National Institute for Health and Clinical Excellence

Epilepsy guideline
3rd consultation
Guideline Consultation Comments Table
27 July – 24 August 2011

Type	Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	Association for Clinical Biochemistry	1	Full	13.5.5 Recommendation 212	520	Fifth bullet point: 'Pregnancy' as an indication for monitoring AEDs conflicts with recommendation 211 (page 519) which says 'Do not routinely monitor AEDs in pregnancy'. Either remove 'pregnancy' here, or qualify with "(see recommendations **211 and** 223)"	Thank you for your comment. We have revised this recommendation for further clarity.
SH	Association of British neurologists	12	Full	2.2.4	Line 24	In Methods – the depiction of how a chairman was elected and members selected is unnecessary and could be put in an appendix.	Thank you for your comment. This is a standard section of the guideline methods.
SH	Association of British neurologists	14	Full	10.3.09	185 line 12	The warning about sodium valproate should contain guidance that young woman contemplating taking this drug be seen in an epilepsy clinic for counselling.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1. 11 and 1.15.1 4.
SH	Association of British neurologists	16	Full	10.5.8	266 line 2	The recommendation to use sodium valproate as a first line drug for JME not only reflects the evidence we have, but the day to day experience of neurologists with and interest in epilepsy. NICE should not dilute this statement But again a guideline recommending young women be fully counselled should be added.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1.11 and 1.15.1 4.
SH	Association of British neurologists	13	Full	2.4.1.1	46	Begins two pages of research suggestions. These guidelines are to review what is best evidence practice and these suggestions disrupt the flow of the document. It would be better to put all the research suggestions into an appendix.	Thank you for your comment. The research recommendations are a standard section of the guideline.
SH	Association of British neurologists	4	Full	1.9.3.2 1.9.3.3	86 87	In section 1.9.3.2 and 1.9.3.3. & summary points 86 and 87 carbamazepine, lamotrigine, oxcarbazepine and sodium valproate are recommended as first line treatments for focal epilepsy "unless unsuitable" – this term is imprecise. The majority of adult neurologists in the UK would not offer sodium valproate as a first line in focal epilepsy – especially when the patient is a young woman, because of the risks of teratogenicity and side effect profile, and perceived lack of efficacy in these epilepsies.	Thank you for your comment. The GDG considers that the current wording of the recommendation reflects the clinical and health economic evidence reviewed as part of the guideline development process and allows for a certain degree of choice and flexibility which should be exercised with clinical judgement. Please also refer to section 10.3.9 of the full guideline

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							for further detail of the GDG considerations that underpin these recommendations. The GDG also feels that it has adequately addressed the issues related to the teratogenicity of sodium valproate in the relevant recommendations.
SH	Association of British neurologists	7	Full	1.9.3.6	89	Retigabine should be included bearing in mind recent guidance issued by NICE	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	Association of British neurologists	1	Full	General	General	We would like to draw the Guideline's committee's attention to the submission by Professor Marson which we agree with.	Thank you for your comment. The GDG have worked closely with Professor Marson and his team as peer reviewers in drafting this guideline.
SH	Association of British neurologists	2	Full	General	General	We consider 2 weeks in August when a large number of people are on holiday – including most of the government- inadequate to make fully considered response.	Thank you for your comment. We appreciate your concern and as a result NICE extended the consultation period from 3 to 4 weeks.
SH	Association of British neurologists	3	Full	General	General	The Association of British Neurologists welcome's this document as it does any attempt to improve care for patients with acute and chronic neurological conditions, but does not endorse it.	Thank you for your comments. NICE does not ask SH to endorse their clinical guidelines through formal badging. We have given careful consideration to your comments and have responded to your comments below.
SH	Association of British neurologists	5	Full	General	General	Levetiracetam is cited as a second line treatment because of cost effectiveness. This guidance is at odds with many adult neurologists' practise, most of whom use levetiracetam as a first line drug. NICE does not seem to have taken account of the drug's capacity to be titrated to a therapeutic dose more quickly than lamotrigine and it's lack of interactions with other drugs. Because of this recommendation there is a danger that if patients find carbamazepine and oxcarbazepine "unsuitable" or cannot tolerate them they will be offered valproate, which for reasons alluded to above most neurologists in the UK would consider unsuitable. This guideline is likely to be	Thank you for your comment, and we do appreciate that this is a complex issue. Levetiracetam has been positioned within the restraints of the evidence available, Further, its position will become clearer once generic pricing is available.

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						ignored in practice.	Similarly, 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. Please also refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, and to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC seizures and IGE.
SH	Association of British neurologists	6	Full	General	General	NICE has calculated cost effectiveness for levetiracetam on 2010 prices – but it will soon come off licence presumably making it cheaper.	As outlined in appendix P (Section P.2.2.9), the costs for all drugs were taken from the BNF published in March 2011. According to the NHS Drug Tariff, which is update more frequently than the BNF, this cost had not changed as of June 2011. We are aware that levetiracetam has come off patent and several generic manufacturers have recently gained marketing authorisation. In anticipation of generic production, we performed sensitivity analyses around the cost of levetiracetam to determine at what cost reduction it might

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							become cost effective compared to alternative AEDs. This is described in full in section P.3.2.1 and P.3.2.3 in appendix P and summarised in the linking evidence to recommendations sections under section 10.3.9 of the full guideline.
SH	Association of British neurologists	8	Full	1.9.4.1	General	Section recommendations are sound, only if the GTCS are presumed to be due to an Idiopathic Generalised Epilepsy or JME. There is no doubt that everyday clinical experience and the evidence we have points to valproate being the most effective drug in JME and IGE. Sodium Valproate, however, is teratogenic, and in some has significant adverse effects. Nice should consider rewording this guideline, and adding a recommendation that VPA should not be started in young women without proper counselling ideally done in an epilepsy clinic.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1.11 and 1.15.1 4.
SH	Association of British neurologists	9	Full	1.9.4.1	General	If the patient has GTCS with no compelling evidence that they are a manifestation of JME, or an IGE then we believe lamotrigine should be offered first, especially in young women. Recommending VPA for a first GTCS is contrary to most neurologist's practise and this guideline will be ignored.	Thank you for your comment. The GDG considers there only to be evidence to recommend lamotrigine if sodium valproate is considered unsuitable, which might include young women. For further detail on the GDG considerations that underpin these recommendations, please refer to section 10.5.9 of the full guideline. The GDG considers that the safety issues surrounding the use of VPA in young girls and women is fully and adequately explored in recommendation 1.15.1 4.
SH	Association of British neurologists	10	Full	1.15.3.19	General	The guidance on AED monitoring during pregnancy is unclear. Should AED levels be monitored if the neurologist thinks seizures may in crease? Or after the woman reports and increase in seizures? We would draw you attention to the interaction between estrogen and lamotrigine and the fact that some neurologists now routinely measure lamotrigine levels in pregnancy.	Thank you for your comment however it relates to an issue outside of the scope of the update of this guideline. We appreciate that this issue is of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to

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							inform any future update of this guideline.
SH	Association of British neurologists	11	Full	General	General	It is a very long document and one wonders what it's true purpose is. There are some good educational sections in it, for example the section on the use of the EEG. But it is bloated with endless comparisons between individual drugs which could be rendered more digestible in tabular form.	Thank you for your comment. As a result of complex data that has been analysed, it is standard format of the guidelines to present all the evidence statements and GRADE tables with the comparisons between the different pharmacological options listed in the scope.
SH	Association of British neurologists	15	Full	General	General	The recommendations on Levetiracetam are at odds with many consultant adult neurologist's practice and will probably be ignored.	Thank you for your comment, and we do appreciate that this is a complex issue. Levetiracetam has been positioned within the restraints of the evidence available, Further, its position will become clearer once generic pricing is available. Similarly, the GDG felt unable to includelevetiracetam 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. Please refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, and to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC seizures and IGE.
SH	Association of	5	Full	General	Gene	Levetiracetam is cited as a second line treatment because of cost effectiveness.	Thank you for your comment, and

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	British neurologists				ral	This guidance is at odds with many adult neurologists' practise, most of whom use levetiracetam as a first line drug. NICE does not seem to have taken account of the drug's capacity to be titrated to a therapeutic dose more quickly than lamotrigine and it's lack of interactions with other drugs. Because of this recommendation there is a danger that if patients find carbamazepine and oxcarbazepine "unsuitable" or cannot tolerate them they will be offered valproate, which for reasons alluded to above most neurologists in the UK would consider unsuitable. This guideline is likely to be ignored in practice.	we do appreciate that this is a complex issue. Levetiracetam has been positioned within the restraints of the evidence available, Further, its position will become clearer once generic pricing is available. Similarly, 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. Please also refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, and to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC seizures and IGE.
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SH	Association of British neurologists	14	Full	10.3.09	Page 185 line 12	The warning about sodium valproate should contain guidance that young woman contemplating taking this drug be seen in an epilepsy clinic for counselling.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1.11 and 1.15.1 4.

