

Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association of British Neurologists	Guideline	005	003	We have to ensure that this does not metamorphose into consultant neurologists with special interest in epilepsy/epileptologist or epilepsy specialist nurses only - a generally trained neurologist as 1st fit assessor should be acceptable given the number of referrals and paucity of "epilepsy specialist" in most places	Thank you for your response. We agree and the recommendation states the assessment should be carried out by a clinician or paediatrician who has the required expertise to assess a first seizure and diagnose epilepsy and this would include a general neurologist.
Association of British Neurologists	Guideline	005	016	Video footage should be shared using a secure platform linked to individual electronic health records	Thank you for your response. The handling and storage of patient data would be determined locally by the service provider.
Association of British Neurologists	Guideline	005	020	Change wording to 'Ensure person with first suspected seizure has had a 12 lead ECG'	Thank you for your comment. The committee consider the wording of the recommendation to be clear.
Association of British Neurologists	Guideline	006	010	EEG ideally within 72 hours is fine. In most places this is totally unachievable though	Thank you for your response. The committee acknowledge this can't always be achieved but the time-frame of 'within 72 hours' has been added to encourage a quicker ECG and ideally bring about a restructure where ECGs are offered sooner.
Association of British Neurologists	Guideline	006	020	If there is diagnostic uncertainty, ambulatory EEG would only be helpful if individual was having frequent events	While the Committee agreed that ambulatory EEG is most helpful if events were captured, it was also thought that interictal recordings could be very helpful. For example, it would aid diagnostic formulation if there were frequent inter-ictal spike wave discharges or subclinical seizures. As such, it was

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					not thought appropriate to limit ambulatory EEG to those in whom clinical seizures were frequent .
Association of British Neurologists	Guideline	009	005	This is a reasonable suggestion as it puts the onus on the neurologist and the suspicion of autoimmune aetiology	Thank you for your comment.
Association of British Neurologists	Guideline	010	010-011-015	Always discussing SUDEP at the 1st appointment I think is overly prescriptive and will also be unnecessarily frightening to many, one has to be far more sensitive about this.	Thank you for your comment. The issues to raise at the first appointment where those identified within the evidence review as being important to patients and their families or carers. The health care practitioner would need to tailor their discussions according to individual needs and circumstances as outlined in recommendation 2.1.2.
Association of British Neurologists	Guideline	010	010	Needs clarification, refers to self-managing 'epilepsy' but then talks about first appointment. SUDEP would be reasonable discussion in someone with newly diagnosed epilepsy to equip them with knowledge needed to inform decision about commencing anti-seizure medication.	Thank you for your comment. The committee have considered the wording and believe it is clear. The discussion of the points listed at the first appointment should support people to self-manage their epilepsy in the future.
Association of British Neurologists	Guideline	016	005	Rec 4.1.4 The authors are suggesting an add on treatment with second intention monotherapy rather than a sequential monotherapy that is what current evidence suggest especially when first monotherapy fails	Thank you for your comment, the committee asserted in their discussions that 'unsuccessful' could also mean there had been some partial response and therefore did not think it appropriate to completely remove the first drug before starting a new one. The aim is to remove the first drug whilst adding the second so that the second drug would be the only one they were taking, as outlined in the bullet points.

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Association of British Neurologists	Guideline	019	001	Rec 4.3.3 as it is phrased it means that any European should have a negative HLA screening test for CBZ, OXC and ESL. This is unrealistic.	Thank you for your comment. This recommendation has been revised so that it does not restrict prescribing of these drugs and the requirement for HLA screening has been removed. The recommendation now focuses on raising awareness that there can be a risk of serious skin reactions.
Association of British Neurologists	Guideline	019	001	Should patients be warned about the risk of arteriosclerosis before using Carbamazepine?	Thank you for your comment. It is not possible for the guideline to warn of all the risks of all the antiepileptic medications recommended. The guideline makes recommendations about the risk of serious skin reactions in phenytoin, carbamazepine, oxcarbazepine and eslicarbazepine acetate because this is an acute issue that would need to be dealt with immediately.
Association of British Neurologists	Guideline	022	023	There are quite a few patients with drug resistant epilepsy who are stable for many years who could be given "SOS" type appointments rather than annual reviews, we have to prioritise newly diagnosed patients and patient's early on in their epilepsy lives with difficult control	Thank you for your response. In this scenario the frequency would need to be determined in consultation with the individual based on their needs.
Association of British Neurologists	Guideline	024	003	the two year recommendation is rather ambitious for people who have achieved (eventually) seizure freedom after lots of tortuous medication trials- I think many of us	Thank you for your comment. It is not a requirement that medication is discontinued after 2 years. Rather, the recommendation states that an individualised assessment is carried out to determine if this is

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11/11/2021 – 22/12/2021

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				would be very reluctant to see this in a guideline, whilst two years would be appropriate for children/young adults who became seizure-free on the 1st medication, for others one should perhaps be more conservative nearer 3-5 years?	appropriate. If it is not then the person would remain on their medication.
Association of British Neurologists	Guideline	024	008	Rec 4.6.8 Would like to know the evidence about monitoring Levetiracetam blood levels in pregnancy when it is well known that Levetiracetam has quite considerable intra-individual and inter-individual variability.	Thank you for your response. Please see review 8 for the evidence considered when drafting recommendation 4.6.8.
Association of British Neurologists	Guideline	032	General	I would not use Lamotrigine and Levetiracetam as third line treatment for absences.	Thank you for your comment. This recommendation is based on evidence, which suggested that lamotrigine and levetiracetam were effective in the treatment of absence seizures (including childhood absence epilepsy). The committee decided to recommend these as third-line treatments because ethosuximide showed to have better outcomes than lamotrigine, including better seizure control. Compared to sodium valproate, lamotrigine showed to be less effective for seizure control, although there were not differences between both ASMs for adverse events and treatment withdrawal. Furthermore, when lamotrigine was compared with placebo, it showed to be more effective for seizure control and no adverse events were reported in neither of the trial arms. There was a placebo-controlled trial for levetiracetam which showed better seizure control in people who received

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					levetiracetam and no clinically important differences in terms of adverse events.
Association of British Neurologists	Guideline	038	General	Is there a place for Rufinamide? Experience suggests it may be less effective in real-world practice.	Thank you for your comment. Although there was no evidence assessing the effectiveness of rufinamide as monotherapy treatment, the committee agreed that it was appropriate to extrapolate from the add-on evidence as these ASMs are commonly used in clinical practice for tonic or atonic seizures/drop attacks.
Association of British Neurologists	Guideline	060	016	Rec 9.2.3 I would rephrase "offer assessment" with "offer routine screening"	Thank you for your suggestion but we think the wording is clear.
Association of British Neurologists	Guideline	060	020	Rec 9.2.4 I would rephrase "be alert to anxiety" with "offer routine screening"	Thank you for your suggestion but we think the wording is clear
Association of British Neurologists	Guideline	060	020	Rec 9.2.4 I would recommend rephrasing "Follow the recommendations in" with "Follow the recommendations taking into account specific individual needs of people with epilepsy meaning seizure risk and drug-drug interactions"	Thank you for your suggestion but we think the wording is clear
Association of British Neurologists	Guideline	061	003	Section 10. The authors have completely forgotten suicide as one the causes of premature death in epilepsy. Suicide represents 11.5% of all causes of death in epilepsy and it has been now included among the causes of increased mortality in epilepsy by the ILAE Task Force on mortality with a 2 to 5 increased risk as compared to the general population. Epidemiological studies have	Thank you for your comment. We have added being alert to the increased risk of suicide to the recommendations and to the discussion of evidence review 15

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				shown that epilepsy per se (without psychiatric comorbidities) are associated with an increased risk of suicide as compared with the general population but this increases exponentially in people with epilepsy with psychiatric disorders. We would strongly recommend the authors to add the early screening and management of mental health problems in epilepsy as an intervention for suicide prevention. Suicide screening and risk assessment would be unrealistic at this stage although a number of centres have already started doing so.	
Association of Paediatric Chartered Physiotherapists	Evidence review 04	022	002	As AHP this rings true when trying to liaise concerns to other professionals	Thank you for your response. We agree communication between health professionals and knowing where to seek advice is important.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	026	005	Women are mentioned, but young boys we work with find medication changes just as frustrating. Should the wording be altered to reflect this? Or is the purpose to solely discuss women and young females?	Thank you for your response. This is a summary of the findings from evidence which focusses on females.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	027	028	How much empowerment is being given to young people and their families? Do commonly see that advice might be provided and not followed. Can this be monitored more closely by better	Thank you for your response. Please see recommendations 2.1.1 – 2.1.3 in the information and support section which ensure the involvement of children and young people during conversation with their healthcare providers for information and shared

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				communication through all professionals involved?	decision-making. Please also see recommendations in section 4.5 for guidance on monitoring and review.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	028	040	Is this a fault of the healthcare/education system for not educating young children on Epilepsy?	Thank you for your response. Please see the information and support section of the guideline. Recommendations have been made to ensure children and young people are given appropriate information to support their needs.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	035	012	Some information regarding these topics would be useful to be available to AHP's who are not familiar/specialist in these areas. Information is not easy to come across and quite often instead comes from IST's	Thank you for your response. Local and national epilepsy charities and patient organisations are a useful source of information. This is highlighted within the information and support recommendations.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	041	010	Does there need to be an AHP in every environment (including schools) trained in Epilepsy first aid?	Thank you for your response. This is probably not feasible, but schools should be given advice if they have students with epilepsy.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	045	038-039	Up until what age does this apply? If a child is deemed to have capacity and is age 15/16+ should they be part of this decision?	Thank you for your response. Recommendations have been made to ensure children and young people are given appropriate information to support their needs and included in decision-making. Please see section 2 of the guideline: information and support.
Association of Paediatric Chartered Physiotherapists	Evidence review 04	050	016	This also works both ways, parents become extra vigilant and start almost looking for problems. Some Children with multiple learning difficulties where parents have a lot to contend with we	Thank you for your response.

