boon P, Vonck K, D'Have et al. Cost-benefit of vagus nerve stimulation for refractory epilepsy. Acta Neurol Belg 1999;99:275-280.</p> <p>The mean yearly epilepsy-related direct medical costs per patient dropped from 6,682 US\$ (range: 829-21,888 US\$) to 3,635 US\$ (range: 684-12,486 US\$) (p=0.0046). The mean number of hospital admission days was reduced from 16 days/year (range: 0-60) to 4 days/year (range: 0-30) (p=0.0029).</p> <ul style="list-style-type: none"> ○ This study was conducted in Canada <p>Upton A. Vagal stimulation for intractable seizures. Adv Exp Med Biol 2002;497:233-239.</p> <p>The cost of stimulators compares with the cost of the chronic use of 3 anti-convulsant drugs over the replacement life of the stimulator. However, most studies have involved the use of vagal pacemakers as a supplement to the use of medications.</p> <ul style="list-style-type: none"> ○ This study compares utilization during the year before VNS implantation with utilization during the 4 years afterward for 138 patients retrospectively reviewed in the Kaiser Permanente HMO of Northern California (US). <p>Bernstein AL, Barkan H, Hess T. Vagus nerve stimulation therapy for pharmaco-resistant epilepsy. Effect on health care utilization. Epilepsy & Behaviour 2006:</p> <p>Compared with utilization during the year before implantation, results during the fourth quarter of Year 4 revealed impressive decreases in utilization of all four aspects measured: a 91% decrease in outpatient visits, a 99% decrease in emergency department visits, a 67% decrease in hospital lengths of stay, and a 70% decrease in number of hospital admissions.</p> <p>These decreases in healthcare utilization applied to the entire group, irrespective of changes in seizure frequency.</p> <ul style="list-style-type: none"> ○ This study was conducted in Sweden during the late 1990s and early 2000s and uses American dollars. It tracked 43 patients, compared costs from 18 months before implantation with the 18 months afterward, and showed considerable savings for all patients. <p>Ben-Menachem E, Hellstrom K, Verstrappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology 2002; 59 (Suppl 4):S44-S47.</p>	<p>Please respond to each comment</p>

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						<p>For all patients, intensive care unit (ICU) costs were reduced from 46,875 US\$ to 0 US\$, ER visits from 13,000 US\$ to 9,000 US\$, and ward stays from 151,125 US\$ to 21,375 US\$. Total hospital costs for the 43 patients studied before VNS Therapy were 211,000 US\$ and after 18 months of treatment were reduced to 30375 US\$, an average annual cost savings of approximately 3,000 US\$ per patient. The costs savings applied to all patients, irrespective of whether they responded to VNS Therapy. VNS Therapy resulted in annual reductions of approximately 3,000 US\$ in unplanned hospital costs per study patient. Such direct savings sustained over the battery life of the VNS Therapy System can equal or exceed the purchase price of the device.</p> <ul style="list-style-type: none"> ○ This paper is from Australia and describes a case series of 26 children who received VNS Therapy for a minimum of 18 months. In the extract, the abbreviation, SE, stands for status epilepticus. The comments regarding cost apply to a single patient, but they drive home the very high cost inherent with refractory epilepsy. <p>Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus Nerve Stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. Epilepsia 2008 epub.</p> <p>Hospitalization for treatment of SE decreased significantly in two of the four patients with recurrent SE decreased significantly in two of the four patients with recurrent SE and ceased altogether in two. One patient who had 55 epilepsy-related admissions over the 16 months before VNS implantation had only two epilepsy-related admissions in the 21 months following VNS implantation. The resultant savings to the hospital in <2 years were greater than the costs of five VNS devices and their implantation procedures.</p> <ul style="list-style-type: none"> ○ Many patients with uncontrolled seizures experience drop seizures that lead to injuries and result in healthcare utilization of ED visits and hospitalizations. VNS Therapy has been shown to decrease the number of drop seizures experienced by patients with epilepsy.¹² ○ Cost Utility Analysis of VNS for Adults with medical refractory epilepsy Seizure-R Forbes 2003;12:249-256 ○ Cost Utility Analysis of VNS for Adults with medical refractory epilepsy-An update: R Forbes Seizure Eur J Epic (2007) <p>In the original Health Technology Assessment by Forbes (2002) the cost utility of VNS therapy was calculated as £28,849 per quality-adjusted life year(QALY) Following technical improvements with increased battery life expectancy along with follow up data that repeatedly demonstrates reductions in seizure frequency between 40-55%, a re-appraisal was performed by Forbes in 2007 and the revised cost utility for VNS is significantly less at £4,423 per QALY gained.</p>	

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						<ul style="list-style-type: none"> ○ Characteristics and Clinical and Economic Outcomes in MEDICAID patients receiving VNS therapy for treatment of Refractory Epilepsy: Sandra L Helmers et al; Poster presented at AES 2010 <p>A retrospective cohort study design will be applied, using data from 5 Medicaid State claims databases (01/97-06/09), including Florida, Iowa, Kansas, Missouri, and New Jersey. Patients receiving VNS, who had ≥1 neurologist visit with a diagnosis of epilepsy (ICD-9 345.xx, 780.3, or 780.39), ≥1 medical procedure claims for VNS implantation, ≥1 AED dispensing, and ≥6 months of pre- and post-VNS health plan continuous enrollment are included. The pre-index period spanned from the latest of the start of enrollment, first diagnosis for epilepsy, or a prescription filled for an AED until the first VNS implantation date (index date), while the post-index period spans from the index date until the earliest of the VNS removal, death, end of enrollment, or data end date. Patients' observation period was divided into 90-day intervals (i.e. quarter) and outcomes were repeatedly measured at each quarter. Morbidity will be measured by frequency of hospitalizations, hospital length of stay, emergency room visits, outpatient visits, neurologist visits, fractures, motor vehicle accident-related injuries, head injuries, and status epilepticus events. Univariate and multivariate Poisson regression models will be used to estimate the incidence rate ratios of the morbidity outcomes between the pre- and post-index period. Univariate and multivariate regression models will also be used to estimate the healthcare cost difference (quarterly) between the pre- and post- index period.</p> <p>Based on this large cohort of over 1,600 patients, we found that implantation of the VNS in patients with refractory epilepsy was associated with:</p> <ul style="list-style-type: none"> Lower use of healthcare resources and lower occurrence of epilepsy-related co morbidities compared to the period before VNS implantation Significant net total healthcare cost savings beginning about 1.5 years post implantation <p>VNS for refractory epilepsy may both improve clinical outcomes for patients and result into significant savings for public payers Further research on privately insured patients to replicate potential cost savings for managed care organizations, and to further evaluate the impact of adjunctive AED use on patients' outcomes are warranted</p>	