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SH	Association of British neurologists	16	Full	10.5.8	Page 266, line 2	The recommendation to use sodium valproate as a first line drug for JME not only reflects the evidence we have, but the day to day experience of neurologists with and interest in epilepsy. NICE should not dilute this statement But again a guideline recommending young women be fully counselled should be added.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1.11 and 1.15.1 4.
SH	British nuclear medicine society					No comment	Thank you for your comment.
SH	Defence medical services	1	Full	General		We welcome the updated guideline and within the current version have no comments. However, whilst perhaps not directly in the scope of the there exists a wide variation in practice in the use of prophylactic use of anti epileptic drug (AED) therapy post penetrating and non-penetrating traumatic brain injury and its applicability merits consideration. This topic is also not covered within the head injury NICE guidelines.	Thank you for your comment. The GDG have not addressed this issue in this update. Stakeholders are encouraged to submit these comments to inform the scope of the head injury guideline which will be updated next year. Further information can be found on the NICE website by following this link: **Head injury**
SH	Epilepsy Action	1		General		We are grateful to the Guideline Group that the majority of the recommendations we put forward in the second consultation have been incorporated into the third edition of the Guideline draft. We refer particularly to the additional information on bone health, and warning of the possible visual effects of vigabatrin.	Thank you for your comment.
SH	Epilepsy Action	3	Full	57	19	***Recommendation 25.*** ***In children and young people, a sleep EEG is best achieved through sleep deprivation or the use of melatonin. [2004, amended 2011]*** Melatonin use is not recommended for adults, only for use with children and young people. This is because some studies suggest melatonin can increase the frequency of seizures. This guideline defines young people as those up to, and including, the age of 17 years. However a 17 year old may hold a driving licence, or wish to hold a driving licence shortly, and so melatonin use (and seizure induction) may not be a practical step. Therefore we would like the Guideline Group to specify at what age melatonin use should cease.	Thank you for your comment however it relates to an issue outside of the scope of the update of this guideline. We appreciate that this issue is of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.

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SH	Epilepsy Action	4	Full	72	22	Currently, recommendation 221 reads: ***If emergency contraception is required for women and girls taking enzyme-inducing AEDs, the dose of levonorgestrel should be increased to 1.5 mg and 750 micrograms 12 hours apart. [2004]*** We believe these dosage levels have now changed and this information is now incorrect. BNF 61 (March 2011) states: *"The effectiveness of levonorgestrel, and possibly ulipristal, is reduced in women taking enzyme-inducing drugs (and possibly for 4 weeks after stopping) … the dose of levonorgestrel should be increased to a total of 3 mgs taken as a single dose (unlicensed dose-advise women accordingly)."* We would like the Guideline Group to look at amending this information in line with the latest BNF recommendations.	Thank you for your comment. We have revised recommendations 1.15.2.4 and 1.15.2. to be in line with current BNF dosages.
SH	Epilepsy Action	2	Full And NICE	1.3 Introduction	23 5	We are surprised that the Guideline Group, after updating the prevalence statistics for Draft 2, has again changed prevalence statistics for this version, significantly revising down the prevalence of epilepsy in the process. We do not believe this that the Guideline Group has demonstrated justification, or provided evidence, to support this decision As a member of the Joint Epilepsy Council, we are able to disclose that the upcoming revision of the epilepsy prevalence statistics (by the Joint Epilepsy Council) will revise upwards the number of people with epilepsy in England and Wales. The new figures will state that there are 496,000 in England and 32,000 in Wales. These figures will be formally adopted before the end of 2011. It is acknowledged that exact figures for the numbers of people with epilepsy are difficult to produce. This is due to complicating factors such as misdiagnosis rates, inconsistent reporting, variations in the definition for active epilepsy and anti-epileptic drugs (AEDs) being prescribed for other conditions. A variety of sources were reviewed in the production of the new data including, in	Thank you for your comment. The GDG considers that this is the best estimate available. As part of an overall editorial review, further information has been added to the full guideline introduction that acknowledges the figures for misdiagnosis

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						particular, the General Practice Research Database (GPRD) Data sets, Quality and Outcomes Framework prevalence data and NHS Information Centre for Health and Social Care and the IMS Health Disease Analyzer. The prevalence and incidence figures used in this report are based on an analysis of GPRD data applied to the Office of National Statistics (ONS) mid-year population estimates 2010. The Joint Epilepsy Council is more than happy to share the full calculations and methodology for the prospective prevalence statistics, if the Guideline Development Group would like a copy. We believe these figures are the most fair and accurate available, and the best reflection of epilepsy prevalence. The methodology used is similar, if not more accurate, to the current (widely used) prevalence statistics, and statistics produced by other organisations for a range of other conditions. The distinction made in the Full Guideline (page 24, line 5) that up to 124,500 people may have a diagnosis of epilepsy, when they do not, is helpful as long as it is accompanied by an estimate for the number of people with epilepsy who have the condition, but are not diagnosed and are not receiving treatment for it. An estimate for this figure is not included. It is important that the NICE Guidelines accurately reflect the most accurate and up-to-date statistics at time of publication. We still believe the best way to define the number of people with epilepsy is to count the number of people diagnosed with the condition, receiving treatment for it. We believe this is the most accurate figure available and would appreciate the Guideline Development Group reverting back to the information included in Draft 2, for simplicity and consistency.	
SH	Epilepsy Action	7	Full	199 onwards	491	We make the comments below in the belief that they fall within the scope of the Guideline review, as they are concerned with the pharmacological treatments of epilepsy. Section 13 of the Full Guideline is entitled 'Women of childbearing age', but women have distinct care needs pre-peri and post menopause too. For example guidance	Thank you for your comment. The GDG considers that recommendations 1.15.1.1 and 1.15.1.2 cover these issues.

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						on the potential interaction between hormone replacement therapies and AEDs, particularly lamotrigine. This is not covered adequately in point 199 on page 491. The review has overlooked the pharmacological management of epilepsy during peri- menopause. In particular, Epilepsy Action would welcome the inclusion of guidance regarding potential interaction between the use of hormone replacement therapies (HRT) and AED. Epilepsy Action would also welcome specific guidance relating to the potential impact of the oestrogen component of HRT on lamotrigine levels.	
SH	Epilepsy Action	8	Full	210	518	The wording for the following point is uses an incorrect term in second sentence. We recommended that this is adjusted to read as follows: *Lamotrigine and simultaneous use of any oestrogen-based contraceptive can result in a significant reduction of lamotrigine levels and lead to loss of seizure control. When she stops using oestrogen based contraceptives, the dose of lamotrigine may need to be adjusted. [new 2011].*	Thank you for your comment, however the GDG has decided to maintain the current wording of the recommendation 1.15.2.9, as they did not agree with the change from " a woman or girl to "she".
SH	Epilepsy Action	5	Full	89	61	Since the last draft guideline was published, a NICE single technology appraisal has approved retigabine for the adjunctive treatment of partial onset (focal) seizures in adults with epilepsy. We are sure that the Guideline Group is aware of this development and will now be including retigabine as a treatment option, under recommendation 89 (section 1.9.3 in NICE guideline) for adults. This in itself is indicative of how quickly drug developments for epilepsy can occur. (The European Medicines Agency is now reviewing extending the use of zonisamide as a monotherapy option for newly-diagnosed epilepsy patients with focal seizures). This is why the guideline should make all its drug recommendations in the context of the lifetime of the Guideline, not just what is available or cost-effective at the time of publication.	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	Epilepsy Action	9	Full	126	64	We do not believe levetiracetam should be recommendation as a second-line treatment based on cost alone. Levetiracetam is widely prescribed in clinical practice, in part because it has a low probability for interactions and a mechanism of action that allows easy addition to	Thank you for your comment, and we do appreciate that this is a complex issue. Levetiracetam has been positioned within the restraints of