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				have to be careful of unconscious fabricated illness.	
Association of Paediatric Chartered Physiotherapists	Evidence review 05	013	013	As AHP's in the community patients will quite often ask us questions about where they can be supported/signposted too. It would be useful for professionals to be supplied with the information that can be passed onto Children/families.	Thank you for your response. Links to epilepsy charities and organisations will be provided via the epilepsy guideline on the NICE website 'information for the public' page.
Association of Paediatric Chartered Physiotherapists	Evidence review 07	005	Outcomes box	Do physical concerns/outcomes need to be addressed/looked at also as well as psychological?	Thank you for your response. The outcomes prioritised for this review were based on data the guideline committee felt would be most beneficial when considering the best approach to monitoring people with epilepsy.
Association of Paediatric Chartered Physiotherapists	Evidence review 07	014	036	Understandable due to the risks involved with pregnancy that females are prioritised, however, should support groups be provided for/should males be prioritised when it comes to ad hoc appointments then?	Thank you for your response. Aside from girls/women of child-bearing potential on high-risk teratogenic medication, the other prioritised groups, i.e., people with learning disabilities, children, people with drug-resistant epilepsy, people at high risk of SUDEP, people with difficult relevant comorbidities (i.e., complex psychosocial situations /cognitive/mental health problems) and people on high-risk anti-seizure medication, are inclusive of males.
Association of Paediatric Chartered Physiotherapists	Evidence review 20	007	Waiting box	In community, is definitely the case that in services where communication is best, care is more efficient and patients transition can be managed in a smoother manner.	Thank you for your response.

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Association of Paediatric Chartered Physiotherapists	Evidence review 20	017	038-039	This seems to be a very positive step to put into place . Would this also be done for those individuals with learning disabilities and resources according to their cognitive development age be provided?	Thank you for your response. Yes, please see recommendation 2.1.4.
Association of Paediatric Chartered Physiotherapists	Evidence review 20	019	003-016	Contradictory to the guideline, the Evidence review document is not saying that transitions for those with complex needs are less well planned, but that there are more agencies involved to consider and communicate with so it takes longer. This is perhaps a more accurate representation – Does the wording of the guideline need to be changed to reflect this?	Thank you for your response. The guideline has been amended to reflect this.
Association of Paediatric Chartered Physiotherapists	Guideline	General	General	Evidence review regarding time to take off medication	Thank you. We are unable to address this comment as we are not clear what is it referring to.
Association of Paediatric Chartered Physiotherapists	Guideline	007	008	Some Children and young people require general anaesthetic in order to tolerate an MRI. Only specialist centres provide this facility and therefore this will take a lot longer to receive the results of an MRI. Does this fall under the contraindicate category if they require GA?	Thank you for your comment, the committee acknowledge that this timescale may be challenging for some trusts, however it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards. A 6 week wait for an MRI is also in line with the pledge on waiting times in the NHS Constitution for England. Not meeting this target is not a contraindication, examples of which are

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					set out in the rationale and impact section for these recommendations.
Association of Paediatric Chartered Physiotherapists	Guideline	017	007	It is interesting that the person/family have such a large impact on decision for treatment or not, this is ?a new approach to treatment. Does this need re-wording?	Thank you for your comment, the recommendation has been amended to clarify that this should be after a discussion with the person or their family/carers to consider the risks.
Association of Paediatric Chartered Physiotherapists	Guideline	018	002	Signposting for women and girls – does terminology need to be more inclusive? This applies to future sections also which describes women and girls (pg 20).	Thank you for your response. Where subgroups of people have been mentioned, the information/recommendation provided are specifically for that population.
Association of Paediatric Chartered Physiotherapists	Guideline	021	020	Annual reviews? A year is a long time to undertake if individuals concerned are at high risk of SUDEP/seizures are uncontrolled.	Thank you for your response. The committee agreed that regular monitoring should be on at least a 12-month schedule because this guaranteed a minimum of one follow up per year (reflecting usual practice) but also allowed for more frequent follow-ups if need dictated.
Association of Paediatric Chartered Physiotherapists	Guideline	056	010	The rationale states that if a young person has cluster seizures the emergency care plan should be followed. As Health professionals – we need to all have access to these emergency care plans then and they need to be readily made available. Should individuals also have 'Epilepsy passports'? So that if they are moving from place to place it is apparent to the individuals involved in their	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned.

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11/11/2021 – 22/12/2021

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				care/daily routine if they have had a number of seizures.	
Association of Paediatric Chartered Physiotherapists	Guideline	059	017-017	Phraseology is a little vague – what does co-ordinated care and MDT approach entail?	Thank you for your response. The recommendation made is to ensure continued communication between the various healthcare teams involved in the care of people with epilepsy and learning disabilities or mental health conditions, to allow coordinated care.
Association of Paediatric Chartered Physiotherapists	Guideline	060	030	What does neurodevelopment mean? Phraseology is ambiguous needs to specifically state developmental delay or are they referring to purely cognitive delay? Do they want screening for developmental delay?	Thank you for your comment. Neurodevelopmental disorders are defined as: a specific language delay or disorder, a learning (intellectual) disability or global developmental delay, a developmental coordination disorder. We have cross referred to the Autism spectrum disorders in under 19s and autism spectrum disorders in adults where further detail is provided.
Association of Paediatric Chartered Physiotherapists	Guideline	074	022	The rationale states 6 weeks until MRI, is this a feasible amount of time? Especially for those who might need general anaesthetic in order to tolerate an MRI?	Thank you for your comment, the committee acknowledge that this timescale may be challenging for some trusts, however it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards. A 6 week wait for an MRI is also inline with the pledge on waiting times in the NHS Constitution for England.
Association of Paediatric Chartered	Guideline	123	026-028	The rationale states that transition for those without learning disabilities is planned a lot better than for those with learning disabilities.	Thank you for your response. The discussion was summarising the evidence which highlighted additional struggles children/young people with

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Stakeholder	Document	Page No	Line No	Comments	Developer's response
Physiotherapists				From both a personal experience and a professional experience this is the opposite of what I have experienced, my experience has been very much that individuals with more complex needs and a more complex transition receive a better, thought through transition.	epilepsy and learning disabilities and their parents have during transition, and the delay in transition when compared to those without learning difficulties.
Bial Pharma UK Ltd	Guideline	019	001-005	<p>The Marketing Authorization Holder (MAH) is concerned that this recommendation places very strong restrictions on the use of eslicarbazepine acetate that are not justified by up to date evidence.</p> <p>The recommendation is based on the MHRA safety advice "Carbamazepine, oxcarbazepine and eslicarbazepine: potential risk of serious skin reactions" [Drug Safety Update December 2012, vol 6, issue 5: A1].</p> <p>The MAH believes the MHRA safety advice "Carbamazepine, oxcarbazepine and eslicarbazepine: potential risk of serious skin reactions" [Drug Safety Update December 2012, vol 6, issue 5: A1] is out of date and does not reflect either the tolerability data captured within the clinical trials or the up to date evidence base and specifically, the post-marketing</p>	Thank you for your comment. This recommendation has been revised so that it does not restrict prescribing of these drugs and the requirement for HLA screening has been removed. The recommendation now focuses on raising awareness that there can be a risk of serious skin reactions.