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SH	Cyberonics Inc.	13.01		422	13	<p>Please insert each new comment in a new row.</p> <p>Primary Evidence – Although there have been no published RCT's since 2000 there are a number of papers that have demonstrated the efficacy of VNS for both seizure reduction and quality of life improvements in both adults and paediatrics including:</p> <p>Renfroe JB, Wheless JW. Earlier use of adjunctive vagus nerve stimulation therapy for refractory epilepsy. <i>Neurology</i> 2002;59(suppl 4):S26-S30.</p> <p>DeHerdt V, Boon P, Ceulemans B, Hauman H, Lagae L, Legros B, Sadzot B, Van Bogaert P, et al. Vagus nerve stimulation for refractory epilepsy: A Belgian multicenter study. <i>Eur J Paediatric Neurology</i>, 2007;11:261-269.</p> <p>Vonck K, Thadani V, Gilbert K et al. Vagus nerve stimulation for refractory epilepsy: A transatlantic experience. <i>J Clin Neurophysiol.</i> 2004; 21(4): 283-289.</p> <p>Labar D, Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. <i>Seizure.</i> 2004; 63:1124-1126.</p> <p>Balabanov A, Rossi MA: Epilepsy surgery and vagal nerve stimulation: what all Neurologists should know. <i>Semin Neurol</i> 28:355-363, 2008</p> <p>Rossignol E, Lortie A, Thomas T, et al: Vagus nerve stimulation in pediatric epileptic syndromes. <i>Seizure</i>, 2008</p> <p>Nei M, O'Connor M, Liporace J, et al: Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. <i>Epilepsia</i> 47:115-122, 2006</p> <p>De Herdt V, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. <i>Eur J Paediatr Neurol</i>_2007 Sep;11(5):261-9.</p> <p>Kostov H, et al. Is vagus nerve stimulation a treatment option for patients with drug resistant idiopathic generalized epilepsy? <i>Acta Neurol Scand Suppl</i>_2007;187:55-8.</p> <p>¹You SJ, et al. Comparison of corpus callostomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. <i>Brain Dev</i> 2008 Mar; 30(3):195-9</p> <p>Rossignol E, et al. Vagus nerve stimulation in pediatric epileptic syndromes. <i>Seizure</i> 2009 Jan; 18(1):34-37.</p>	<p>Please respond to each comment</p> <p>Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment.</p> <p>The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management.</p> <p>NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.</p>

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						<p>Please insert each new comment in a new row.</p> <p>Holmes MD et al. Effect of vagus nerve stimulation on adults with pharmaco-resistant generalized epilepsy syndromes. <i>Seizure</i> 2004; 13:340-345.</p> <p>Faught E, et al. Nonadherence to antiepileptic drugs and increased drugs and increased mortality: Findings from the RANSOM study. <i>Neurology</i> 2008; 71(20):1572-1578.</p> <p>Faught E, Weiner J, Guerin A. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: Findings from the RANSOM study. <i>Epilepsia</i>. 2009;50(3):501-509.</p>	Please respond to each comment
SH	Epilepsy Action	15.00	General			<p>Firstly, can we thank the Guideline Development Group (GDG) for taking on-board, and acting upon, the majority of comments submitted by Epilepsy Action in the first guideline consultation.</p> <p>We welcome this second opportunity to comment, but would have appreciated longer than the two week window to consult and formulate a response. Therefore this response is based upon the information we have received and processed in this time, and may not be a comprehensive review of the guideline.</p>	Thank you for your comment.
SH	Epilepsy Action	15.01	General			<p>In NICE's 2009 consultation into the scope of the review of the guidelines for epilepsy, Epilepsy Action raised serious concerns about the limiting nature of the review's proposed focus. We believe that there have been significant advances and changes in the treatment of epilepsy since the first guideline was being constructed in 2003, significant enough to merit a full guideline review. The proposed focus was carried through to the review itself, and we know has now lead to disagreements in the epilepsy community about the merit of the guideline update, and the reputation of the guideline itself.</p> <p>We hope that the next time NICE reviews these guidelines, it does so by conducting a full review and that in future, serious concerns raised at early stages are fairly investigated.</p>	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.

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SH	Epilepsy Action	15.02	Full	22	37	<p>Please insert each new comment in a new row.</p> <p>In the previous consultation, Epilepsy Action requested that the Guideline include the latest incidence figures for epilepsy based upon the latest population figures. Thank you for agreeing to update these figures. While the figures in the Full Guideline have been updated accordingly, the figures used in the NICE Guideline have not, and remain the 2004 figures. Could the GDG please update the figures in the NICE Guideline to match those now used in the Full Guideline, for accuracy and consistency.</p>	<p>Please respond to each comment</p> <p>Thank you for highlighting this; we have amended accordingly. Further we have updated the figures in the light that QOF figures are likely to be an overestimate.</p>
SH	Epilepsy Action	15.03	Full	22	38	<p>Thank you for updating the incidence figures in the Full Guideline, in-line with the latest available data. There is however one typographical error in this information. The Quality and Outcomes Framework (QOF) includes a register of all those receiving treatment by anti-epileptic drugs (AEDs) who are aged 18 and over (indicator EPILEPSY6), not aged 15 and over as is stated. The QOF does not record the number of under-18s who receive treatment by AED.</p>	<p>Thank you for your comment. This has been corrected.</p>
SH	Epilepsy Action	15.04	Full	57		<p>In the first consultation of this guideline, we put forward a suggestion for an additional recommendation based on bone health issues (stakeholder comments response, page 97, 30.0.5). We cannot agree with the GDG that recommendation 1.9.1.1 is sufficient to warn of the risks posed to bone density by continuing treatment on certain anti-epileptic drugs.</p> <p>Bone health issues are a concern for many on long term AED treatment, namely enzyme-inducing AEDs carbamazepine, phenytoin, primidone, phenobarbital and the non-enzyme inducing sodium valproate (MHRA Drug Safety Update, Volume 2 Issue 9, April 2009).</p> <p>The MHRA drug safety update indicates to us that the associated risks of long term AED treatment, and ways to minimise these risks, are not being adequately discussed with patients.</p> <p>We believe this clinical guidance should include indicators for appropriateness to prescribe vitamins or order further investigations (such as a DEXA scan). It should also include a warning of the cardiotoxic effects of AEDs, the potential for suicidal ideation and the effects of prolonged AED use on bone density (including potential impact on bones post-menopause).</p>	<p>Thank you for your comment. We have now added an additional recommendation for further clarity. Please see recommendation 1.9.17.1 in the NICE guideline. Please also refer to recommendation 1.19.17.10.</p>