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						existing drug treatment. The evidence that has informed in the Guideline process has shown that levetiracetam is a clinically effective drug for the treatment of focal seizures. Epilepsy Action wants the safest, most-effective AEDs to be available to all those who may benefit from them. Recommendation 126 (NICE Guideline recommendation 1.9.3.3) states that levetiracetam is not cost effective at current 2011 unit costs – and then quotes a price from the National Health Service drug tariff and states this is "at the time of publication". The price then quoted is unlikely to be the true price at publication, as this is the July 2011 price. This guideline however will not be published until 2012 – when generic competition will have reduced the cost of levetiracetam. For the guideline to be accurate it will need to reflect the true price at publication. In fact, we believe the evidence of generic introduction in epilepsy and other therapeutic areas has always produced savings of the order NICE is suggesting are required for levetiracetam to be cost effective. Generic competition is already reducing the price to pharmacies such that it meets the current 'condition' that it is 50% less than the current price in the draft guideline. We understand due to the mechanism of setting the Tariff, this reduction will not be reflected in the Tariff until round about January 2012. We are not aware however, even when a generic tariff is set, where the "cost" of levetiracetam can be identified, as this will be a combination of the generic Tariff and the brand price for those prescriptions written by brand, and not just the price in the generic Tariff. It is also unclear how NICE expects clinicians to identify this price and check it meets NICE's criteria as set out in the current draft. This is going to be especially difficult, if not impossible, during a busy consultation where the Dr may or may not have access to a computer. Given the historic price reductions in all drugs when generic competition is introduced we would submit it would be perfectly reasonable and pragmatic to remove the caveat as written as unnecessary and almost impossible to implement in a clinical setting. We are further concerned that the caveat as written may lead to local misinterpretation, local 'unfavourable' interpretation or even ignoring levetiracetam as an option as the prescriber would have to source the data during a busy consultation.	the evidence available. Further, its position will become clearer once generic pricing is available. The wording of the recommendation has been amended for publication in light of the 3rd consultation however; the developers believe it would be inappropriate to remove the caveat included at this stage. Similarly, 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.

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						We suggest therefore the caveat will not be required when the guideline is published in January 2012 and should be removed. If NICE needs to caveat the choice of levetiracetam, just in case the price shoots up again or the reductions anticipated aren't realised, then we would suggest a re-wording of the caveat. A statement along the following lines would be better and less likely to compromise the treatment options for people with epilepsy. NICE would need to ensure a simple mechanism for clinicians to identify this cost of levetiracetam during a consultation. Suggested re-wording - Levetiracetam is cost effective at a unit cost of £1.37 per 1500mg dose or lower. If the cost is above this figure it should not be prescribed.	
SH	Epilepsy Action	6	Full	13	General	We are aware that we are repeating comments on sections of the Guideline that are out of the scope of the review. However we feel very strongly that to allow the current information to go forward unchanged would be to the severe detriment of some women, who will as a result receive out-of-date or sub-optimal treatment. The evidence for the section 'Women of childbearing age' references the increased risk of maternal death in women with epilepsy. However the draft Clinical Guideline excludes some of the important recommendations from The Confidential Enquiry into Maternal and Child Health (CEMACH) to reduce this risk. This includes the importance of urgent referral to a specialist for opinion when presenting in pregnancy, and urgent referral for pregnant women reporting worsening seizures to her epilepsy specialist. We strongly believe that all the recommendations of CEMACH related to making pregnancy and birth safer for women with epilepsy should be considered for inclusion in the guideline, with notes as to why a recommendation was excluded if that is the decision of the Guideline Group.	Thank you for your comment however it relates to an issue outside of the scope of the focussed 3rd consultation of the update of this guideline. It is inappropriate to include recommendations from other guidelines in a NICE evidence based guideline. However we appreciate that this issue is of continued importance and we will ensure that your comments are forwarded to the NICE Implementation team to support activity following publication as required.
SH	Epilepsy Society	1	Full	10.3.4.3	154	Line 19 refers to the 'current 2011 cost' of levetiracetam in reference to comparisons with controlled-release carbamazepine for monotherapy treatment of focal seizures in adults. As generic versions of levetiracetam are recognised as becoming available and are	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the

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						likely to be widely available at a lower cost than Keppra (on which the overall comparison was made), this would have a bearing on the cost effectiveness comparison on which this recommendation was made. **We would suggest that recommending prescribing of levetiracetam as a first line therapy for focal seizures is made a standard** (rather than a caveat) in deference to this expected reduction in cost. This would simplify the recommendation (and avoid the onus on prescribing doctors to carry out price comparisons before prescribing, which could potentially lead to inconsistency in supply).	NICE guideline.
SH	Epilepsy Society	2	Full	10.3.9	207	Recommendation 87 – see comment 1 above for rationale.	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.
SH	Epilepsy Society	3	Full	10.4.6	218	This section relates to anti-epileptic drugs used for adjunctive therapy for refractory focal seizures in all ages. The anti-epileptic drug retigabine has just been approved for use as adjunctive therapy for adults with focal seizures (NICE technology appraisal guidance 232, July 2011) but has not been included in this comparison. This seems incongruous with NICE's own recommendations and may result in a lack of prescription of this drug even though NICE has approved it's use as appropriate for this group. It also means that the NICE guideline will appear out of date when it is published after the technology appraisal has been completed.	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	Epilepsy Society	4	Full	10.4.9	266	Recommendation 89 – see comment 3 above for rationale.	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.
SH	Epilepsy Society	5	NICE	1.9.3.3	26	Levetiracetam is only offered under a caveat on cost. See comment 1 above for rationale.	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.

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SH	Epilepsy Society	6	NICE	1.9.3.5	27	Retigabine is not mentioned here (see comment 3 above for rationale).	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	ESNA	2	Full		308	This should reflect clinical practice with Levetiracetam being used sooner in both focal and generalised epilepsy	Thank you for your comment, and we do appreciate that this is a complex issue. Levetiracetam has been positioned within the restraints of the evidence available. Further, its position will become clearer once generic pricing is available. Similarly, 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. Please also refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, and to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC seizures and IGE.
SH	ESNA	1	Full		39 -40	Suggesting depot provera should be given 10 weekly instead of 12 weekly in combination with Carbamazepine is contrary to all recent publications in this area that suggest 12 weekly administration is effective. If left unchanged this will be confusing.	Thank you for your comment. This recommendation has been removed from the guideline as the GDG considered it was no longer valid.

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SH	Glaxosmithkline UK Ltd	3	Full	Appendices S-T	General	GSK acknowledges the rationale and implementation of the alterations to the economic modelling and resultant additional analyses.	Thank you for your comment.
SH	Glaxosmithkline UK Ltd	4	Full	General	General	GSK acknowledges the amendments made to the draft clinical guideline post consultation 2 and continues to look forward to the publication of this guideline and the value it will bring to patients and the NHS.	Thank you for your comment.
SH	Glaxosmithkline UK Ltd	2	NICE	1.9.3	26 -27	GSK acknowledges the changes made to section 1.9.3 of the NICE guideline.	Thank you for your comment.
SH	Glaxosmithkline UK Ltd	1	NICE	1.9.3.6	27	NICE has now issued a TAR for retigabine (Trobalt) as part of a single technology appraisal (TA232): "Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate has not provided an adequate response, or has not been tolerated." http://guidance.nice.org.uk/TA232/Guidance/pdf/English The guidance is in line with the NICE clinical guideline section 1.9.3.6. To ensure consistency of the information provided to the NHS, it would seem appropriate to make reference to TA232 in this section of the clinical guideline.	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
PR	NETSCC, HTA –Referee 1	1	Full	General		The work has fulfilled the declared intentions of the scope.	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	2	Full	General		The methods employed are valid and comply with NICE's Guidelines Manual	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	3	Full	General		Overall, I think the quality of the health economics analysis is very good.	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	4	Full	Appendices P to S		As far as I could discern, it is only in appendix S that the year of the prices used for costs is explicitly stated (page 79, line 7). In footnote c on page 83 it is stated that the costs for the evaluations for focal seizures are expressed in 2010/11 prices, but I could not find any statements to this effect in the relevant appendices. An explicit statement of year of prices should be made in each appendix.	Thank you for your comment. The costing year (2010) has now been inserted into the relevant sections of Appendices P through S.
PR	NETSCC, HTA –Referee 1	5	Full	Appendices P to S		I appreciate the GDG considered the issue of whether or not to include the costs associated with adverse events and side effects in the model, and decided it was	Thank you for your comment. It would have been ideal to