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				<p>pharmacovigilance data available for eslicarbazepine acetate.</p> <p>The MHRA safety advice is based only on the <u>structural relationship</u> between carbamazepine and eslicarbazepine acetate, not on any actual evidence of potential harm.</p> <p>The metabolism and metabolites of carbamazepine and eslicarbazepine acetate are different, and the assumption that both medicines would have similar carbamazepine-induced cutaneous reactions rates is not justified. Carbamazepine is metabolised via the epoxide pathway of biotransformation to carbamazepine 10, 11-epoxide which is the major circulating metabolite for carbamazepine [Tegretol SmPC, https://www.medicines.org.uk/emc/product/1040/smpc].</p> <p>Eslicarbazepine acetate is structurally different from carbamazepine at the 10,11 position. This molecular variation results in differences in metabolism, where eslicarbazepine acetate is metabolised solely to (S)-licarbazepine that subsequently undergoes a minor chiral inversion</p>	

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11/11/2021 – 22/12/2021

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				<p>to (R)-licarbazepine, thus preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11-epoxide [Perucca E, et al, <i>Epilepsy Res.</i> 2011 Sep;96(1-2):132-9; Bialer M and Soares-da-Silva P. <i>Epilepsia.</i> 2012 Jun;53(6):935-46].</p> <p>Furthermore, it has been reported that the 10,11-epoxide metabolite of carbamazepine could be specifically responsible for triggering hypersensitivity reactions via forming covalent adducts with serum proteins [Yip V, et al. <i>Covalent adduction of carbamazepine 10, 11-epoxide with human serum albumin and glutathione S-transferase pi: implications for carbamazepine hypersensitivity.</i> <i>Lancet.</i> 2014;383:S114].</p> <p>Therefore, the assumption that eslicarbazepine acetate would have similar carbamazepine-induced cutaneous reactions rates does not seem justifiable.</p> <p>Of the severe carbamazepine-induced cutaneous adverse drug reactions listed in the MHRA safety advice, since the launch of eslicarbazepine</p>	

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				<p>acetate in 2009 and up to 21 April 2021, there have been a worldwide total of:</p> <ul style="list-style-type: none"> - 23 reported cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (3.81 per 100,000 patient-years of exposure) - 10 reported cases of Stevens-Johnson syndrome (1.66 per 100,000 patient-years of exposure) - 2 reported cases of Toxic Epidermal Necrolysis (0.33 per 100,000 patient-years of exposure) - 6 reported cases of Toxic Skin Eruption (0.99 per 100,000 patient-years of exposure) <p><i>[Reference: BIAL – Portela & C^a, S.A., PERIODIC SAFETY UPDATE REPORT / PERIODIC BENEFIT RISK EVALUATION REPORT for Eslicarbazepine acetate, 23June2021- Data on file, DLP 21 April 2021]</i></p> <p>The EudraVigilance data analysis system (EVDAS) provides the Electronic Reaction Monitoring Report (eRMR) containing all aggregated safety data. This tool is provided by the EMA for monitoring the safety of drug use, facilitating prioritisation, detection, evaluation and documentation of suspected adverse drug</p>	

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				<p>reactions and safety signals in EudraVigilance. This allows the calculation of Relative Odds Ratio (ROR): the proportion of cases for a drug–reaction/event combination, in relation to the proportion of cases that would be expected if no association existed between the drug and the reaction/event.</p> <p>For the following MedDRA Preferred Terms – “Drug reaction with eosinophilia and systemic symptoms”, “Erythema multiforme”, “Stevens-Johnson syndrome” and “Toxic epidermal necrolysis”, eslicarbazepine acetate has a significantly inferior ROR than carbamazepine and oxcarbazepine, which suggests a smaller risk from eslicarbazepine acetate for such adverse events compared to these drugs.</p> <p>Based on the most up to date data, the RORs have been calculated as follow for each specific relevant adverse drug reaction:</p> <ul style="list-style-type: none"> - <u>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</u>: carbamazepine 61.04, oxcarbazepine 6.51, eslicarbazepine acetate 5.59 	

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<ul style="list-style-type: none"> - <u>Stevens-Johnson syndrome</u>: carbamazepine 29.04, oxcarbazepine 8.23, eslicarbazepine acetate 1.14 - <u>Toxic Epidermal Necrolysis</u>: carbamazepine 20.38, oxcarbazepine 2.79, eslicarbazepine acetate 0.23 - <u>Toxic Skin Eruption</u>: carbamazepine 9.28, oxcarbazepine 2.90, eslicarbazepine acetate 3.46 <p>As we can see from the analysis above, the risk for eslicarbazepine acetate is currently identified as substantially lower than both carbamazepine and oxcarbazepine, which confirms the difference between the products in terms of safety profile.</p> <p>Furthermore, there has been a clinical case in the published literature in which a patient with proven HLA-A*31:01 haplotype responded to treatment with eslicarbazepine acetate without any serious adverse events despite developing a severe skin rash following treatment with carbamazepine [Kay L, et al. <i>Seizure</i>. 2017 Apr;47:81-82]. While the MAH recognise that this is a single case report, it further challenges the relationship between severe skin reactions in patients of HLA-A*31:01 haplotype and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>eslicarbazepine acetate, and would also support the chemical structural difference between the two drugs.</p> <p>None of the three anti-seizure medications (carbamazepine, oxcarbazepine and eslicarbazepine acetate) Summary of Product Characteristics report mandatory genetic screening prior their initiation as they state: "There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment"</p> <p><i>Tegretol SmPC</i>, https://www.medicines.org.uk/emc/product/1040/smpc; <i>Oxcarbazepine SmPC</i> https://www.medicines.org.uk/emc/product/8483/smpc; <i>Zebinix SmPC</i> https://www.medicines.org.uk/emc/product/4460/smpc].</p> <p>Finally, we note that treatments such a lamotrigine and levetiracetam, which have shown much higher rates of severe skin reactions in the EVDAS-eRMR system mentioned above, are not</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>subject to restrictions. The relative Odds Ratio (ROR) in terms of proportion of cases for a drug–reaction/event combination in relation to the proportion of cases that would be expected if no association existed between the drug and the reaction/event (as above) for these drugs (and in relation to eslicarbazepine acetate) are:</p> <ul style="list-style-type: none"> - <u>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</u>: lamotrigine 25.83, levetiracetam 6.16 and eslicarbazepine acetate 5.59 - <u>Stevens-Johnson syndrome</u>: lamotrigine 38.45, levetiracetam 3.04 and eslicarbazepine acetate 1.14 - <u>Toxic Epidermal Necrolysis</u>: lamotrigine 21.96, levetiracetam 4.5 and eslicarbazepine acetate 0.23 - <u>Toxic Skin Eruption</u>: lamotrigine 5.84, levetiracetam 1.53 and eslicarbazepine acetate 3.46. <p>Eslicarbazepine acetate has the lowest ROR for the adverse drug reactions listed above compared not only to carbamazepine and oxcarbazepine, but also lamotrigine and levetiracetam. For all the reasons listed the MAH</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is concerned that this recommendation places very strong restrictions on the use of eslicarbazepine acetate that are <u>not justified</u> by up to date evidence.	
Bial Pharma UK Ltd	Guideline	019	009-011	The MHRA safety advice – “Carbamazepine, oxcarbazepine and eslicarbazepine: potential risk of serious skin reactions” dates to 2012 and the MAH considers it does not reflect the up to date evidence base and specifically, the post-marketing pharmacovigilance data available for eslicarbazepine acetate.	Thank you for your comment. This recommendation has been revised so that it does not restrict prescribing of these drugs and the requirement for HLA screening has been removed. The recommendation now focuses on raising awareness that there can be a risk of serious skin reactions.
Bial Pharma UK Ltd	Guideline	019	001	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been revised throughout.
Bial Pharma UK Ltd	Guideline	031	002	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been amended throughout.
Bial Pharma UK Ltd	Guideline	031	008	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been amended throughout.
Bial Pharma UK Ltd	Guideline	084	012	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been amended throughout.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Bial Pharma UK Ltd	Guideline	092	012	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been amended throughout.
Bial Pharma UK Ltd	Guideline	092	029	As the active substance is eslicarbazepine acetate, the MAH requests that acetate is included after eslicarbazepine.	Thank you for your comment, this has been amended throughout.
British Paediatric Neurology Association	G u i d e l i n e	General	General	The guidance refers to people with epilepsy and does not differentiate between children and adults in relation to specialist management, e.g. p 42 'Ensure that people with Dravet syndrome have a neurologist with expertise in epilepsy involved in their care'. We are concerned that this does not emphasise the need for children under 16 years of age to be managed by a paediatric neurologist or a paediatrician with expertise in epilepsy but refers to 'neurologist' as the specialist.	Thank you for your comment, the recommendation has been amended to specify that a paediatric neurologist should be involved in the care of children with Dravet Syndrome.
British Paediatric Neurology Association	G u i d e l i n e	21	020 - 021	We are concerned that the recommendation does not advise that all young people following transition to adult services and all adults with epilepsy should have an annual review with a neurologist.	Thank you for your response. The guideline committee agreed that adults who have good control over their epilepsy symptoms may not need and/ or want to be seen by their healthcare provider on a regular basis. Therefore, recommendation 4.5.1 lists the subgroups of people with epilepsy who would benefit from at least annual monitoring reviews. Recommendation 4.5.2 does ensure that all children and young people are reviewed at least annually irrespective of their comorbidities.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Paediatric Neurology Association	Guideline	47	12	We are concerned that the possible adverse effects of vigabatrin are discussed with parents, including somnolence and the possible adverse effect on visual field function, explaining the balance between the benefits of this treatment versus possible adverse effects and the difficulty with assessing the possible adverse effect on visual fields in children.	Thank you for your comment. Recommendation 4.1.1 states that the risk and benefits of any medication for any form of epilepsy should be discussed with the person (and their family/carers as appropriate) before starting that medication.
British Specialist Nutrition Association	Evidence review 12	General	General	The disclaimer at the beginning of the Evidence review 12 should be repeated within the guideline itself to further clarify that the recommendations in the draft NICE guideline, including those related to the use of non-pharmacological treatments such as the ketogenic diet need to be considered alongside individual needs, preferences and values of patients or service users.	Thank you for your response. The disclaimer has been included at the start of each review chapter; however, it is not in the standard template of the guideline document. We will pass on your suggestion to the NICE editors.
British Specialist Nutrition Association	Evidence	21	006 - 009	There is a wide evidence base for the efficacy, use, recommendation and implementation of the ketogenic diet (Kossoff et al 2018). The guideline committee state they were aware of cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life. However,	Thank you for your response. Please be assured the points raised were taken into consideration when discussing evidence. The recommendations made are evidence-based and therefore need to focus on the evidence included in the Cochrane review. However, the guideline committee have amended the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	R e v i e w 1 2			this evidence does not appear to have been fully taken into consideration, with the focus of the evidence review being based only on results from randomised control trials (RCT) in the Cochrane review. Meeting the stringent criteria of Cochrane reviews in clinical studies concerning nutritional interventions has difficulties, as they are very resource intensive and there are frequently challenges in: Blinding -in the case of the ketogenic diet, blinding is extremely difficult as an individual's dietary intake is radically altered, Finding an appropriate control- the ketogenic diet as food or as a feed is very different to a standard diet or feed, Patient recruitment and adherence-the ketogenic diet a requires large changes to nutritional intake/routine /lifestyle and response to the ketogenic diet typically may take 3 months or more, Patient numbers- due to the factors involved above there are difficulties recruiting patients and attrition rates are high. Whilst we acknowledge that Cochrane reviews evaluate the highest quality of clinical evidence in selecting RCT, these types of studies in the field of nutrition are often infeasible. Evidence based clinical practice in nutrition and dietary	drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see recommendation 8.1.1.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intervention is generally based upon a broader range of clinical evidence.	
British Specialist Nutrition Association	Guideline	57		BSNA is concerned that the wording of the recommendation in section 8.1.1 in relation to use of Ketogenic diet is not clear and suggests the ketogenic diet should be explored only as a last resort treatment after all other treatment options. It is not clear what is meant by "all other treatment options" and we are concerned that there is a risk that the option of ketogenic diet therapy in this complex patient group with drug resistant epilepsy will be limited. This recommendation could therefore affect patient access to ketogenic diet therapy when anti-epileptic drugs have been unsuccessful in controlling their epilepsy. BSNA proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration	Thank you for your response. The recommendation for ketogenic diets has been amended to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>of the use of a ketogenic diet.' If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to:</p> <p>'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with drug-resistant epilepsy if appropriate AED treatment options have been unsuccessful or certain childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (see the section on treating childhood-onset epilepsies).' This will provide clarity that patients with drug resistant or complex epilepsy should have continued access to ketogenic diet therapy services, whilst further research is conducted, rather than unnecessarily restricting patient access to ketogenic diet therapy services. We believe this is in line with the guideline committee's intent: (Evidence review 12, page 21, lines 10-14) 'The guideline committee were mindful of the importance of keeping ketogenic diets as an option for people in whom other treatment options have been exhausted. They therefore agreed that although ketogenic diets should not be routinely recommended, it should</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				continue to be available as a treatment option within the NHS based on individual clinical need.'	
British Specialist Nutrition Association	G u i d e l i n e	113	22 - 25	There is a wide evidence base for ketogenic diet therapy as an option for the effective management of drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the body of evidence to demonstrate that ketogenic diet therapy can be effective in a number of these patients, it is important that NICE is cautious about any changes to relevant clinical guidance. BSNA is concerned that the proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, despite long-standing evidence that it is an effective treatment. BSNA is also concerned that the change in recommendations in the guideline could lead to a reduction in offering ketogenic dietary therapy services and options for patients which will limit the ability to conduct further research in future as recommended on the effectiveness and long term tolerability of ketogenic diets.	Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions. The committee further discussed the evidence and amended the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation. The committee acknowledge the need for further evidence in this area and have thus drafted a research recommendation.
British Specialist	G u	113	27-28	Since the introduction of NICE CG137 in 2012, patient numbers have increased from 101 in 2000	Thank you for your response. The committee have amended the recommendation for ketogenic diets to