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						<p>We believe there is a duty to ensure patients and doctors are aware of the long-term risks. We believe these risks, the available evidence, and the number of AEDs involved are sufficient to warrant a guideline recommendation discussing and reviewing side-effects.</p> <p>We do not understand why some side-effect profiles, such as specific issues for expectant mothers, can be mentioned within the guideline, yet bone health is not.</p> <p>We ask the GDG to look again at whether a recommendation along these lines is appropriate, given that this issue falls within the remit of the review and the review recommends many of the potentially risky AEDs.</p>	
SH	Epilepsy Action	15.05	Full	58	22	<p>In the August 2010 consultation, we asked for levetiracetam to be considered as a first line treatment for generalised epilepsies (Stakeholder comments response, p106, 30.1.7). The GDG rejected this request, on the grounds that there is no available evidence for levetiracetam as a monotherapy, and it is not currently licensed for this indication.</p> <p>While levetiracetam is appropriately listed for those seizure types where it is licensed. This is monotherapy and adjunctive treatment of partial seizures (with or without secondary generalisation), and as adjunctive treatment of myoclonic and primary generalised tonic clonic seizures (British National Formulary 60, September 2010, p285).</p> <p>However we know levetiracetam is also widely prescribed, off-licence, as a first-line treatment of generalised seizures in adults and children. This is in part because of its low probability for interactions and it's mechanism of action allowing easy addition to existing drug treatment.</p> <p>While it may be wise for the drug manufacturers to apply for a licence for this indication, this will not improve the drug's status now and could mean impractical advice is issued on best treatments until this guideline's next review.</p> <p>However, we believe a compromise on this issue can be reached and we again ask that levetiracetam be included as a possible first-line treatment for generalised seizures in adults and children, on the basis of lower-grade evidence and clinical opinion.</p> <p>A similar exception for non-licensed use has been created for the use of oxcarbazepine for generalised-tonic clonic seizures. While oxcarbazepine is not-</p>	<p>Thank you for your comment. The GDG felt unable to include Levetiracetam as first line treatment for IGE as there was no evidence based on the criteria used to support its inclusion. There is only such evidence for adjunctive therapy.</p>

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						<p>Please insert each new comment in a new row.</p> <p>licensed for this use, it is included in the guidelines, with the caveat that at the time of publication, licensing has not been granted. Similarly at various other points, clobazam, gabapentin, lamotrigine, zonisamide, eslicarbazepine acetate, pregabalin, topiramate and levetiracetam itself are recommended for certain seizures with warning that the drug is not licensed for this use.</p> <p>Epilepsy Action does not oppose any of these recommendations, and we believe a similar, satisfactory position can be agreed for the future use of levetiracetam for generalised seizures. We want the widest possible range of treatment options at the disposal of the epilepsy specialist, for the benefit of people with the condition.</p>	Please respond to each comment
SH	Epilepsy Action	15.06	Full	59	24	<p>With regards to the recommendations for the treatment of infantile spasms, we would like to see a repeat of the safety warning specific to vigabatrin, which is stated in clause 85 (page 58).</p> <p style="padding-left: 40px;">'Carefully consider the risk–benefit ratio when using vigabatrin because of the risk of an irreversible effect on visual fields.'</p> <p>We believe the same grounds exist for the inclusion of a warning in infantile spasms, as for the recommendation of possible adjunctive use for focal seizures. We see no reason why this safety warning should not also be included here.</p>	Thank you for your comment. We have now added the warning to recommendations 1.9.8.2 and 1.9.8.3.
SH	Epilepsy Action	15.07	Full	66	30	<p>We believe the warning that higher doses of sodium valproate bring greater risks than lower doses, should be extended to include the similar higher risks from polytherapy. We propose the wording,</p> <p style="padding-left: 40px;">“Specifically discuss the risk of continued use of sodium valproate to the unborn child, being aware that higher doses of sodium valproate (>800 mg/day) and polytherapy treatments are associated with a greater risk than with lower doses (< 800 mg/day)”.</p>	Thank you for your comment. We agree and have added your suggestion to the recommendation.

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SH	Epilepsy Action	15.08	Full	66	35	<p>Please insert each new comment in a new row.</p> <p>We request a further change regarding a new clause concerning treatments for women. Currently, the clause reads,</p> <p style="padding-left: 40px;">'Aim for seizure freedom before conception and during pregnancy (particularly for women and girls with generalized tonic-clonic seizures) but consider the risk of adverse effects of AEDs and use the lowest effective dose of each AED'</p> <p>We would like the direction 'avoiding polytherapy where possible' to follow. This is in-line with the Guideline's advice on treatment by a single AED where possible. (Clause 50, lines 35-39 on page 55). Monotherapy should be desired in all patients taking anti-epileptic drugs.</p>	<p>Please respond to each comment</p> <p>Thank you for your comment. We agree and have added your suggestion to the recommendation.</p>
SH	Epilepsy Action	15.09	Full	73 & 74		<p>We would like to remind the GDG that a page is missing from the Full Guideline, to accompany the care pathways on pages 73 and 74. This page includes 'Box A'.</p> <p>We know the GDG are aware of this error.</p>	<p>Thank you for your comment. This has now been revised.</p>
SH	Epilepsy Action	15.10	Full	519		<p>In the previous consultation, The Royal College of General Practitioners suggest that the use of 'tertiary epilepsy specialist should be avoided as it is not defined, with its meaning unclear (Stakeholder comments response, p170, 19.0.3). In response, the GDG state that the glossary has been updated accordingly. However upon examination, we do not believe the term 'tertiary epilepsy specialist' has been added to the glossary of the Full Guideline. We would welcome the addition of this definition to the next version of the Full Guideline, to fulfil the action from the first consultation.</p>	<p>Thank you for your comment. This has now been added to the glossary.</p>

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SH	ESNA	19.00	General			Please insert each new comment in a new row. NICE have responded and amended the guideline on the feedback from the first consultation which we welcome	Please respond to each comment Thank you for your comment.
SH	ESNA	19.01	Full	403		We still have some concerns concerning the advice that Keppra should be used as a 2 nd line AED when in practice it is increasingly used 1 st line	The GDG recognises the difficulty with this issue and the position of levetiracetam. It has been positioned within the restraints of the evidence available, Further, its position will become clearer once generic pricing is available.
SH	ESNA	19.02	Full	P9, 11		We are pleased to see you have included the need to adopt a counselling approach	Thank you for your comment.