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						OK not to include them on the grounds that they could be assumed to disappear with dose adjustment or treatment withdrawal, and can be expected to require no further treatment. While this may be true, it doesn't sit comfortably with me. Is there no way that the potential impact of adverse event/side effect costs could be investigated in the models? The SANAD trial reported frequencies of adverse events – could these not be used in some way? On a related issue, is it not possible that the data from Jacoby et al on the frequency of patient contacts with various health services include contacts to manage adverse events/side effects?	incorporate costs/disutilities associated with individual drugs; however for a variety of reasons, it's not practical given the data we have available. The trials report incidence of adverse events/side effects but they do not give any indication of how those individual Adverse Effects (AEs) affected treatment consequences. In other words, based on the evidence we have (RCTs and SANAD), we are unable to differentiate between AEs that resulted in a change of treatment and those that were tolerable enough to carry on with the same drug. Therefore it would be very difficult to estimate and apply some kind of weighted disutility or cost to either those who withdraw due to adverse events or to those who carry on with the same drug treatment. Furthermore, the GDG made the point that there is an enormous degree of variation between patients as to what one is willing to tolerate in order to avoid seizures (i.e. some patients find a side effect like memory problems tolerable whereas others do not – and this depends slightly on the severity/impact of the seizures at baseline). As you correctly identify, some of the data from Jacoby et al would be likely to capture some of the

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							miscellaneous resource use associated with drug treatment, including management of adverse events/side effects. Although Jacoby et al do not state the reasons for health care contacts specifically in their costing study, 96% of adults and 87% of children were on AED therapy and presumably some may have been experiencing or had experienced adverse events/side effects arising from treatment. When estimating the costs of starting or switching AED therapy for the economic model, we also allowed for several GP and neurology specialist consultations in order to account for the dose adjustment and management of adverse events/side effects issue. In conclusion, the GDG did not think that the exclusion of costs/disutilities associated with AEs was likely to impact the results or the conclusions of the analyses.
PR	NETSCC, HTA –Referee 1	6	Full	Appendix Q		I'm afraid I found Table 30 on pages 49-50 difficult to interpret. Some text describing the data in the table would be very helpful.	Thank you for your comment. We have reconsidered inclusion of this table and ultimately decided to delete it and present important results in a narrative fashion. We think this makes the findings clearer.
PR	NETSCC, HTA –Referee 1	7	Full	Appendix Q		When considering changes in the cost of levetiracetam (page 50), it is not clear to me why LEV is compared to topiramate when lamotrigine is excluded. On the whole I found this section, and Table 31 in particular, difficult to understand	Thank you for your comment. We have tried to make this section clearer, both through better

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							labelling in the table as well as explanatory text.
PR	NETSCC, HTA –Referee 1	8	Full	Appendix Q		Should the ICER of £296,500 (page 52, line 28) and that of £298,500 (page 50, line 15) correspond with one another?	Thank you for your comment. Ideally, for technical accuracy these figures should match given that neither oxcarbazepine nor levetiracetam were subject to variation in this particular sensitivity analysis. However, because all deterministic sensitivity analyses were performed probabilistically, there were occasionally slight variations from the base case. In this case, the total cost for the adjunctive levetiracetam strategy was £4 more costly than in the base case, whilst the total cost for adjunctive oxcarbazepine was the same. The QALY difference between the strategies in the sensitivity analysis was the same as in the base case. This extra £4 resulted in an ICER between the strategies increasing from £296,500 (from the base case) to £298,500 in the sensitivity analysis.
PR	NETSCC, HTA –Referee 1	9	Full	Appendix Q		On page 53, line 38 the report states that if patients have tried one or both of lamotrigine and oxcarbazepine, then gabapentin should be recommended for adjunctive therapy. This contradicts what is aid in lines 30-33 on page 53, i.e. if patients have not tried both lamotrigine and oxcarbazepine, then they are likely to be cost-effective adjunctive therapies. It is my understanding that it is only if patients have tried both lamotrigine and oxcarbazepine that gabapentin should be recommended. If they have only tried one, then the other should be tried as an adjunctive drug.	Thank you for your comment. We have amended the text to make this point clearer.
PR	NETSCC, HTA –Referee 1	10	Full	Appendix R		The same point as the previous one can be made in relation to the statements in lines 7-9 and lines 43-44 on page 76.	Thank you for your comment. We have amended the text to make

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							this point clearer.
PR	NETSCC, HTA –Referee 1	11	Full	Appendix P		Page 17, line 13: insert 'of' between 'estimates' and 'GP'	Thank you. This has been inserted.
PR	NETSCC, HTA –Referee 1	12	Full	Appendix P		Page 20, line 27: delete 'costs'	Thank you. This has been deleted.
PR	NETSCC, HTA –Referee 1	13	Full	Appendix P		Page 23, line 3: replace 'X' with the appropriate number	Thank you. This has been corrected.
PR	NETSCC, HTA –Referee 1	14	Full	Appendix P		Page 29, line 35: replace 'with' with 'which'	Thank you. This has been corrected.
PR	NETSCC, HTA –Referee 1	15	Full	Appendix R		Page 57, line 7: '6' needs to be a superscript	Thank you. This has been corrected.
PR	NETSCC, HTA –Referee 1	16	Full	Appendix R		Page 63, line 4: Missing reference	Thank you. The reference has been inserted.
PR	NETSCC, HTA –Referee 1	17	Full	Appendix R		Page 75, line 26: 'Incorporate' should be 'incorporated'	Thank you. This has been corrected.
PR	NETSCC, HTA –Referee 1	18	Full	General		I would judge the recommendations arising from the economic evidence to be justified and complete	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	19	Full	General		The limitations of the economic evidence are, by and large, highlighted and discussed.	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	20	Full	General		For such a large document, the authors have done a good job in terms of presentation and readability.	Thank you for your comment.
PR	NETSCC, HTA –Referee 1	21	Full	General		The research recommendations pertaining to the economic evidence are clear and justified.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	1	Full	General		no – the guideline seems to have fulfilled the declared intentions of (a) comprehensively updating the 2004 guideline, and (b) having dedicated sections on pregnant women, the older patients, and those with learning disabilities.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	2	Full	General		Yes. In all aspects the quality of the methods seems high, and the methodology seems consistently appropriate to the task at hand.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	3	Full	General		As far as I can tell, all the methodology complies with NICE's Guidelines Manual	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	4	Full	General		have not commented on the health economics as this is out with my expertise as a clinical trialist / statistician	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	12	Full	General		did not identify any recommendations which were out of kilter with the evidence presented.	Thank you for your comment.
PR	NETSCC, HTA	13	Full	General		Through previous primary research (as a collaborating statistician) I am reasonably	Thank you for your comment.