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Nutrition Association	i d e l i n e			to 754 in 2017 (Whiteley et al, 2020), with an increase in centres accepting adult patients with a waiting list thereby showing the impact of the recommendation of the ketogenic diet therapy. Therefore, BSNA is concerned that the changes to the NICE recommendations will have a significant impact on current clinical practice. BSNA requests that NICE further examines any potential impact changes to the NICE guidelines will have on clinical practice.	clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.
British Specialist Nutrition Association	R e g i s t e r o f i n t e r e s	general	general	Whilst we understand the need to avoid conflict of interest in the creation of guidelines, we note from the register of interests that certain committee members with expertise in ketogenic diet therapy were not actively involved in drafting the recommendations in this area. Given that clinical expertise in the use of the ketogenic diet is confined to a small group of clinicians, it would seem that relevant expertise and knowledge is potentially missing from the discussion on the benefit of the diet for patients in clinical practice.	Thank you for your response. As per the NICE conflict of interest policy, people with a direct interest in the topic of discussion were excluded. Other committee members with knowledge and experience of ketogenic diet but without a conflict of interest drafted the recommendations.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	t s				
Clive Treacey Independent Review	General	General	General	<p>Thank you for the opportunity to comment on the Epilepsies in children, young people and adults guideline. Please find attached a response on behalf of Beverley Dawkins, Independent Chair to the Clive Treacey Independent Review. The response draws on the epilepsy findings of Review and we recommend that the response is read in tandem with the final Report - please see link below.</p> <p>https://www.england.nhs.uk/midlands/wp-content/uploads/sites/46/2021/12/Confidential-Embargoed-Copy-Clive-Treacey-Independent-Review-Final-Report-8.12.21.pdf</p> <p>If it would be helpful, Beverley would be very pleased to share the findings of the review and reflection son the guideline directly with the Committee.</p>	Thank you for your comments.
Clive Treacey Independent Review	Guideline	General	General	<p>NICE EPILEPSY GUIDELINES CONSULTATION CLIVE TREACEY INDEPENDENT REVIEW COMMENTS</p> <p>In December 2021, NHSE/I Midlands concluded an independent review into the care, treatment</p>	Thank you for your comment, and your comprehensive description of the failings that lead to the tragic death of Clive Treacey. The committee considered your comments, and the suggestions you made when redrafting the guideline. They considered a separate section for people with learning disabilities,