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SH	ESNA	19.03	Full	P25		Please insert each new comment in a new row. We are not convinced about sodium valproate as 1st line for focal epilepsy above the use of keppra	Please respond to each comment Further re-analysis has been conducted to ascertain the validity of the recommendation for first line treatment in focal seizures.
SH	GlaxoSmithKline UK	9.00	Full	General comment	General comment	As a registered stakeholder GSK has no specific comments on Consultation 2 of the draft guideline and reiterate our comments from the first consultation process. GSK continues to support the proposed treatment pathway including the recognition of a refractory group of patients, the criteria set out to identify these patients and the appropriate specialist care required. GSK looks forward to the publication of this guideline and the value it will bring to both patients and the NHS.	Thank you for your comment.
SH	Medtronic Ltd	2.00	NICE	General		With acknowledgment to NICE's feedback that Surgical interventions were ' <i>outside of the scope of the update guideline, which only addressed the pharmacological management of the epilepsies</i> ' We would recommend that this is explicitly stated in the guideline title or introduction rather than the general partial update term, as the reader may draw the conclusion that all treatments both surgical and pharmacological have been reviewed and updated.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Medtronic Ltd	2.01	NICE	General		Accepting that the update was for the pharmacological management of epilepsy, to continue to include certain surgical interventions while failing to include surgical interventions that have entered standard practice since the original 2004 publication is inequitable (we refer the development group to the evidence provided at 1 st consultation stage). The decision therefore should be to equitably consider all the possible technologies if not, exclude specific reference to techniques in favour of a generic reference as suggested in point 3 below.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical

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							guideline to determine whether it needs to be updated.
SH	Medtronic Ltd	2.02	NICE	38	11	Within this section we suggest that reference be made to the fact that other interventions e.g. interventions (surgical) for the management of refractory epilepsy have not been reviewed as part of this update. Or statements to similar effect. Therefore further acknowledging the importance of Tertiary centre referral in the 'complex or refractory epilepsy patient' group.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	National Society for Epilepsy	5.00	full	58	4	We would suggest that sodium valproate is a counter-intuitive choice as first line treatment for focal seizures due to the risk to an unborn child of malformations (as per recommendation 81).	The GDG consider that the risk of malformation for pregnant women taking sodium valproate has been sufficiently highlighted. Further re-analysis has been conducted to ascertain the validity of the recommendation for first line treatment in focal seizures.
SH	National Society for Epilepsy	5.01	Full	58	8	If the cost of generic levetiracetam is now known, could this be simplified as a first-line treatment for focal seizures?	Thank you for your comment. The cost of generic levetiracetam in the UK is still unknown; therefore, the GDG has chosen this wording order to reflect current information and also give guidance to health professionals, commissioners and patients about the circumstances under which levetiracetam should be considered alongside other first-line treatments for focal seizures.
SH	National Society for Epilepsy	5.02	Full	67	26	We would suggest that, in clinical practice, additional methods of contraception (such as barrier methods) are not advised as necessary for women and girls using Depo Provera.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	National Society	5.03	Full	408	7	Although 'generic prescribing' was listed as not being reviewed (as it is "not a key	Thank you for your comment. The PPRS has

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	for Epilepsy					Please insert each new comment in a new row. clinical question") we would suggest that reference to the outcome of the Department of Health's consultation on 'The proposals to implement 'Generic Substitution' in primary care, further to the Pharmaceutical Price Regulation Scheme (PPRS) 2009' be made. One of the key levers against allowing generic substitution was cited by DH as being due to the representations from a number of other stakeholders, such as "...those representing people with epilepsy". Furthermore, anti-epileptic drugs were specifically cited as key issue around the need to "exclude certain categories of medicines". Including reference to this would reiterate the rationale against generic prescribing and towards consistency of formulation.	been already mentioned in the full guideline in section 10.1.
SH	National Society for Epilepsy	5.04	Full	462		Recommendation 201 refers to 'see recommendation 211'. Should this refer to recommendation 200?	Thank you for your comment. This has been revised.
SH	National Society for Epilepsy	5.05	Full	478	18	This states that up to 50% of individuals with epilepsy are likely to have a specific, or more global learning disability. We would suggest that this statistic is incorrect, and wonder if this is a typographical error?	Thank you for your comment. This section has been revised.
SH	NHS Direct	3.00	Full			NHS Direct have no comments on the content and welcome the guideline.	Thank you for your comment.
SH	Nottinghamshire Healthcare NHS Trust	10.00	Full	10	7	Wording order. Put buccal midazolam first as in line 2 it is the first line treatment and discussed first	Thank you for your comment, we have now revised this.
SH	Nottinghamshire Healthcare NHS Trust	10.01	Full	25	22	Strongly disagree that if the first drug is ineffective to only offer one of the alternatives from that list of four. In practice this is often not helpful (except perhaps in frontal lobe epilepsy). We would try a drug with a different mechanism such as Levetiracetam. This is nearly always the first add on/switch as so often works.	The GDG recognise the issue in clinical practice however this is allowed under 1.9.3.2 (in the NICE guideline) which allows a clinician to use levetiracetam.
SH	Nottinghamshire Healthcare NHS Trust	10.02	Full	25	28	What is the evidence that Levetiracetam is not cost effective at that price? How chose 50% reduction in cost? Also of note Levetiracetam is coming off patent. Why is this the only drug with such emphasis on cost?	Thank you for your comment. A full discussion covering each of these issues is already included in the linking evidence to recommendations sections under 10.3.9.
SH	Nottinghamshire Healthcare NHS Trust	10.03	Full	26	7	We would generally offer Zonisamide before topiramate. From our clinical experience we consider it to have a more favourable side effect profile. Also worthy of use before gabapentin.	Thank you for your comment. The GDG considers that there is no evidence to support offering zonisamide above topiramate.
SH	Nottinghamshire Healthcare NHS Trust	10.04	Full	28	19	We would generally offer Zonisamide before topiramate. From our clinical experience we consider it to have a more favourable side effect profile.	Thank you for your comment. The GDG considers that there is no evidence to support offering zonisamide above topiramate.
SH	Nottinghamshire Healthcare NHS Trust	10.05	Full	32	14	We would generally offer Zonisamide before topiramate. From our clinical experience we consider it to have a more favourable side effect profile.	Thank you for your comment. The GDG considers that there is no evidence to support offering zonisamide above topiramate.
SH	Nottinghamshire Healthcare NHS Trust	10.06	Full	33	13	We would generally offer Zonisamide before topiramate. From our clinical experience we consider it to have a more favourable side effect profile.	Thank you for your comment. The GDG considers that there is no evidence to support offering zonisamide above topiramate.