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	–Referee 2					knowledgeable about some of the evidence base, and this subset seemed accurately updated from 2004 and appropriately summarized. As a methodologist, I am not able to comment on the subject matter of the rest.	
PR	NETSCC, HTA –Referee 2	14	Full	General		Yes. There is a clear methodological approach stated which seeks to systematically 'score' the evidence, with an initial score of high quality and then points deducted for pre-specified methodological failings. As such the limitations of the evidence – including complete absence of evidence – are systematically described.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	15	Full	General		For each recommendation, there is then a specific discussion of how the limitation in the evidence might influence the robustness of the interpretations.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	16	Full	General		The report is excellently presented. The structure is logical and clear, and the recommendations flow from the presentation of the evidence.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	17	Full	General		It was interesting that all the evidence summaries were narratives, and there were very few graphs e.g. forest plots to summarise the most recent meta-analysis on a topic. However, given the length of the Guideline, and that this level of detail and presentation would be available in the source publications, this was understandable and appropriate.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	18	Full	General		The research recommendations seemed to follow clearly from the evidence summaries and narratives regarding each intervention for every patient subgroup considered.	Thank you for your comment.
PR	NETSCC, HTA –Referee 2	19	Full	General		The only major concern I had reading the Guideline was the lack of prominence given to discussion of the fundamental issues of first the misdiagnosis of epilepsy and second, once epilepsy is diagnosed, the misclassification of what the type of epilepsy was. Although the authors did a good job of examining the evidence for both these aspects, this did not seem to be emphasized in the recommendations for research or in the recommendations sufficiently clearly. That is, more research is needed on the issues of diagnosis and classification, and until we are confident in both, relying on detailed guidelines on highly structured sequential approaches to treating different epilepsies needs considerable caution. First off, you may be treating the wrong epilepsy, and more insidiously, the entire evidence base to date is likely to be contaminated with these underlying issues of misdiagnosis and misclassification.	Thank you for your comment, however it relates to an issue outside of the scope of the update of this guideline. We appreciate that this issue of diagnosis is of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.
PR	NETSCC, HTA –Referee 2	20	Full	Preface		'new GMS contract' – spell out GMS	Thank you for your comment. This has been revised.
PR	NETSCC, HTA –Referee 2	29	Full	General		The authors talk of odds ratios and then Page 140 line 1 it is hazard ratios – but in Table 10-29 it is 'relative risk' – is this a generic term to cover all these statistics? And also, in the Table – 'multivariate' looks like it should be 'multivariable'?	Thank you for your comment. However we are unable to modify this section as it pertains to the 2004 guideline methods and

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							evidence review.
PR	NETSCC, HTA –Referee 2	26	Full	10.1	124 Line 18	'2009 PPRS' – spell out PPRS.	Thank you for your comment. This has been revised.
PR	NETSCC, HTA –Referee 2	27	Full	10.2 1	133 Line 4	(and elsewhere in the report) ' There were no significant differences … 60% vs 61%' – useful wherever possible to give the difference between the randomised groups and the associated 95% confidence interval, not just isolated point estimates.	Thank you for your comment. However we are unable to modify this section as it pertains to the 2004 guideline evidence review.
PR	NETSCC, HTA –Referee 2	28	Full	10.2.6	136 line 17	(and elsewhere) – will it be generally understood what a 'failsafe plan' is?	Thank you for your comment however it relates to an issue outside of the scope of the update of this guideline. We appreciate that this issue is of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.
PR	NETSCC, HTA –Referee 2	10	Full	10.32	147 Line 9	I did not really understand fully the rationale for this 'threshold of contamination' approach – whilst appreciating the problem that if the results are aggregated within a trial report on different types of epilepsy, then there is a danger of swamping an analysis with irrelevant findings, nonetheless completely excluding a trial seems drastic. The worry would be that the more pragmatic trials taking 'all comers' might be more likely to be excluded. Did the authors consider any sensitivity type analyses where such trials were added in, and/or downweighted somehow to reflect the mixture?	Thank you for your comment. The GDG accepted that these thresholds, whilst arbitrary, reflect the degree of imprecision in clinical practice and likely inclusion error. Studies were excluded where the proportion of patients with the seizure type of interest was less than the cut off point for both focal and primary generalised seizures. We did not conduct sensitivity analysis where such trials were included. The trials which were excluded on the basis of contamination were mainly from the adjunctive therapy for focal seizures review where there was

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							a lot of data from studies which did match our criteria.
PR	NETSCC, HTA –Referee 2	21	Full	1.2	22 Line 22	'60% of people have convulsive seizures' – ambiguous – presumably that is 60% of epileptics?	Thank you for your comment. This has been revised to read 60% of people with epilepsy.
PR	NETSCC, HTA –Referee 2	22	Full	1.4	25 Line 4	Couldn't make sense of the numbers – '…15.5 billion; the cost of antiepileptic drug use being E400,000' – 400,000 for a lifetime? Need to state clearly the unit of time.	This is cost in 2004; ie for 12-monthperiod. Wording has been altered to clarify in the text.
PR	NETSCC, HTA –Referee 2	23	Full	1.5	26 Line 21	'a majority of children (77%, 17/22)' – this is a very small sample size, and the authors should put a 95% confidence interval around this to emphasise that this estimate is very imprecisely estimated, and then reflect that in the use of the estimate in the report?	Thank you for your comment. However we are unable to modify this section as it pertains to the 2004 guideline introduction.
PR	NETSCC, HTA –Referee 2	11	Full	1.6	27 Line 14	'… and despite some of the perceived methodological limitations' – this describing SANAD, which is stated as being one of the major reasons to update the guideline. Really need to be more specific about what these methodological limitations are – elsewhere buried in the detail there is mention of it being open, rather than blinded, for example – but is this the extent of the 'methodological limitations'? These should be described and discussed more fully in this dedicated section. Also, why 'perceived' – is there dispute about this? Also, might be worth making explicit that Prof Tony Marson was the SANAD chief investigator and an external peer reviewer of the guideline?	Thank you for your comment. Full details of the quality assessment of the SANAD trial can be found in the relevant seizure type/syndrome evidence review chapters and Appendix N of the full guideline. Professor Tony Marson and Dr Catrin Tudur Smith are listed as expert reviewers in the guideline development group members section. DOI forms were completed, submitted and reviewed by the guideline development group in accordance with accepted NICE processed.
PR	NETSCC, HTA –Referee 2	24	Full	2.23 and 2.24	30-31	For both the 2004 and 2011 writing/development groups, there does not seem to be a statistician named?	Thank you for your comment. The project teams for both the 2004 and 2012 felt that a statistician would not be required as a full GDG member.
PR	NETSCC, HTA –Referee 2	25	Full	2.3	32 Lines	In 2004, there were 72 KCQ's; in 2011 there were just 22. It would be useful to explain what the reduction was driven by e.g. whether the 72 were updated and	Thank you for your comment. There were 22 **new** questions in

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					13 and 21	these 22 were new and distinct from the 72; or at the other extreme the 22 were a direct subset of the 72, with the other 50 no longer considered of interest and/or relevance?	the 2011 guideline, as this was a partial update of the pharmacological management section and not a full update of the 2004 guideline.
PR	NETSCC, HTA –Referee 2	9	Full	2.41	33 Line 18	It would seem that in neither the 2004 nor this 2011 update 'no systematic attempt was made to search 'grey literature'' – given that much of the evidence base is sparse and labeled as being of 'very poor quality' this seems a bit of a surprising omission – it could have been that for some of the less mainstream topics, the grey literature may have held useful information? It would be worth discussing this as a possible limitation, perhaps?	Thank you for your comment. We acknowledge that this may be more relevant for the topics covered under the 2004 guideline. However for the 2012 update guideline, there was a good body of evidence on RCT data for almost all the defined clinical questions.
PR	NETSCC, HTA –Referee 2	6	Full	2.6	37 Line 3	'Fixed effects (Mantel-Haenszel) techniques were used to calculate risk ratios' – some analysts prefer random effects models when there is considerable heterogeneity – did the authors consider this approach, and/or meta-regression to understand the sources of heterogeneity – in these analyses? For example, length of follow up and dose might be potentials drivers of heterogeneity in this context?	Thank you for your comment. We have checked the data for random effects models where there was considerable heterogeneity and this did not alter the result significantly. This is now more accurately reflected in the relevant section of the guideline.
PR	NETSCC, HTA –Referee 2	7	Full	2.7	37 Line 36	'one high quality individual patient data network meta analysis' – good to see the IPD analyses included, but it was not completely clear how the authors had avoided included the data twice – once from the individual study, and once again from the studies inclusion in the IPD network meta analysis?	Thank you for your comment. The guideline analyses focus on the pair-wise comparisons between treatments and/or placebo. The IPD NMA estimates the indirect treatment effect of A versus B using evidence from trials comparing drug A with C, and trials comparing drug B with C, so the data was not included twice and is a logical next step following individual pair-wise meta-analyses.
PR	NETSCC, HTA –Referee 2	8	Full	2.7	39 Line 17	'Any trial dose outside these ranges was not included in the meta-analysis' – how many sections were affected by this and how many trials were excluded as a result – this seems a bit arbitrary, and not just in terms of efficacy but also more	Thank you for your comment. Most of the exclusions were particular arms of the trial where