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>and death of Clive Treacey. Clive, who had a learning disability and suffered from complex epilepsy, sadly died in January 2017 at the age of 47 following an epileptic seizure at a privately run hospital for people with learning disabilities. Clive spent much of his life moving between many care providers who struggled to meet his needs and support him to live the life he wanted. The review finds that Clive's death was <i>'potentially avoidable' due to 'multiple, system-wide failures in delivering his care and treatment that together placed him at a higher risk of sudden death'</i>. In relation to epilepsy, the review finds that <i>'Clive's epilepsy care overall fell far short of acceptable practice for someone with complex intractable (drug-resistant) epilepsy. At Danshell Cedar Vale (now Cygnet Health Care), his final placement, this placed him at higher risk of sudden death'</i>.</p> <p>This consultation response draws specifically on Clive's experience of health and care as an individual with complex epilepsy. Epilepsy dominated Clive's life and impacted heavily on the quality of care and outcomes he experienced. The Review echoes epilepsy findings identified in Learning from the Lives and Deaths of People</p>	<p>as you suggested. After a detailed discussion it was decided to keep the recommendations within their relevant sections to ensure that people with learning disabilities and complex needs are considered by all healthcare professionals throughout their journey of care. NICE are however, considering developing a tool to sit alongside the guideline that does draw out the specific considerations for people with learning disabilities that would be more accessible. In relation to your points about training and competency frameworks, this is unfortunately outside the scope of this guideline and NICE do not usually make recommendations about the content of competency frameworks. Similarly, residential settings were not included in the scope of this guideline and therefore we are unable to make recommendations about them. As you note, the guideline makes recommendations about the involvement of specialists, and recommendation 6.2.1 includes the need for specialist involvement specifically relating to people with Lennox Gastaut Syndrome. The recommendations for Epilepsy Specialist Nurses have also been amended to clarify that they should be the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>with a Learning Disability Reviews (LeDeR) more widely.</p> <p>This consultation response should be read in tandem with the Clive Treacey Independent Review Report, which sets out detailed findings and recommendations in relation to epilepsy. Specifically for NICE, the Review recommends:</p> <p><i>With a view to providing better guidance for clinicians, carers and care professionals in relation to epilepsy and challenging behaviour linked to epilepsy and its management, the National Institute for Health and Care Excellence (NICE) should consider reviewing current guidelines in relation to:</i></p> <ul style="list-style-type: none"> • <i>epilepsy and special consideration for people with a learning disability</i> • <i>challenging behaviour and learning disabilities.</i> <p>General Comments</p> <p><i>Do the guidelines sufficiently respond to the needs of people with a learning disability who suffer from epilepsy?</i></p> <p>The Committee's greater attention to the needs of people with learning disability and epilepsy in</p>	<p>liaison between all services involved in a person's care to ensure people do not 'fall through the cracks'.</p> <p>NICE guidelines do not usually make direct recommendations as to how services should be commissioned, as this will partly be down to local service configurations. However, the committee hope that the recommendations they have made will ensure that commissioners are able to recognise the services needed to deliver a high quality of care and commission them accordingly.</p> <p>As you note the committee have made recommendations regarding the risks of SUDEP that are applicable to people with learning disabilities. These include the following sections of the guideline: 2 information and support needs, 3 referral to tertiary epilepsy services, 4.5 monitoring and review, 9.1 providing co-ordinated care, 9.2 support and treatment, 10 reducing the risk of epilepsy related mortality including SUDEP and 11.2 transition from children's to adults' epilepsy services. Risk factors and interventions to reduce the risk of epilepsy related death has been included in the guideline and the committee made recommendations for recognising and managing risk. However, the guideline has not reviewed the evidence for the SUDEP safety checklist</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>response to the findings of LeDeR is very welcome. The new guidelines refer to adjustments required for people with a learning disability more consistently throughout the guideline. This should prompt users of the guideline to consider how services and responses need to be tailored to meet the needs of people with a learning disability throughout the epilepsy pathway.</p> <p>However, we find that the revised guideline does not sufficiently respond to the issues of care quality affecting people a learning disability and epilepsy in its current form and recommend including a specific strengthened section on learning disability. This is important because the lives, experiences and needs of people with a learning disability and epilepsy can be very different to that of the general population with epilepsy. People with a learning disability are more likely to be cared for by others in residential settings, specialist hospitals or by their own families and carers. Decisions are more likely to be taken by others on their behalf. For people with a learning disability like Clive, it is standards of day-to-day care provided in care settings that are likely to have the biggest impact on quality of life and prevent risk of premature death. The</p>	<p>tool because it did not address the review question and therefore we cannot make recommendations for its use. Evidence for risk prediction tools for epilepsy related mortality including SUDEP was reviewed in the guideline, but the evidence was not strong enough to recommend any specific tool. The committee recognised the value of having such a tool and decided to make a research recommendation to develop and validate a risk prediction tool for all-cause mortality including SUDEP.</p> <p>People with learning disabilities may have other comorbidities and have complex health needs and the committee have also highlighted when specialist or additional support may be required within the information and support, monitoring reviews, and transition planning from child to adult epilepsy services recommendations.</p> <p>The recommendations in the NICE guidelines Challenging behaviour and learning disabilities and Mental health problems in people with learning disabilities were reviewed by the committee who agreed this provided relevant valuable guidance on patient centred general principles of care for health professionals, families and carers in managing the</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>revision to this guideline has the potential to address a significant gap in standards of epilepsy care and management for people with a learning disability- this is where there is the potential to have the biggest impact on practice. Whilst the guidelines speak well to clinicians, we recommend that they are strengthened to cater more specifically for those more directly involved in the coordination and management of epilepsy care for people with a learning disability. These are:</p> <ul style="list-style-type: none"> - commissioners of care (health and social care) for people with a learning disability including health commissioners, social workers, community learning disability teams and approved mental health practitioners - health and social care providers - regulatory bodies overseeing care quality - Individuals with a learning disability and their families - Advocates – providing statutory and non-statutory advocacy <p>We recommend the inclusion of a specific section for people with a learning disability that covers the following:</p>	<p>care and supporting people with epilepsy with learning disabilities or with mental health difficulties.</p> <p>The committee recognise the importance of joined up care using a MDT co-ordinated approach for all people with epilepsy, and particularly those with specialist needs that may be under the care of different teams. The committee agree information needs to be shared amongst those involved in providing care, more frequent reviews of care may be required and have reflected this within the recommendations in section 2. information and support needs and section 4.5 monitoring and review sections of the guideline. Because mental capacity and decision making is applicable to all NICE guidelines Information and links to the Mental capacity Act is available from the link NICE's information on making decisions about your care in the epilepsy guideline. The committee have also included links to NICE's guidelines on medicines adherence that covers mental capacity and decision making with regards taking medication.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>1. Care quality and safety: The Independent Review concluded that <i>Clive's epilepsy care overall fell far short of acceptable practice for someone with complex intractable (drug-resistant) epilepsy. At Danshell Cedar Vale (now Cygnet Health Care), his final placement, this placed him at higher risk of sudden death</i>'. The learning from this review clearly identifies that the management of day-to day epilepsy care is critical to the safety of people with a learning disability and epilepsy. The standard of epilepsy care provided in specialist hospital and community care settings, in Clive's case, was often poor. Of particular concern was the standard of care delivered by front line staff, in Clive's case, generally health care assistants. There was poor observation and recording of his seizures, the failure to implement key components of his care plan and to escalate issues such as lack of compliance with medication, wearing his epilepsy helmet and use of CPAP machine. The level of training and awareness of epilepsy amongst care staff was sometimes very limited and they were not sufficiently equipped to manage complex and drug-resistant epilepsy. The high risk of</p>	