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SH	Nottinghamshire Healthcare NHS Trust	10.07	Full	34	9	Please insert each new comment in a new row. Zonisamide should be added to this section as an option. From our clinical experience we consider it to have a more favourable side effect profile.	Please respond to each comment Thank you for your comment. The GDG considers that there is no evidence to support offering zonisamide above topiramate.
SH	Nottinghamshire Healthcare NHS Trust	10.08	Full	37	6	"enzyme-inducing drugs" and sodium valproate	Thank you for your comment. We agree and have added this to the recommendation.
SH	Nottinghamshire Healthcare NHS Trust	10.09	Full	52	20	Additional support may be required and reasonable adjustments made to facilitate access to services	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Pfizer Limited	16.00	Response to first consultation /Appendix P & Q			There is a typo in the response; a 56 pill pack of 150mg pregabalin is £64.40 not 64.60 as stated. However, we believe that the correct price was used in the cost calculations.	Thank you for your comment. This has been corrected.
SH	Pfizer Limited	16.01	Appendices	Appendix P & Q		It is regrettable that NICE could not accommodate flat pricing (same pill price regardless of dose) in the revised modelling. We believe that the approximation costing method of using a weighted mean price with an implied mean and a manually adjusted standard error in a gamma distribution is an adequate approximation when sufficient simulations are used (>500). We estimate based on 1,000 simulations that the mean cost is £525.45. However, we found a minimum estimated cost of £194.22 and a maximum of £1,225.73 which fall outside the costs found in the real world for pregabalin. As we stated in our previous comments pregabalin is licensed for two (BD) and three (TD) times a day dosing so 6 month costs would be £420.04 (£2.30 per day) or £630.06 (£3.45 per day) for all patients.	Thank you for your comment. We have now accommodated the flat pricing of pregabalin in the revisions to the cost-effectiveness analysis of adjunctive therapy.

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SH	Pfizer Limited	16.02	NICE version	26	15 and footnote	<p>Please insert each new comment in a new row.</p> <p>The footnote for 'pregabalin' has been changed and now reads: "** At the time of publication ([month year]), this drug did not have UK marketing authorisation for this indication and/or population (please see appendix E for specific details about this drug for this indication and population). Informed consent should be obtained and documented" .</p> <p>We are concerned that this footnote will be misinterpreted. Pregabalin <i>is indicated</i> as adjunctive therapy in <i>adults</i> with partial seizures with or without secondary generalisation. It would be clearer if the footnote specified that "at the time of publication, pregabalin did <i>not</i> have UK marketing authorisation <i>for use in children</i> (BNF). Pregabalin is not recommended for use in children younger than 12 years of age and adolescents (12–17 years of age) owing to insufficient data on safety and efficacy (SPC)" as in appendix E.</p>	<p>Please respond to each comment</p> <p>Thank you for your comment. We have carefully considered your comment and decided not to change the aforementioned footnote. The footnote is consistent with all other AED licensing footnotes. In order to keep footnotes to a minimum we included the same footnote and so more details can be given in appendix E.</p>
SH	Royal College of Nursing	17.00	General			<p>The Royal College of Nursing welcomes this second consultation on the update of the Epilepsy guidelines.</p>	<p>Thank you for your comment.</p>
SH	Royal College of Nursing	17.01	Full	403		<p>We are still concerned about this guideline's relevance to practice in 2011, particularly concerning the advice that Keppra should be used as a second line AED.</p> <p>In practice it is used as a first line AED and for good reason. It is not metabolised by the liver and so is excellent when managing people who may be continuing to consume large volumes of alcohol.</p> <p>It is also not known to have any drug-drug interactions and it is about to come off patent and so will be comparable with Carbamazepine and Lamotrigine!</p>	<p>Thank you for your comment.</p>

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SH	Royal College of Nursing	17.02	Full	403		Please insert each new comment in a new row. Additionally, we are not sure, that in practice we would really consider placing Vigabatrin as a first line treatment choice. It is really only used for children with West Syndrome.	Please respond to each comment Thank you for your comment. Please see recommendations 1.9.8.2 and 1.9.8.3.
SH	Royal College of Paediatrics and Child Health	8.00	General	General	General	The College thinks it would be useful to have more information on investigations in children and young adults, when to consider metabolic screening and when to initiate trial of pyridoxine in young infants.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.00	Full	102	36	Agree with the recommendation	Thank you for your comment.
SH	Royal College of Pathologists	1.01	Full	102	37	Agree with the recommendation	Thank you for your comment.
SH	Royal College of Pathologists	1.02	Full	102	40	Vague compared to recommendation 36. Suggest include specific tests as in 36 and add "blood and urine investigations to exclude an inborn error of metabolism"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.03	Full	122	10	Add "If formulation/brand must be changed, consider confirming bioequivalence by measuring the plasma drug concentration"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment.

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							The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.04	Full	128	11,13	Agree, but greater clarity needed as to whether these recommendations refer solely to AED level monitoring or other blood tests also (as in recommendation 67)	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.05	Full	128	17-18	Replace "electrolytes, liver enzymes" with "renal and liver function tests". Replace "vitamin D levels and other tests of bone metabolism" with "indicators of bone metabolism". Vitamin D levels not generally required.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.06	Full	401	Recommendation 147	"A finger prick test" is dangerously vague. Suggest "a properly calibrated point-of-care testing device, with levels <3.0 mmol/L confirmed by laboratory testing"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of	1.07	Full	404	1	"Blood levels of thiopental sodium" are not generally available and very rarely	Thank you for your comment.