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						importantly in terms of safety seems a bit odd leaving these trials out?	the dosage was outside of the advised range. We included the other arms of the trial (if within range) in the meta-analyses. Five trial arms were completely excluded due to dosage. These are detailed in the relevant section of the guideline.
PR	NETSCC, HTA –Referee 2	5	Full	2.7	40 Line 38	The only major methodological comment I have concerns the statement '… we needed to recalculate the data reported in studies based on the assumption that participants who were missed out did not experience the event of interest' – several points: 1. This is a crude way of dealing with missing outcomes, and makes a very strong assumption about the data. 2. So were the findings presented robust to this tactic? For example, did the authors run a sensitivity analysis in which this assumption was not made, and the data from the trials analysed as reported? 3. If the trial was high quality, and the proportion of missing outcomes was small (e.g. <5% of those randomised), and roughly equal between randomised groups, then probably little bias will accrue. However, if these missing outcomes are more extensive, and if there is differential missingness between the arms, then the bias can be serious by assuming all missing outcomes are negative – indeed, in extreme it can overwhelm the estimated treatment effect. 4. Also, assuming all the missingness is at one level inflates the information in the sample and tends to reduce the variability. We should see more information and justification on this aspect of the analysis, with reassurance that it did not overly influence the findings.	Thank you for your comment. 1. ITT data analysis was selected for the 2012 guideline as it is often recommended as the least biased way to estimate intervention effects in randomized trials and is considered the most conservative analysis for tests of differences of drugs. We have highlighted the limitations to this approach in the methods section to ensure that it is clear that we have used a conservative approach to analyse the data. 2. Thank you for your comment. We have conducted a sensitivity analysis where there was a high differential drop-out of participants (over 20% difference) to confirm whether findings were robust to our approach. This was only found in the older people review. We acknowledge that this was not adequately reflected in the methodology section or the individual chapters. This has now been amended. For information, we did not look at studies from the focal and generalised tonic-clonic

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							reviews as we felt that this issue was covered by the IPD network meta-analysis. However we did test the difference of using available case analysis rather than the ITT method of analysis on outcomes where a study had a differential drop-out over 20% in the older people review. The outcomes that changed were seizure freedom (from significant to non-significant), incidence of poor co-ordination (from non-significantly higher to significantly higher in the carbamazepine arm compared to the lamotrigine arm) and incidence of dizziness (from non-significantly higher to significantly higher in the carbamazepine arm). As the recommendation for older people was based on adverse events and not seizure freedom, it did not change the recommendation as the evidence to recommendations states that 'carbamazepine had significantly higher incidence of death and somnolence compared to lamotrigine but there was no significant difference between the two drugs when carbamazepine was in the sustained-release formulation'. The findings from available case analysis increased the amount of adverse events for the carbamazepine arm compared to the ITT results. The carbamazepine sustained-release

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							study did not have a differential drop-out so those results remained. This has now been reflected in the relevant methodology section and discussed in the full guideline.
SH	Nottingham University Hospital Trust	2		1.9.3.3	26	As above	Thank you for your comment. We have now further revised this recommendation to provide greater clarity on when to consider recommending Levetiracetam.
SH	Nottingham University Hospital Trust	1	Full	1.9.3.2	26	NICE clearly have a fixed view about Levetiracetam that no amount of comment will change. 10 years of clinical experience with approaching 4000 patients with epilepsy, more than half of which have focal epilepsy suggests that adding another sodium channel drug if CBZ or LTG have not controlled seizures does not work. The retention rate studies demonstrate the greater effectiveness of Levetiracetam over other add on drugs in this situation. If LTG is poorly tolerated it is reasonable to try CBZ next. I believe it utterly unreasonable to have to try all four first line drugs before moving on to Levetiracetam if current cost does not change. I think it deplorable to recommend that patients have to put up with the serial drug changes that I doubt will be beneficial or they should with cope the significantly greater side-effects of valproate, rather than try Levetiracetam. NICE boldly talks about "patient centred care". Do NICE really mean it? I will be ignoring the advice in this subparagraph. The rest of the guide has much to admire about it.	Thank you for your comment. We have now further revised this recommendation to provide greater clarity on when to consider recommending levetiracetam.
PR	Peer reviewer – 1	1	Full	General		Whether it was possible for guideline recommendations and analysis to include children ranging from 28 days to 17 years but I will leave for other colleagues comments as well.	Thank you for your comment.
PR	Peer reviewer – 1	2	Full	Appendices		I have no comments to make on K, N, O, P, Q, R, S.	Thank you for your comment.
PR	Peer reviewer – 1	3	Full	General		Being a paediatrician, I have more knowledge of epilepsy in children compared to adults.	Thank you for your comment.
SH	Pfizer Ltd	1	NICE version	1.9.3.6	27	As noted in our previous response to the second consultation, under the heading *"Adjunctive treatment in children, young people and adults with refractory focal seizures"* the footnote for 'pregabalin' still reads: *"At the time of publication ([month year]), this drug did not have UK marketing authorisation for this indication and/or population (see appendix E for details).*	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

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						Informed consent should be obtained and documented." We remain concerned that this footnote could be misinterpreted to suggest that pregabalin is not licensed for refractory focal seizures. However, pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation. It would be clearer if the footnote specified that "*at the time of publication, pregabalin did not have UK marketing authorisation for use in children (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 is detailed in appendix E.	licensing footnotes and is in line with NICE editorial guidance on advice for drugs without marketing authorisation for specific indications. In order to keep footnotes to a minimum we included the same footnote and so more details can be given in appendix K.
SH	Royal College of Nursing	1	Full	General	General	RCN's main concern is to ensure the document explicitly outlines the need to consider issues around epilim and the female of childbearing age.	Thank you for your comment. The GDG feel that advice is appropriately reflected in all relevant recommendations referring to sodium evaporate.
SH	Royal College of Nursing	2	Full	General	General	There is a need to reflect practice in terms of the use of Keppra for Idiopathic Generalised Epilepsy. (This is important when women of childbearing age are considered.)	Thank you for your comment, and we do appreciate that this is a complex issue. 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. Please also refer to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC seizures and IGE.
SH	Royal College of Nursing	3	Full	General	General	My feeling is this document is a vast improvement on the initial versions which were absolutely at odds with practice and whilst it is not perfect – the support seems reasonable now.	Thank you for your comment.

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SH	Royal College of Paediatrics and Child Health	6	Full		145	Recommendation 83 would be better worded: '…discuss the possible risks of malformation and disordered neurodevelopment…'. Use of the term 'neurodevelopmental delay' implies that there will be neurodevelopmental 'catch up', which might not be the case. This could thus be confusing for parents and set unrealistic expectations that may become entrenched.	Thank you for your comments. The GDG acknowledged your concerns and have revised the recommendation to read "neurodevelopmental impairments".
SH	Royal College of Paediatrics and Child Health	9	Full	Appendix O	3	It is hard to believe that carbamazepine is significantly better that sodium valproate. We note this requires further research.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	8	Full	Appendix K	4	We note that sodium valproate is first drug of choice in generalised tonic-clonic seizures, not carbamazepine.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	7	Full		516	In recommendation 207, the term 'disordered neurodevelopment' would be preferable to 'neurodevelopmental delay'.	Thank you for your comments. The GDG have acknowledged your concerns and have revised the recommendation to read "neurodevelopmental impairments".
SH	Royal College of Paediatrics and Child Health	1	Full	General	General	We think the guidance is fine.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	2	Full	General	General	We think the guidance is fine. The guidance appears to be generally sound, given the at times very limited evidence base the authors have to go on. Overall, it is clear and comprehensive, and offers helpful guidance to relevant clinicians.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	3	Full	General	General	We found the guidelines generally very detailed, useful and reasonably easy to follow.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	4	Full	General	General	We note it is being increasingly recommended that discussions should be held with, and referrals made to, epilepsy specialists. Hopefully, Paediatric Neurology services have sufficient capacity to accommodate this increased workload.	Thank you for your comment.
SH	Royal College of Paediatrics and Child Health	5	Full guidel	General, but	General	There is very little mention of the potential risks of using certain anticonvulsants in Inherited Metabolic disorders (IMD). Specific risks particularly relate to the usage of sodium valproate, which can have potentially life-threatening consequences in some	Thank you for your comment. The GDG acknowledge the concern about sodium valproate use in