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>epilepsy-related death and sudden death was not systematically and comprehensively understood or mitigated.</p> <p>Day service, residential and supported living teams have most contact with people with a learning disability living with epilepsy and are all too often seen as the unskilled part of the workforce.</p> <p>The Review recommend: that health and social care providers must ensure that the care they provide for people with a learning disability and epilepsy is compliant with NICE epilepsy care standards and that all staff are trained and supported to meet these standards.</p> <p>We recommend that specific detail is included in the guideline about how epilepsy care is delivered and monitored to ensure good quality and safe day to day care management.</p> <p>We also recommend that the revised guideline considers the epilepsy skills and competencies required of any provider and commissioning organisations supporting people with a learning disability. To support effective implementation, we propose an epilepsy competency framework and also</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>incorporation of these standards in contract specifications.</p> <p>2. Commissioning an oversight of epilepsy care: Clive moved through an extraordinary number of care settings in his life, experiencing varying quality of epilepsy care. There are some examples of good care, but for the large part, this review finds that Clive was placed in residential and inpatient settings that were not effectively equipped to meet Clive's epilepsy needs. Consequently, Clive found himself moving frequently, sometimes quite urgently and reactively because of his epilepsy. On one occasion, a care setting was not able to keep Clive safe because of the risks posed by stairs. In other settings, the level of injuries Clive was sustaining due to seizures meant that the service could no longer cope. Many struggled to understand the relationship between Clive's epilepsy and his behaviour.</p> <p>The review finds that Clive should not have been placed in services that were unable to demonstrate capability in supporting his</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>complex epilepsy. There appears to have been a lack of specialist epilepsy expertise or epilepsy standards which informed the commissioning of community and inpatient care provision for Clive. Although specifications for Clive's care emphasised the importance of good epilepsy management and care, it is likely that the commissioners responsible lacked the specialist expertise of what good epilepsy care looks like, sometimes acting reactively to find Clive a placement.</p> <p>The Review recommends that:</p> <ul style="list-style-type: none"> - <i>In commissioning care provision (specialist hospital or community) for people with a learning disability and epilepsy, commissioners at a local level (health and social care) should actively assure themselves that care providers are delivering a standard of epilepsy care that is compliant with NICE standards.</i> - <i>Commissioning organisations at a local level (health and social care) should ensure commissioners of care provision for people with a learning disability are equipped with or able to access specialist epilepsy expertise to commission safe and</i> 	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p><i>effective care for people with a learning disability and epilepsy.</i></p> <ul style="list-style-type: none"> - <i>Regional NHSE/I Learning Disability and Autism Programmes should undertake a capacity and training needs audit to review the capacity and skills of staff to commission safe care for people with learning disabilities who have complex needs including epilepsy.</i> <p>We recommend that revised guideline includes specific reference to safe and effective commissioning of epilepsy care, which is of particular relevance to people with a learning disability.</p> <p>To support effective quality assurance and oversight of epilepsy care we recommend that quality teams in the NHS and local authorities should have access to support to enable them to know what good should look like for those organisations serving people with epilepsy who also have a learning disability.</p> <p>3. SUDEP & Risk of Epilepsy Related Death: We welcome the specific focus in the guideline on SUDEP and attention to modifiable risk</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>factors. SUDEP is the most common cause of premature death in adults with epilepsy. We know that individuals with a learning disability and other co-morbidities experience increased risk of unexpected death including SUDEP or dying from an accident or injury. It is suggested that SUDEP rates can be as high as 42% in people such as Clive who have over 15 years' history of drug-resistant seizures.</p> <p>In Clive's case, although epilepsy care plans flagged the risk of SUDEP, understanding, awareness and effective mitigation of risk was lacking. For example, the role of sleep apnoea in his epilepsy and the need to ensure compliance with wearing his CPAP machine at night- in fact this machine was broken for the last 7 weeks of his life.</p> <p>The Review recommends that commissioners of care for people with a learning disability and epilepsy must ensure that health and care providers take a risk management approach to epilepsy-related death, as recommended in the NHS Right Care Epilepsy Toolkit. This should specifically include application of a standard risk template for people living with epilepsy that crosses</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>organisational boundaries, such as the SUDEP and Seizure Safety Checklist tool.</p> <p>In our view there is a need to emphasise the increased risks of SUDEP for people with a learning disability and for practical clear guidelines on how to assess and manage epilepsy risk (SUDEP) for people with a learning disability for staff in these settings. Improved application of tools such as the SUDEP Action Safety toolkit would be beneficial.</p> <p>4. Complex health needs: People with a learning disability are more likely to have complex health needs and multiple comorbidities/ co-occurring conditions and it is important to understand the inter-relationship between these and epilepsy. As stated above, in Clive's case there was poor delivery of care in regard to his sleep apnoea and the use of his CPAP machine. A further example is that Clive's weight increased by 27kg in the last eight months of his life following his admission to Cedar Vale. In May 2016, Clive weighed 86kg. This rose to 93kg in August, 100kg in October and 113kg in January 2017. Clive's weight gain not only</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>increased his cardiac risk, but also affected his sleep apnoea and increased his risk of seizures. This highlights the need for the holistic approach that includes a wider assessment of comorbidities/ co-occurring conditions when assessing and treating people with a learning disability and epilepsy. See also recommendation below on improved care coordination.</p> <p>5. Epilepsy and challenging behaviour: The Review found that the link between Clive's epilepsy and challenging behaviour was overstated and disproportionately influenced the generally held view that Clive required a hospital setting, depriving him of the opportunity to better manage his behaviours, and prolonging his detention. Limited formulation, often arising from the belief that Clive's behaviour was entirely linked to his epilepsy, prevented the full utilisation of person-centred planning and applied behavioural analysis and therefore limited any chance to obtain optimum change in behavioural presentation. The expert clinical view was that: "This over emphasis on epilepsy being the cause resulted in diagnostic overshadowing and prevented the</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>team from considering how Clive's environment, detention in hospital, relationship with peers etc was impacting upon him."</p> <p>Drawing on a two-day telemetry assessment in 2011, Clive's Consultant Epileptologist and Neuropsychiatrist reported some observed patterns in behaviour linked to a six-week cycle that included two weeks of seizures, two weeks of relative stability and then two weeks of more challenging behaviours. It is also recognised that psychiatric and behavioural side effects are common, undesirable effects associated with anti-epileptic medication use, as confirmed by the expert Pharmacist supporting this review. Levetiracetam, which Clive had been taking, is reported to have the greatest psychiatric and behavioural side effects. Records demonstrate that treatments were adjusted over the years to minimise these side effects. However, Clive's Consultant also reported to the Coroner's inquest that many incidents of behaviour deemed to be challenging were unrelated to seizures, seemed to occur when Clive was more well, and were likely to be</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>impacted on by wider factors affecting his mental health.</p> <p>The expert Pharmacist supporting the review was also of the opinion that “fluctuations in his [Clive’s] seizure pattern and behaviour seem more associated with other factors in his life rather than medications.” We asked the expert ESN to consider this aspect of his assessment and treatment, and she explained that: “In Lennox-Gastaut, there is an association between cognitive dysfunction, anxiety, irritability, depression, aggression and behaviour problems, which can significantly impact on a person’s mental health and wellbeing.” However, she further explained that there may have been a number of influences on Clive’s behaviour and that “a comprehensive function analysis of the association between behaviour and epilepsy is needed”.</p> <p>The lack of concrete understanding about the association between Clive’s epilepsy and behaviours deemed to be challenging had a profound impact on his life. Detention under the Mental Health Act could have been avoided or ended sooner had there been better comprehensive understanding and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>support of Clive's behaviour. Instead, the view that Clive's behaviour was largely to do with his epilepsy and was unchangeable meant that there was a view that hospital was the only option for him. For the large part of Clive's stay in hospital, providers did not pursue fully the possibilities for reducing and mitigating risks that would have enabled a move back into the community. The consequence of the limited formulation (linked to epilepsy) and understanding of behaviour meant that Clive did not, for much of his life, receive the right care and support he needed for his epilepsy or behaviour. We welcome the reference to mental health and link in the guideline to NICE's guidelines on mental health problems in people with learning disability. However, our concern is that this guideline does not sufficiently respond to the specific issues in relation to epilepsy and challenging behaviour affecting people with a learning disability highlighted above and in more detail in the review.</p> <p>We recommended the need for better guidance for clinicians, carers and care professionals in relation to epilepsy and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>challenging behaviour linked to epilepsy and its management.</p> <p>We recommend that the revised guideline considers the epilepsy skills and competencies required of mental health providers supporting people with a learning disability. To support effective implementation, we proposed a epilepsy competency framework and also incorporation of these standards in contract specifications.</p> <p>We suggest that members of Mental Health Review Tribunals should also have access to robust training to ensure informed decisions are taken for people with a learning disability and epilepsy.</p> <p>We also recommend further research into the issues highlighted in relation epilepsy and challenging behaviour.</p> <p>6. Specialist epilepsy oversight and management – Clive's review highlights the importance of consistent specialist oversight and management. It also highlights the importance of effective communication between commissioners, care providers and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>specialist epilepsy teams in care planning for people with a learning disability. Clive's epilepsy was reviewed by his Consultant Epileptologist and Neuropsychiatrist or his epilepsy specialist nurse within the team twice a year. Clive valued the management and continuity of care provided by this Consultant and his team, and the family speak highly of the consistency in support he provided. However, his family reported that prior to this there was not a consistent or coordinated approach. We welcome the draft guidance on the importance of early diagnosis and treatment. However, this needs to emphasise that there must be equality of access for children and adults with a learning disability as we are aware of wider concerns that this is not always the case. Clive's family also played a key role in ensuring that the same consultant continued to oversee his epilepsy when he moved from setting to setting to ensure consistency of approach. In our view this is important to reduce the risk of a fragmented approach. Although advice from Clive's specialist epilepsy team was sought on occasion, expert</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>advice suggests that the complexity and severity of Clive's epilepsy would have benefited from additional direct specialist input and advice to inform his care planning and delivery. Records also suggest that Clive's Consultant Epileptologist and Neuropsychiatrist was not always provided with an accurate recording of his seizure activity or experience of day-to-day care on which to advise. Certainly, it was the case that the Consultant was unaware of the fact that Clive had not had use of a working CPAP machine for his sleep apnoea, or the extent to which he had been refusing epilepsy medications, or an up-to-date picture of Clive's seizure patterns, as staff had failed to supply this information at their last appointment in December 2016. These were all matters disclosed to him when he attended the inquest.</p> <p>For people with a learning disability and epilepsy we recommend the adoption of a multi-disciplinary approach, linking with epilepsy teams more comprehensively for care planning and management.</p> <p>We welcome the focus in the guideline on the role of epilepsy specialist nurses, they</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>have a valuable role to play in improving standards of care. We recommend that an epilepsy nurse specialist role should be part of every community learning disability team. Their role should primarily be about capacity/ skills building amongst providers and the wider MDT as well as individuals and their carers. They should also be skilled and experienced in supporting people with a learning disability.</p> <p>7. Care coordination/ multi-disciplinary working: We know that many people who have epilepsy and a learning disability do not always receive the holistic care they need. They often have many professionals involved in their health and social care and this care can be fragmented. This was evident in Clive's experience. We welcome the recommendation in the guideline that there is coordinated care for people with epilepsy who have a mental health condition using a multi-disciplinary approach. However, we suggest that the focus on good care coordination and joined up multi-disciplinary working should not be</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>restricted to people with epilepsy and mental health conditions, although this is specifically important and should remain.</p> <p>At Cedar Vale, the last specialist hospital in which Clive was detained, internal multi-disciplinary meetings to review Clive's care were held. However, we identified that Clive would have benefited from the Cedar Vale team working in a multi-disciplinary way with the wider system of professionals engaged in his care including his GP and consultant epileptologist or specialist epilepsy nurse, social workers and care coordinators. This would have enabled a better coordinated response not only to issues arising in relation to health issues (medication, chest pains, weight gain, sleep apnoea and multiple attendance at A&E in the last 9 months of his life) but also in supporting him to move out of hospital to live the life he wanted. It would also have enabled better understanding and awareness of Clive's epilepsy needs across professionals.</p> <p>We recommend that the guidelines acknowledge that people with a learning disability are more likely to experience comorbidities/ co-occurring conditions and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>complex health needs and specifically recommends <i>effective communication and liaison between health and social care professionals across the relevant services involved in the care of people with epilepsy and a learning disability to agree and plan care across services.</i></p> <p>8. Mental Capacity: We cannot see reference in the revised guidelines to the importance of assessing and responding to issues of mental capacity, which are critical for people with learning disability. The need for better understanding and application of the MCA has been highlighted in successive LeDeR reports. Poor understanding of mental capacity and requirements of the MCA can have a profound impact on care and treatment of people of people with a learning disability and epilepsy. In Clive's case, there was no evidence of a proper assessment of Clive's mental capacity in relation to his epilepsy treatment for the majority of his time at Cedar Vale. There were conflicting views on his mental capacity. The expert ESN supporting the review explained that the assessment relating to Clive's mental capacity to the treatment for his epilepsy and other</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>aspects of physical healthcare would not be covered by the Mental Health Act assessment for capacity in relation to his psychiatric treatment: "The lack of a definitive MDT decision on his mental capacity in relation to his epilepsy treatment, confusion and differing opinions in his care team in relation to capacity had serious and profound implications to the treatment of his epilepsy.</p> <p>We recommend there is specific reference included in the guidelines in relation to effective application of the Mental Capacity Act (MCA).</p> <p>9. Medication and treatment: An expert pharmacist provided a detailed examination of the epilepsy medications Clive was prescribed. He notes that Clive was prescribed a wide range of anti-epileptics during his life, which was a common experience of people who suffer refractory epilepsy. The failure to respond to the exposure of such a wide range of anti-epileptics is also a common feature of Lennox-Gastaut epilepsy. Despite the</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>availability of many new anti-epileptic medications with differing mechanisms of action, he noted that overall outcomes did not improve for Clive. Overall, his view is that the prescribing practice was generally in line with what might be expected for someone with Clive's profile of drug-resistant epilepsy. The main question in regard to Clive's epilepsy medication was the impact of missed medication and how this was managed in the last weeks of his life. Sometimes Clive refused medication, and sometimes it was missed because he was sleeping. The expert Epilepsy Nurse commented that "the staff members administering the medication appeared to believe that he had capacity to make the decision to refuse his medication and that it was his choice." She observed that the care plan for refusal of his medication stated he was to be offered the medication on four occasions with the implication that he had the mental capacity to make that decision. If it was assumed that he had capacity this would be a reasonable strategy, assuming staff also informed him of the risks of not taking his medication. Given the severity of</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>his epilepsy, non-compliance with medication, she believed, would be associated with an increased risk of death. If Clive was unable to understand the consequences of not taking his medication as prescribed, then he could not have made a capacitated decision around the medication for epilepsy. The ESN explained that if Clive had lacked capacity (as indicated at September 2016: see above), the care team should have made a best-interest decision relating to epilepsy medication. This would have needed to include a clear account of the implications of not taking anti-epileptic medication as prescribed and considering the necessity and proportionality of any alternative medication administration strategy, which could include various stages of increasing restriction up to and including a covert administration plan if deemed necessary and proportionate.</p> <p>The expert Pharmacist found that in general it was not clear how the impact of the range of medications prescribed were monitored and reviewed. This is of serious concern, and more comprehensive steps should have been taken to review the risks and benefits of the</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>combination of prescribed drugs at regular intervals – in line with NICE Guidance and best practice outlined in the STOMP campaign (stopping over-medication of people with a learning disability or autism)</p> <p>In response to the issues highlighted above, we welcome the recommendation in the revised guideline on regular monitoring of epilepsy medication is welcome. We propose that specific reference is made to the national STOMP campaign and resources. We also recommend that specific reference is included in the medication section of the guideline in relation to the importance of mental capacity and decision making in relation to medication for people with a learning disability who have epilepsy.</p> <p>10. Equal access: The new guidelines recognise that people with a learning disability may struggle to access services, may need help to get appropriate referrals and recommend that specialised assessment and management for people with a learning disability – this is welcomed. They helpfully make suggestions on how the information and support needs of</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>individuals with a learning disability can be addressed.</p> <p>We recommend that this section should be further strengthened to include:</p> <ul style="list-style-type: none"> - Reference to Equality 2010 and the legal requirement to make reasonable adjustments as well the accessible information standard. - Reference more comprehensive resources on making personalised reasonable adjustments that are available to guide professionals. - Highlight the need to think carefully about the known barriers of diagnostic overshadowing. In Clive's case, his epilepsy came to define him, and there was a tendency for health professionals to attribute wider health complaints to epilepsy. Health and care professionals did not always effectively assess the pain he was in, did not always listen to his family who knew him best, and failed to lower the threshold of suspicion when diagnosing conditions, and failed to make the reasonable adjustments Clive required to help him access healthcare. 	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>11. Information and health literacy for individuals and carers</p> <p>Reference in the guidelines to information and health literacy for individuals and their carers is welcomed. Too often there is an assumption that all people with a learning disability are unable to manage their healthcare. Understanding mental capacity and support required is important in supporting individuals to manage their own healthcare and live independent lives. Clive had a mild learning disability and understood his health needs and treatment relatively well. Clive's family believe he took his medication and treatment seriously and was mindful of the risks. However, there is limited evidence of professionals working with Clive to support him to self-manage and make informed decisions himself.</p> <p>For example, Clive suffered from sleep apnoea and was required to use a CPAP machine at night. We know that compliance with CPAP machines can be difficult for all users, but with good compliance it has the potential to significantly improve daytime</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>drowsiness and general health and reduce seizure frequency.</p> <p>We recommend clearer guidance and support for individuals and carers on understanding risks and self-management of epilepsy. Although linked we recommend that this addressed separately to the need for reasonable adjustments, which is a legal requirement to ensure services are accessible for disabled people.</p> <p>We recommend the development of tools to support self management of epilepsy for people with a learning disability and their carers.</p>	
Danone	E v i d e n c e r e v	General	General	<p>The disclaimer at the beginning of evidence review 12 should be repeated within the guideline itself to further clarify that the recommendations in the draft NICE guideline, including those related to the use of non-pharmacological treatments such as the ketogenic diet need to be considered alongside individual needs, preferences and values of patients or service users.</p>	<p>Thank you for your response. The disclaimer has been included at the start of each review chapter; however, it is not in the standard template of the guideline document. We will pass on your suggestion to the NICE editors.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	i e w 1 2				
Danone	E v i d e n c e r e v i e w 1 2	21	006-009	There is a wide evidence base for the efficacy, use, recommendation and implementation of the ketogenic diet (Kossoff et al 2018). The guideline committee were aware of cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life. However, this evidence does not appear to have been fully taken into consideration, with the focus of the evidence review being based only on results from randomised control trials (RCT) in the Cochrane review. Meeting the stringent criteria of Cochrane reviews in clinical studies concerning nutritional interventions has difficulties, as they are very resource intensive and there are frequently challenges in: Blinding -in the case of the ketogenic diet, blinding is extremely difficult as an individual's dietary intake is radically altered, Finding an appropriate control- the ketogenic diet as food or as a feed is very different to a standard diet or feed, Patient	Thank you for your response. Please be assured the points raised were taken into consideration when discussing evidence. The recommendations made are evidence-based and therefore need to focus on the evidence included in the Cochrane review. However, the guideline committee have amended the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see recommendation 8.1.1.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recruitment and adherence-the ketogenic diet a requires large changes to nutritional intake/routine /lifestyle and response to the ketogenic diet typically may take 3 months or more, Patient numbers- due to the factors involved above there are difficulties recruiting patients and attrition rates are high. Whilst we acknowledge that Cochrane reviews evaluate the highest quality of clinical evidence in selecting RCT, these types of studies in the field of nutrition are often infeasible. Evidence-based clinical practice in nutrition and dietary intervention is generally based upon a broader range of clinical evidence. Therefore, we are concerned that the Cochrane review may not reflect the full range of clinical evidence on the use of ketogenic diet therapy in drug-resistant or complex epilepsy. We agree that further research is required to support ketogenic diet therapy in clinical practice, however we believe the current draft recommendation 8.1.1 will lead to limited patient access to ketogenic diet services and thereby limit future research. There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. There is a wide evidence base for the efficacy, use, recommendation and implementation of the ketogenic diet (Kossoff et al 2018). The guideline committee were aware of cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life. However, this evidence does not appear to have been fully taken into consideration, with the focus of the evidence review being based only on results from randomised control trials (RCT) in</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>the Cochrane review.</p> <p>Meeting the stringent criteria of Cochrane reviews in clinical studies concerning nutritional interventions has difficulties, as they are very resource intensive and there are frequently challenges in:</p> <ul style="list-style-type: none"> • Blinding – in the case of the ketogenic diet, blinding is extremely difficult as an individual's dietary intake is radically altered. • Finding an appropriate control – the ketogenic diet as food or as a feed is very different to a standard diet or feed. • Patient recruitment and adherence – the ketogenic diet a requires large changes to nutritional intake/routine/lifestyle and response to the ketogenic diet typically may take 3 months or more. • Patient numbers – due to the factors involved above there are difficulties recruiting patients and attrition rates are high. <p>Whilst we acknowledge that Cochrane reviews evaluate the highest quality of clinical evidence in selecting RCT, these types of studies in the field of nutrition are often infeasible. Evidence-based clinical practice in nutrition and dietary</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>intervention is generally based upon a broader range of clinical evidence. Therefore, we are concerned that the Cochrane review may not reflect the full range of clinical evidence on the use of ketogenic diet therapy in drug-resistant or complex epilepsy. We agree that further research is required to support ketogenic diet therapy in clinical practice, however we believe the current draft recommendation 8.1.1 will lead to limited patient access to ketogenic diet services and thereby limit future research.</p> <p>There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al 2018), it is important that NICE is cautious about any changes to relevant clinical guidance.</p> <p>Nutricia, in alignment with the British Specialist</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations.</p> <p>Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration of the use of a ketogenic diet.'</p> <p>If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to:</p> <p>'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with</p> <ul style="list-style-type: none"> • drug-resistant epilepsy if appropriate AED treatment options have been unsuccessful or • certain childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut 	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>syndrome (see the section on treating childhood-onset epilepsies).'</p> <p>This will provide clarity that patients with drug resistant or complex epilepsy should have continued access to ketogenic diet therapy services, whilst further research is conducted, rather than unnecessarily restricting patient access to ketogenic diet therapy services. We believe this is in line with the guideline committee's intent: (Evidence review 12, page 21, lines 10-14) 'The guideline committee were mindful of the importance of keeping ketogenic diets as an option for people in whom other treatment options have been exhausted. They therefore agreed that although ketogenic diets should not be routinely recommended, it should continue to be available as a treatment option within the NHS based on individual clinical need.'</p> <p>References: Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. <i>Epilepsia</i>. 2010 Jun;51(6):1069-77. doi:</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: Epilepsia. 2010 Sep;51(9):1922. PMID: 19889013 Kossoff EH, Zupec-Kania BA, Auvin S, et al Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175-192. Published 2018 May 21. doi:10.1002/epi4.12225 Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group (nih.gov)	
Danone	Guideline	General	General	We request the committee clarify if Glut1 Deficiency Syndrome is included within the scope of the draft recommendations.	Thank you for your response. Glut 1 deficiency syndrome is not excluded from the scope (please see scope document), however there was no evidence for this population in the Cochrane review included for the ketogenic diet chapter.
Danone	Guideline	General	General	We request the committee clarify if the use of Cannabidiol (CBD) as a treatment of epilepsy is included within the scope of the draft guidelines and consultation. As NICE will be aware, there is a	Thank you for your comment. In accordance with NICE process, the guideline must refer to any existing Technology Appraisals relating to the guideline. Therefore, the recommendations for Dravet syndrome