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	Pathologists			405	1	Please insert each new comment in a new row. requested. They are also not mentioned in the protocols in Appendix F. Suggest remove this reference (or replace with "blood levels of thiopental may be required, by referral to specialist laboratory"	Please respond to each comment To add that measurement is related to the maintenance AEDS and not thiopental sodium.
SH	Royal College of Pathologists	1.08	Full	461	Recommendation 200	Agree	Thank you for your comment.
SH	Royal College of Pathologists	1.09	Full	462	Recommendation 201	Consider adding after 4 th bullet point (management of pharmacokinetic interactions) "e.g. changes in bioavailability, changes in elimination, co-medication with interacting drugs"	Thank you for your comment. We agree and have revised the recommendation.
SH	Royal College of Pathologists	1.10	Full	462	Recommendation 201	Reference to pregnancy is incompatible with recommendation 200, which says routine measurement in pregnancy not required. Please remove or clarify	Thank you for your comment. The GDG considers this to be clear and not contradictory.
SH	Royal College of Pathologists	1.11	NICE	20	13	Agree with the recommendation	Thank you for your comment.
SH	Royal College of Pathologists	1.12	NICE	20	15	Agree with the recommendation	Thank you for your comment.
SH	Royal College of Pathologists	1.13	NICE	20	18	Vague compared to recommendation 36. Suggest include specific tests as in 36 and add "blood and urine investigations to exclude an inborn error of metabolism"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.14	NICE	23	9	Add "If formulation/brand must be changed, consider confirming bioequivalence by measuring the plasma drug concentration"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of	1.15	NICE	36	15	Agree with the recommendation	Thank you for your comment.



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	Pathologists						
SH	Royal College of Pathologists	1.16	NICE	36	17	Agree with the recommendation	Thank you for your comment.
SH	Royal College of Pathologists	1.17	NICE	36	24	Consider adding "e.g. changes in bioavailability, changes in elimination, co-medication with interacting drugs"	Thank you for your comment. We agree and have revised the recommendation.
SH	Royal College of Pathologists	1.18	NICE	36	26	Routine monitoring of AED levels in pregnancy is not consistent with recommendation 200 of the full guideline. Remove or clarify reference to pregnancy (see comment 19 below)	Thank you for your comment. The GDG considers this to be clear and not contradictory
SH	Royal College of Pathologists	1.19	NICE	37	3	Replace "electrolytes, liver enzymes" with "renal and liver function tests". Replace "vitamin D levels and other tests of bone metabolism" with "indicators of bone metabolism". Vitamin D levels not generally required.	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.20	NICE	43	12	"A finger prick test" is dangerously vague. Suggest "a properly calibrated point-of-care testing device, with levels <3.0 mmol/L confirmed by laboratory testing"	Thank you for your comment. The scope for the update of the epilepsies guideline was subject to a public consultation for stakeholders to comment. The scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. NICE conducts an update review process 3 years after publication of each clinical guideline to determine whether it needs to be updated.
SH	Royal College of Pathologists	1.21	NICE	44	6 & 11	"Blood levels of thiopental sodium" are not generally available and very rarely requested. They are also not mentioned in the protocols in Appendix F. Suggest remove this reference (or replace with "blood levels of thiopental may be required, by referral to specialist laboratory"	Thank you for your comment. This recommendation has now been revised.
SH	Royal College of Pathologists	1.22	NICE	50	1	Agree – this may be the clarification required for comment 16 above	Thank you for your comment.

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SH	Tony Marson (Cochrane group)	18.00	Full	General		<p>Please insert each new comment in a new row.</p> <p>Our group provided extensive and detailed comments to the first consultation, with many points remaining unresolved. Given the short turnaround time and the resource implications for providing further extensive comments we have elected to provide comments on the substantive methodological problems that seriously undermine the guidance. These problems have serious implications for this guideline, how NICE might approach future guidelines in epilepsy and other chronic diseases, and for future health technology assessment in epilepsy.</p> <p>The main methodological problems relate to the network meta-analyses which provide the evidence that underpins much of the guidance.</p> <ol style="list-style-type: none"> 1. Network meta-analysis of monotherapy studies <ul style="list-style-type: none"> • The primary outcome chosen (12 month remission at 12 months) makes little clinical or methodological sense and should not be used to inform clinical decision making, especially when other data are available. Problems with the outcome include: <ul style="list-style-type: none"> ○ We really need to know about differences in policies of starting differing antiepileptic drugs. In clinical practice a new drug is titrated to an initial dose over 6-8 weeks and then titrated up further according to clinical response. Measuring 12 month remission at 12 months fails to assess the policies. ○ Assessing immediate remission at 12 months lacks power as many remission events are missed. Having looked at the included trials and IPD meta-analyses, we estimate the NICE review includes only 48% of the remission events. ○ Some patients enter an immediate remission due to natural history rather than due to a treatment effect. Measuring immediate remission is likely to lack assay sensitivity. • The primary outcome should be time to 12-month remission as recommended by the ILAE. This should be analyses using time to event analyses, overcoming the problems listed above. • There is little justification for undertaking an aggregate data meta-analysis when there are methodologically superior peer-reviewed individual patient data analyses in the public domain in which time to event analyses have been reported and which possess greater power to explore the outcomes. 2. Network meta-analysis of add-on studies in refractory epilepsy <p>It must be understood that the trials included in this meta-analysis were undertaken to meet the requirements of regulators, not to inform clinical decision making. From</p>	<p>Please respond to each comment</p> <p>Thank you for your comment. We have taken on board your concerns and subsequent to your points further re-analysis has been conducted to incorporate the time to event outcomes used in the IPD meta-analysis and ascertain the validity of the recommendation for first line treatment for focal seizures in light of this.</p>

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						<p>Please insert each new comment in a new row.</p> <p>the perspective of clinical decision making the limitations include</p> <ul style="list-style-type: none"> Highly selected population that reflect a small proportion of patients seen in clinical practice. For example the service in Liverpool has ~7000 patients under active follow-up but was unable to recruit more than 4 patients to such a trial over 12 months. Placebo rather than active control Short duration (typically 12-16 weeks). Forced rapid titration Use of doses (often in dose ranging studies) which are not necessarily taken into common clinical use (e.g. gabapentin too low and topiramate too high). Placebo response rates have increased over time. Considered reason for failure of trials of briveracetam Patient populations have changed over time. <p>While it may be reasonable to summarise evidence about the likely efficacy of a single drug, any indirect comparison in a network meta-analysis (assuming similar placebo groups) is likely to be unreliable. Given the above limitations, NMA in these studies should not be used as a primary source of data to rank (eg inform first and second line add on) treatments. In this scenario, the data from RCTs is inferior to clinical experience and consensus. Indeed blindly following the results of the network meta-analysis is likely to put patients at risk, for example the decision to recommend gabapentin as a first line treatment and levetiracetam as a second line treatment.</p>	Please respond to each comment
SH	UCB Pharma Ltd	20.00	Full	189	2	<p>UCB welcome NICE's recommendation of levetiracetam as a first line treatment for patients with focal seizures when other first line treatments are considered unsuitable or when the acquisition costs are reduced by 50%. This reflects research data and clinical experience and will provide confidence to the many clinicians and patients who have benefited from such use over several years.</p> <p> </p> <p>Epilepsy guidelines second consultation Epilepsy guidelines second consultation </p>	Thank you for your comment.