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			ine, NICE guideline, Appendices	particularly relevant to sections on pharmacological treatment: Section 1.9 of NICE guideline, Section 10 of full guideline and appendix K		groups of IMDs, especially mitochondrial respiratory chain disease, urea cycle defects and fat oxidation disorders. There is a growing body of evidence relating to the potentially fatal consequences of using valproate in certain mitochondrial disorders (see attached paper JD Stewart et al, *HEPATOLOGY* 2010;52:1791-1796 and references from Dr James Davison, IMD clinical fellow at Birmingham Children's Hospital). Other anticonvulsants may also carry certain risks in IMDs. These risks must be specifically highlighted in the relevant sections.	metabolic disorders. However this is not new. Moreover much of the early concern about valproate induced hepatotoxicity is now thought to have been the result of an underlying metabolic disorder. Those most at risk are the very young, where the underlying diagnosis may be unclear. In those where the cause is known eg malformations of cortical development, valproate may be an extremely useful AED. For this reason the GDG feel that the existing guideline, 'that all children presenting with epilepsy under the age of two years, should be discussed with tertiary care', remains adequate and no further adjustment is required.
SH	Royal College of Physicians	1	Full	General		Please take this email as confirmation that the Royal College of Physicians wishes to endorse the comments submitted by the Association of British Neurologists to the above consultation.	Thank you for your comment.
SH	Sanofi	1	Full	General	General	We agree with the UK Group of Consultant Epileptologists' recommendation to include a specific statement concerning the use of sodium valproate in women of child-bearing potential, and welcome the decision of the GDG to include this in the latest draft. Sanofi has and will continue to provide appropriate information and warnings in relation to the potential side-effects and risks associated with the use of sodium valproate, including possible risks to the unborn child, in line with developing scientific knowledge. The management of women of child-bearing age who have epilepsy is highly challenging as uncontrolled seizures in pregnancy may pose substantial risks to both mother and unborn child. Such risks must be balanced against the fact that sodium valproate remains the most effective treatment of generalised epilepsy and, for some patients, it is the only medicine that will provide adequate seizure control. Sanofi advises women with epilepsy who plan to or who may become pregnant to speak to their doctors to seek the most appropriate treatment for their condition, and consider it appropriate that the Guideline also conveys this message.	Thank you for your comment. The GDG considers that this is fully explored in recommendations 1.9.1.11 and 1.15.1 4. Please also refer to sections 10.2.8 and 13.5.5 of the full guideline for further details of the GDG considerations that underpin these recommendations.

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SH	Society of British neurological surgeons					*No comment*	Thank you for your comment.
SH	Society of British neurological surgeons					No comment	Thank you for your comment.
SH	UCB Pharma Ltd	4	Full	10.3.4.3	154 (lines 1-8)	We maintain our objection to subset analysis on withdrawals in the Brodie *et al* study. Statistical analysis may provide a p-value but this is in effect meaningless since the end-point is not adequately powered within the study. Furthermore, dividing withdrawals into sub-sets presents a picture that can be misleading to clinicians and payers alike by clouding the amalgamated withdrawals that are more clinically relevant.  Microsoft Office Word 97 - 2003 Docu	Thank you for your comment. The GDG considered that for the purposes of the decision-making in terms of development of the guideline recommendations it would be useful to have data regarding withdrawal due to adverse events and withdrawal due to lack of efficacy separately.
SH	UCB Pharma Ltd	1	Full	10.3.9	202-207	UCB fully acknowledge the need for levetiracetam to demonstrate cost-effectiveness prior to being recommended as a first line treatment option for focal seizures. There is a risk however that clinicians will read recommendations 85 and 86 (p 202) and consider this as complete guidance for the first-line management of focal seizures in children, young people and adults. It is possible that the physical separation of recommendations 85 and 86 concerning treatments (page 202) and the cost effectiveness of levetiracetam in recommendation 87 (page 207) will prevent levetiracetam from being fully utilised. Since it is highly likely acquisition costs will have fallen to 50% of the June 2011 level by the date of publication (see outline below on generic entry) it would be helpful if there was more of a natural link between recommendations 85, 86 and 87. We ask that recommendation 86 is amended to add in levetiracetam, acknowledging its use is subject to it achieving a defined cost-effectiveness threshold. This re-organisation of recommendation 86 may enable improved interpretation and implementation of the guideline over its lifespan and be more reflective of levetiracetam's acceptable cost-effectiveness which will be the prevailing price for the lifespan of the updated guideline.	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.

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SH	UCB Pharma Ltd	2	Full	10.3.9	207	There are currently three companies with confirmed marketing authorisations to supply generic levetiracetam into the UK. Consilient Health is already supplying generic product to the marketplace. We understand that the actual sale price being offered to customers by Consilient are already up to 80% below June levetiracetam (Keppra ®) prices. In addition, information sourced from the marketplace states that several other generic manufacturers (Teva, Dr Reddy, Sandoz, Lupin, Ranbaxy, Wockhardt, Mylan, Ratiopharm, Actavis) will launch their own generic levetiracetam in the coming 3 months. As of September 1st UCB will have in place price agreements with large chain pharmacies covering 65% of Keppra dispensing outlets at a price reduction of 52% compared with prices in place in June 2011. These agreements will help ensure patients established on Keppra can continue to receive their medication. UCB will continue to seek price agreements with the aim of covering up to 75% of the prescriptions dispensed, allowing pharmacy chains to purchase Keppra at a competitive price to the generic entrants. The Drug Tariff reflects the "real" cost of medicines to the NHS. It is the cost that the NHS must re-imburse pharmacists for the medicines they have dispensed to patients. The last genericised anti-epilepsy medicine, topiramate, became available in October 2009. The Drug Tariff price had caught up with actual commercial prices such that within four months of generic entry the drug tariff price fell by 50%. Given existing sale prices from UCB, Consilient Health and others a drug acquisition cost below 50% of those for June 2011 is anticipation by the close of January 2012.	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.
SH	UCB Pharma Ltd	3	Full	10.3.9	207	**Recommendation 87 contains the line '(levetiracetam) can be acquired for a cost of at least 50% less than current 2011 unit prices'** This guidance offers important challenges for the healthcare professional using the guidance:	Thank you for your comment. We appreciate the importance of your comment and the GDG has made further revisions to recommendation 1.9.3.3 of the NICE guideline.

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						• Current wording does not make it clear how to measure a 50% price fall. The reference Drug Tariff acquisition cost should be June 2011, the last month prior to generic levetiracetam availability. • Acquisition costs for different strengths and formulations will erode at different rates. We ask that NICE reference the full pack price of the most commonly used strength of levetiracetam, 500mg tablets –which accounts for 40% of all levetiracetam sales – and will likely be indicative of the price of the range of presentations. • The majority of epilepsy prescriptions are initiated (though not prescribed) in the secondary care outpatient clinic setting. It is unlikely that such clinicians will be familiar with the Drug Tariff and how to make the appropriate comparisons. We ask that the guidance should state clearly that levetiracetam is cost effective if the 500mg pack price has fallen to £26.15, which is 50% of the June 2011 drug tariff price.	The GDG considered how to present the cost information in the recommendation and concluded that presenting health care professionals with the cost of an average daily dose of 1500 mg was most appropriate as this would enable them to make cost-effective decisions across a range of strengths and pack prices.
SH	UK Chapter of the International League Against Epilepsy (ILAE)	1	Full	General		We remain concerned that the limits of revision of the Epilepsy Guideline have been confined to a pharmacological update, despite the clear need for a more general update in the entire Guideline, with particular respect to the classification of seizures and the epilepsies in children and adults. However, within this limited scope of the update, we recognize that NICE has heard some of the concerns voiced during the first consultation, and has made important improvements, further additions and changes to this second revision.	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. We appreciate that this issue is of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.