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	e l i n e			lack of substantiated, long-term data surrounding the use of CBD as a treatment for drug resistant epilepsy. We would be concerned if CBD was included as a preferred management option ahead of ketogenic diet therapy, which is supported by both robust clinical evidence, healthcare professionals and patients.	and Lennox Gastaut syndrome must refer to TA614 and TA615 relating to cannabidiol and its place in the treatment pathway.
Danone	G u i d e l i n e	39	015-017	There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, in spite of long-standing evidence that it is an effective treatment. There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in	Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions. The committee further discussed the evidence and made amendments to the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, in spite of long-standing evidence that it is an effective treatment. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>for consideration of the use of a ketogenic diet.'</p> <p>If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to:</p> <p>'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with</p> <ul style="list-style-type: none"> • drug-resistant epilepsy if appropriate AED treatment options have been unsuccessful or • certain childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (see the section on treating childhood-onset epilepsies).' <p>This will provide clarity that paediatric patients with tonic or atonic seizures should have continued access to ketogenic diet therapy services which have been shown to be effective in managing tonic and atonic seizures (Vining 2009) whilst further research is conducted, rather than unnecessarily restrict access to ketogenic diet therapy services. We believe this is in line with the guideline committee's intent: (Evidence review 12, page 21, lines 10-14) 'The guideline committee were mindful of the importance of keeping ketogenic diets as an option for people in</p> 	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>whom other treatment options have been exhausted. They therefore agreed that although ketogenic diets should not be routinely recommended, it should continue to be available as a treatment option within the NHS based on individual clinical need.'</p> <p>References: Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. <i>Epilepsia</i>. 2010 Jun;51(6):1069-77. doi: 10.1111/j.1528-1167.2009.02397.x. Epub 2009 Nov 3. Erratum in: <i>Epilepsia</i>. 2010 Sep;51(9):1922. PMID: 19889013 Kossoff EH, Zupec-Kania BA, Auvin S, et al Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. <i>Epilepsia Open</i>. 2018;3(2):175-192. Published 2018 May 21. doi:10.1002/epi4.12225 Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Diet Study Group (nih.gov) Vining EP. Tonic and atonic seizures: medical therapy and ketogenic diet. Epilepsia. 2009 Sep;50 Suppl 8:21-4. doi: 10.1111/j.1528-1167.2009.02231.x. PMID: 19702729.	
Danone	Guideline	43	24-28	There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, in spite of long-standing evidence that it is an effective treatment. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to	Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions. The committee further discussed the evidence and made amendments to the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration of the use of a ketogenic diet.'</p> <p>If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to: 'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with drug-resistant epilepsy if appropriate AED treatment options have been unsuccessful or certain childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (see the section on treating childhood-onset epilepsies).' This will provide clarity that patients with Dravet syndrome should have continued access to ketogenic diet therapy services which have been shown to be more beneficial (>70%) than the average 50% ketogenic diet therapy response (defined as >50% seizure reduction) in managing Dravet syndrome (Kossoff</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				et al, 2018; Dressler et al, 2015; Caraballo et al, 2005) whilst further research is conducted, rather than unnecessarily restrict access to ketogenic diet therapy services. We believe this is in line with the guideline committee's intent: (Evidence review 12, page 21, lines 10-14) 'The guideline committee were mindful of the importance of keeping ketogenic diets as an option for people in whom other treatment options have been exhausted. They therefore agreed that although ketogenic diets should not be routinely recommended, it should continue to be available as a treatment option within the NHS based on individual clinical need.' References	
Danone	Guideline	46		There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the	Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions. The committee further discussed the evidence and made amendments to the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, in spite of long-standing evidence that it is an effective treatment. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration of the use of a ketogenic diet.'</p> <p>If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to: 'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with</p>	
Danone	Gu	49		<p>There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those</p>	<p>Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	d e l i n e			<p>patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the proposed recommendation will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, in spite of long-standing evidence that it is an effective treatment. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist</p>	<p>The committee further discussed the evidence and made amendments to the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				for consideration of the use of a ketogenic diet.' If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to:	
Danone	Guideline	57	9	The recommendation does not make any reference to quality of life (QoL) in relation to differences seen in those who have commenced the ketogenic diet therapy. An online survey conducted in 2018 showed that 49% of parents with children on ketogenic diet therapy reported that ketogenic diet therapy had improved their child's QoL (Williams, E et al, 2018). One publication not included in the Cochrane review showed 87% of adults reported improvements in their QoL after 3 months of commencing dietary intervention (Roehl K. et al, 2021). There are concerns to why the patient and/or parent perspective has not been included in the consultation. NICE guidance (CG137 2012) makes reference to the quality of life as part of its research of secondary outcomes. We request NICE provide further evidence on the impact of ketogenic diet therapy on QoL. References: Williams E, Szewc C, Emlyn-Jones N. Coping with Complex Epilepsy Whilst Striving for a Quality of Life for the Whole Family – Facilitating a Parent's	Thank you for your response. The evidence included in the review was from randomised trials which met the protocol inclusion requirement. It is not possible at this stage to add further evidence for the review. The committee acknowledge the need for further evidence in this area and have therefore drafted a research recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Perspective. Neurodigest 2018 Winter; 4:15-16. Available from: https://neurodigest.co.uk/coping-with-complex-epilepsy-whilst-striving-for-a-quality-of-life-for-the-whole-family-facilitating-a-parents-perspective/ [Accessed 29.12.2021]	
Danone	Guideline	57		Nutricia is concerned that the wording of the recommendation in section 8.1.1 in relation to use of ketogenic diet therapy is not clear. Please can the committee clarify what the 'all other treatment options' includes? Nutricia is concerned that the wording suggests the ketogenic diet therapy should only be explored as a last resort treatment after all other treatment options, and that there is a risk that the option of ketogenic diet therapy in this complex patient group with drug resistant epilepsy will be limited. This recommendation could therefore affect patient access to ketogenic diet therapy when anti-epileptic drugs (AEDs) have been unsuccessful in controlling their epilepsy. There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure	Thank you for your response. The recommendation for ketogenic diets has been amended to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia, in alignment with the British Specialist Nutrition Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration of the use of a ketogenic diet.' If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to: 'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with	
Danone	Gu	113		There are substantial studies to show the efficacy of ketogenic diet therapy in both children	Thank you for your response. Please be assured the points raised were taken into consideration when