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SH	UCB Pharma Ltd	20.01	Full	189	2	<p>Please insert each new comment in a new row.</p> <p>In recommending levetiracetam as a first line treatment option NICE recognise the imminent change in acquisition cost through the inevitable availability of generic levetiracetam in 2011.</p> <p>The Drug Tariff will provide health care professionals with details of acquisition costs. However, acquisition costs published in the Drug Tariff lag 3-6 months behind actual NHS purchasing costs. This is of critical importance in the early phase of generic entry when there can be frequent changes in actual acquisition costs. As the market settles price changes will be less marked allowing the Drug Tariff to be reflective of current prices.</p> <p>Given the life span of the updated epilepsy guidelines and the impact their publication will have on prescribing policies and patient well being UCB ask NICE to provide guidance enabling health care professionals and commissioners to understand the inevitable uncertainty of acquisition costs in the first months of generic entry. Advising local implementation towards the end of 2011 allows access to clearer, more accurate acquisition costs for levetiracetam ensuring more effective implementation of guidelines in line with recommendation 83.</p> <p>Within this guidance UCB would ask that the source of acquisition costs, The Drug Tariff, is made clear.</p>	<p>Please respond to each comment</p> <p>Thank you for your comment. We have added a footnote to the recommendation referencing the NHS Drug Tariff as the source of this acquisition cost.</p>
SH	UCB Pharma Ltd	20.02	Full	147	4-7	<p>Grade 1 evidence¹ supports the recommendation of levetiracetam as a first line option in the management of focal onset epilepsy.</p> <p>UCB continue to have reservations about the manner in which this data has been considered.</p> <p>Section 2.8 of the updated guidelines specifies outcome measures to be extracted from trials. Included are: seizure freedom data, responder rate analysis (proportion of participants experiencing 50% reduction in seizures) – both from ITT cohort assessments, time to overall withdrawal and proportion withdrawing.</p> <p>Furthermore both the outcome measures and definitions on page 38 and Appendix O state that the most ideal measure of effect would appear to be time to exit from study, whether due to lack of efficacy or adverse events.</p> <p>Neither section 2.8 nor Appendix O advise the extraction of proportion of patients withdrawing due to lack of efficacy.</p> <p>Brodie's research finds: Primary end-point:</p> <ul style="list-style-type: none"> levetiracetam has a non-inferior proportion of seizure-free patients for ≥6months on last evaluated dose compared with that reported for CBZ-CR in the per protocol cohort. <p>Secondary end-points:</p> <ul style="list-style-type: none"> Levetiracetam is non-inferior in the intent-to-treat population as reported for the per protocol primary endpoint 	<p>Thank you for your comment. We agree. We have specified the definition given in section 2.8 of the update guideline for the proportion of participants having treatment withdrawn to reflect the two types of treatment withdrawal; withdrawal due to lack of efficacy and withdrawal due to adverse events. Limited studies appear to have reported data on withdrawal due to lack of efficacy; where available this was reported in the section of direct comparisons. In the quality of evidence section in recommendation of levetiracetam as alternative first line monotherapy for focal seizures we reported the results of the trial comparing levetiracetam versus controlled-release carbamazepine.</p>

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						<p>Please insert each new comment in a new row.</p> <ul style="list-style-type: none"> No significant differences in terms of 1-year seizure freedom rates (thus including the 6-month maintenance phase). Additional end-points (without statistical analysis) Observational analysis demonstrates that similar numbers levetiracetam (n=95) & CBZ-CR (n=97) withdrew overall for any reason – a more clinically relevant outcome measure than withdrawal for one or other reason <p>The level of emphasis placed on the withdrawal rate due to lack of efficacy is misleading when primary and secondary outcome analysis supports levetiracetam's non-inferior efficacy to CBZ-CR. Such efficacy combined with similar overall retention is surely of paramount clinical relevance. Given that only four of 21 trials in the network analysis provided this information UCB ask NICE to explain their rationale for this analysis.</p>	Please respond to each comment
SH	UK Clinical Pharmacy Association (UKCPA)	11.00	Full	General		The UKCPA would like to confirm that it has no comments to add to this update.	Thank you for your comment.
SH	UK group of consultant epileptologists	7.00	Full	general		<p>The UK group of Consultant Epileptologists welcomes the inclusion of some of our suggestions in the revised document. However, it remains concerned that despite some improvements "The Epilepsies" NICE Guideline as it stands does not reflect the advances made in clinical epileptology and at present some of its recommendations may be detrimental to patient care. It is unfortunate that there was not an opportunity for a more complete revision of the guideline to be undertaken, and we hope that NICE will undertake this in the near future.</p> <p>Also, the time of 2 weeks given to stakeholders for this second draft is insufficient to examine in depth the changes in the document that have been undertaken. Here are some of key points while also emphasising that there are many more that we do not endorse.</p>	Thank you for your comment. However the scope of the 2011 partial update of the epilepsies guideline was to only address the pharmacological management. We understand the short timeframe. There will be a 3 rd consultation with a longer timeframe.
SH	UK group of consultant epileptologists	7.01	Full	22	1	Once more, we remind the GDG that the recent ILAE report (Berg et al 2010) has not been formally endorsed by the ILAE executive and it has met with significant criticism published in the same issue of Epilepsia. It is just a quadrennial interim report documenting the progresses made and illustrating the complexity of the task of classifying the epilepsies. Therefore, the suggestion that the terms idiopathic, symptomatic and cryptogenic are now redundant is premature. It is also premature for NICE to endorse other suggestions and definitions of this report such as 'Furthermore, although seizures may be focal or generalised in onset, such terminology cannot be applied to syndromes' that would be better removed.	The classifications of the epilepsies so published by the ILAE have always been under the heading of a 'proposal', rather than formal 'acceptance'. It is acknowledged in the most recent publication that the classification of the epilepsies is continually 'work in progress'. Taking this into consideration the GDG felt it important that the current guidelines are kept in line with current proposals. This aside, the word 'redundant' with relation to idiopathic and symptomatic they accepted may be a little strong and this part has been reworded accordingly. Advice against the use of the word cryptogenic was first suggested in the report of 2001.
SH	UK group of consultant	7.02	Full	38	14	The document states that the update was limited to the pharmaceutical management of epilepsy. Thus, several of stakeholder comments were considered to be outside	Thank you for your comment. This is in line with NICE process as the GDG considered