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SH	UK Chapter of the International League Against Epilepsy (ILAE)	2	Full	1.9.1.11 (and elsewhere).		The greater emphasis upon and clarity of the need for special precautions when considering prescribing sodium valproate to women of childbearing potential is welcome and very necessary. This was a very major shortcoming of previous drafts of the Guideline.	Thank you for your comment.
SH	UK Chapter of the International League Against Epilepsy (ILAE)	3	Full	1.9.3.3.		The recommendation that levetiracetam might be prescribed as a first line therapy for partial onset seizures, provided it can be acquired at <50% of current 2011 costs (anticipating a fall in price soon) is welcome and pragmatic, and brings the document more into line with current expert practice.	Thank you for your comment.
SH	UK Chapter of the International League Against Epilepsy (ILAE)	4	Full	1.9.3.6.		The inclusion of a specific precaution regarding consideration of prescribing vigabatrin with regard to the high risk of visual field defects is a mandatory and welcome addition.	Thank you for your comment.
SH	UK Chapter of the International League Against Epilepsy (ILAE)	5	Full	1.9.3.6. and general		Retigabine has been approved by NICE as adjunctive treatment for epilepsy since the last draft was out for consultation. It would be sensible and practical to include retigabine in the alphabetical list of adjuvant treatments available for prescription to adults with resistant partial seizures.	Thank you for your comment. Reference to the STA on retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	UK Chapter of the International League Against Epilepsy (ILAE)	6	Full	1.9.4.4.		Levetiracetam is still not included recommended as a first line treatment for generalized tonic-clonic seizures, even were its cost to fall as expected. This omission is of concern since levetiracetam is currently widely recommended in this situation by clinical experts, on the basis that the benefit to risk ratio in a young woman with epilepsy would favour prescribing levetiracetam rather than sodium valproate (because of stark differences in their known teratogenicity risks)	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. Please also refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, and to sections 10.5.9 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for GTC

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							seizures and IGE.
SH	UK group of Consultant Epileptologists	1	Full	General		The UK group of Consultant Epileptologists welcomes the inclusion of some of our suggestions in the revised documents. 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. Here are some of key points while also emphasising that there are many more that we do not endorse.	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, as it was agreed that substantial evidence that had been published warranted an update of this section. We appreciate that these issues are of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.
SH	UK group of Consultant Epileptologists	2	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 General Assembly, it has met with significant criticism published in two issues of Epilepsia and a new ILAE Commission is working for a new proposal. Your response to our initial points (in italic) are incorrect and misleading as we explain (in regular font): You say: *The classifications of the epilepsies so published by the ILAE have always been under the heading of a "proposal" rather than formal "acceptance"*. This is incorrect. The two ILAE proposals on classifications of 1981 (seizures) and 1989 (syndromes) have been formally accepted by the ILAE General Assembly as the official ILAE position on classification. You say: *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 is also* incorrect: "The current proposals" are just quadrennial interim reports. A new ILAE Commission is now working on these and there may be considerable changes when submitted to the ILAE General Assembly at the 2013	The GDG remain of the opinion that the guideline should move in line with the proposals of the ILAE. For the new proposal, some reorganisation is proposed but the list of syndromes remains as previously. Many of the syndromes would not exist if we continued with the endorsed proposal of 1989.The ILAE commission is currently working on a diagnostic manual, and 'fine tuning' towards an endorsement. Further clarity has been added within the guideline, particularly within the glossary, highlighting

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						International Epilepsy Congress for approval as the official ILAE position on classification. Please, consider the following contradictions. In Table 9.7 you propose to discard terms such as "idiopathic", "generalised" and "focal" epilepsies but these are repeatedly used in the same NICE document as for example:10.13 Idiopathic Generalised Epilepsy (IGE) 10.13.4 Monotherapy for the treatment of Idiopathic generalised epilepsy 10.4.7 AEDs used as adjunctive therapy for adults with refractory focal epilepsy.	the areas where discussion is ongoing, for example, the discussion of idiopathic vs genetic. Terminology has been further clarified for consistency.
SH	UK group of Consultant Epileptologists	3	Full	58 et seq	4	The UK group of Consultant Epileptologists (as most of the stakeholders) remains concerned about some pharmacological recommendations in the revised guidance: (a). The inclusion of sodium valproate as first line AED for monotherapy in the treatment of focal epilepsies. The NICE meta-analysis is flawed for many reasons including that the studies considered are of brief duration and often biased. A number of adverse drug reactions may become apparent after many years of use. Pregnancy is an exclusion criterion for randomised control trials. The difficulties inherent in relying on such meta-analysis is illustrated by vigabatrin, which according to your analysis was found to be a well tolerated and low risk AED of relatively good efficacy. "The re-analysis to incorporate the time to event outcomes used in the IPD meta-analysis" that "ascertained the validity of the recommendation for first line treatment for focal seizures in light of this" is not re-assuring. The caveat "Be aware of teratogenic risks of sodium valproate" is inadequate because "teratogenicity" is not the only serious adverse effect of this drug in women. (b). The low rating of levetiracetam as monotherapy in focal epilepsies (after lamotrigine, carbamazepine, sodium valproate and oxcarbazepine) based on current price considerations (which do not reflect actual cost for the NHS) and despite the fact that generic levetiracetam is now widely available (see http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=levetiracetam&x=10&y=16). The recommendations for its use in juvenile myoclonic epilepsy after sodium valproate and at the same level with lamotrigine and topiramate may also be debatable. The caveat "Be aware that topiramate has a less favourable side-effect profile than lamotrigine, levetiracetam and sodium valproate, and that lamotrigine may exacerbate myoclonic seizures" underlines the inappropriateness of this pharmacological recommendations in juvenile myoclonic epilepsy.	Thank you for your comment. With reference to your points a and b, sodium valproate is only recommended after lamotrigine and carbamazepine have been tried and were considered unsuitable. It must also be noted that this recommendation is also for children and young people where sodium valproate can be used. The GDG feel that the issues related to teratogencity have been fully clarified and caution recommended in the relevant recommendations. Levetiracetam has been positioned within the restraints of the evidence available, Further, its position will become clearer once generic pricing is available. Similarly, the GDG felt the positioning of levetiracetam along with other options for JME was appropriate as there was no evidence identified in the systematic review or to support it

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						(c). The recommendation that oxcarbazepine is a first line AED for monotherapy in "IGE with GTCS only" is inappropriate and unsupported by evidence.	in preference over the other drugs. There is only such evidence for adjunctive therapy. Please also refer to section 10.3.9 of the full guideline for further details on the GDG considerations that underpin the recommendations related to focal seizures, to sections 10.7.6 and 10.13.16 of the full guideline for further detail on the GDG considerations that underpin the recommendations for myoclonic seizures, IGE (including JME), and GTC seizures only.
SH	UKCPA	1	Full	General		The UKCPA neurosciences committee have reviewed the consultation document related to The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care (update). The committee felt able to comment on Section 1.9.3 and 1.9.4 of the NICE guideline and appendix K. The other sections contained information beyond the scope of practice of the committee members. Many of the comments raised by the committee regarding the previous versions of the document have been addressed in previous reviews of the guidelines therefore the group largely supports the document but the committee have raised the following points for your consideration:	Thank you for your comment.
SH	UKCPA	3	Full	General		Could the guidance include consideration of retigabine which is a newly launched product - consideration of the product now will ensure that the guidance is current	Thank you for your comment. Reference to the STA on Retigabine will be added to the guideline in the related NICE guidance section for publication.
SH	UKCPA	2	Full	Appendix K Table 1	2	a) Clarity regarding the choice of medication for prolonged or repeated seizures and convulsive status epilepticus in the community - paraldehyde and olive oil enemas are used in practice and provide a useful alternative	Thank you for your comment however it relates to an issue outside of the scope of the

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						for some patients b) Consideration of the role of IV sodium valproate in status epilepticus. This is a useful first line treatment where phenytoin is contra-indicated c) Consideration of the role of IV levetiracetam in status epilepticus. This is a useful first line treatment where phenytoin and sodium valproate are contra-indicated	focussed 3rd consultation of the update of this guideline. We appreciate that these issue are of continued importance and we will ensure that your comments are forwarded to NICE to be held on record to inform any future update of this guideline.
SH	University hospital of South Manchester	1	NICE	1.9.4.1	27	I recommend a note of caution be made for valproate and the associated higher risk of hepatotoxicity in infants, especially young infants.	The GDG acknowledge the concern, and that many of the children presenting with hepatotoxicity are likely to have had an underlying metabolic defect. It was felt that this is addressed through the existing guideline that all children who present with epilepsy under the age of two years should be discussed with tertiary care.