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	epileptologists					<p>Please insert each new comment in a new row.</p> <p>the scope of the revision. However, there are areas of revision in the current draft that extend beyond pharmacological issues, for example in revision of the glossary and of the introduction. It appears inconsistent to update the glossary and not, for example, appendix A, where important potential revisions were flagged by the UK Group of Consultant Epileptologists. NICE should clarify the process they employed for limiting the revisions of the document, especially in areas which national experts in epilepsies considered important.</p>	<p>Please respond to each comment</p> <p>that it was necessary to update these sections as part of the pharmacological update of the guideline as they were relevant to treatment.</p>
SH	UK group of consultant epileptologists	7.03	Full	62	4	<p>The NICE guidance should be consistent with the GMC recommendations which recognise the limitations of what is feasible in the consultation process.</p> <p>Draft guidance states that children, young people, adults, their families and carers should all be informed about the unlicensed status of buccal midazolam or , other drugs. This would be difficult, often impossible, because of the complexity of the issues involved in pharmaceutical marketing authorisation and the high prevalence of learning disability in this group. Such guidance would also differs importantly from the recommendations of the GMC in 'Good Practice in Prescribing Medicines, Guidance for Doctors', Sept 2008, which states: "You must give patients, or those authorising treatment on their behalf, sufficient information about the proposed course of treatment including any known serious or common side effects or adverse reactions. This is to enable them to make an informed decision (for further advice, see Consent: patients and doctors making decisions together).</p> <p>Some medicines are routinely used outside the scope of their licence, for example in treating children. Where current practice supports the use of a medicine in this way it may not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients, or those authorising treatment on their behalf, require or which they may see as significant. Where patients, or their carers express concern you should also explain, in broad terms, the reasons why medicines are not licensed for their proposed use. Such explanations may be supported by written information, including the leaflets on the use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice produced by the Royal College of Paediatrics and Child Health/Neonatal and Paediatric Pharmacists Group Standing Committee on Medicines.</p> <p>However, you must explain the reasons for prescribing a medicine that is unlicensed or being used outside the scope of its licence where there is little research or other evidence of current practice to support its use, or the use of the medicine is innovative."</p>	<p>Thank you for your comment. The GDG decided to remove the recommendation informing adults, children and young people that buccal midazolam is currently unlicensed.</p>
SH	UK group of consultant epileptologists	7.04	Full	58 et seq	4	<p>The group believes that NICE's meta analysis is flawed. The decision to recommend the offer of sodium valproate as first line treatment for focal seizures in the revised guidance is based largely on the network meta-analysis. The difficulties inherent in relying on such meta-analysis is illustrated by vigabatrin, which according to this analysis was found to be a well tolerated and low risk AED of relatively good efficacy. Vigabatrin is rarely used in clinical practice, because of its adverse effect profile.</p>	<p>Further re-analysis has been conducted to incorporate the time to event outcomes used in the IPD meta-analysis and ascertain the validity of the recommendation for first line treatment for focal seizures in light of this.</p>

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						<p>Please insert each new comment in a new row.</p> <p>Significant adverse effects such as vigabatrin associated-irreversible visual field defects, are not flagged in the meta analysis. This is also the case with sodium valproate, where teratogenicity, polycystic ovarian syndrome, etc., limit the utility of the drug in clinical practice. Unless the revision takes account of these issues and tempers the recommendation for valproate at each mention in the document, there is a strong probability that adverse outcomes will be attributable directly to the revised guidance. Such adverse events also considerably distort the cost effectiveness of valproate treatment – a single avoidable incidence of major congenital abnormality resulting from the drug is likely to cost the health economy many hundreds of thousands of pounds over the individual's lifetime.</p>	<p>Please respond to each comment</p>
SH	UK group of consultant epileptologists	7.05	Full	58	1	<p>There are two recommendations concerning the appropriate counselling of women who are being offered sodium valproate (numbers 81 and 196). In contrast there are at least 13 which recommend the use of the drug as first line treatment in populations which include women of childbearing age (nos 82, 84, 86, 90, 95, 100, 118, 119, 122, 124, 127, 128, 130). In addition, the drug appears to be recommended in section 1.6 in the description of the SANAD study. Where sodium valproate is recommended, the only caveat offered is usually 'unless it is unsuitable'. Readers may not appreciate the disproportionate dangers of sodium valproate to the unborn child, potentially resulting in avoidable major congenital abnormalities and other adverse outcomes of pregnancy. We suggest that the caveat is strengthened in each recommendation for sodium valproate to include the phrase 'unless it is unsuitable and after due consideration of the risk in potential pregnancy and other long term health risks'.</p>	<p>Thank you for your comment. We agree and have now highlighted the need to remember the risk of teratogenesis and added a cross-reference to recommendation 1.9.1.11 each time sodium valproate is recommended.</p>
SH	UK group of consultant epileptologists	7.06	Full		10	<p>In the pharmacological treatment of focal and generalised epilepsies (JME, myoclonic, photosensitivity) this 2nd draft largely ignores the position and documentation of many stakeholders in regard to levetiracetam. Economic comparisons of the product cost may be misleading in regard to actual cost efficacy (see above in 7 the example of sodium valproate).</p>	<p>Thank you for your comment.</p> <p>The GDG made substantial amendments following the first stakeholder consultation to the recommendations to which you refer. The recommendation for levetiracetam in focal seizures has been amended in order to reflect current information and now also give guidance to health professionals, commissioners and patients about the circumstances under which levetiracetam should be considered alongside other first-line treatments for focal seizures. A full discussion of GDG deliberations about this recommendation is detailed already in the linking evidence to recommendations sections under 10.3.9.</p> <p>The GDG also amended the recommendations for first-line treatment of myoclonic seizures and JME to encourage consideration of levetiracetam if sodium valproate is unsuitable</p>

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