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	i d e l i n e			(Kossoff and Wang, 2013) and adults (Williams and Cervenka, 2017), the authors concluded that the use of ketogenic diet therapy in children with refractory epilepsy has been shown to reduce the number of emergency admissions. Another paper showed a reduction of costs in children when treated with the ketogenic diet (Mandel et al, 2002). One centre in the UK (Bristol) has shown the costs required of dietetic time can result in savings from emergency admissions over a two year period (Lord and Magrath, 2010). Nutricia requests that these studies are taken into consideration for this guideline. There is a wide evidence base for the efficacy, use, recommendation and implementation of the ketogenic diet (Kossoff et al, 2018). The guideline committee were aware of cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life. However, this evidence does not appear to have been fully taken into consideration, with the focus of the evidence review being based only on results from randomised control trials (RCT) in the Cochrane review.	discussing the evidence. Although there was some benefit seen for ketogenic diet, there was high risk of bias in the studies due to unclear methodological reporting, missing data, imprecision in the data for many outcomes and heterogeneity observed in data sets. Along with the high-cost implications, the committee could not strongly recommendation ketogenic diets. The committee have amended the recommendation to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Danone				Meeting the stringent criteria of Cochrane reviews in clinical studies concerning nutritional interventions has difficulties, as they are very resource intensive and there are frequently challenges in: Blinding – in the case of the ketogenic diet, blinding is extremely difficult as an individual's dietary intake is radically altered. Finding an appropriate control – the ketogenic diet as food or as a feed is very different to a standard diet or feed. Patient recruitment and adherence – the ketogenic diet a requires large changes to nutritional intake/routine/lifestyle and response to the ketogenic diet typically may take 3 months or more. Patient numbers – due to the factors involved above there are difficulties recruiting patients and attrition rates are high. Whilst we acknowledge that Cochrane reviews evaluate the highest quality of clinical evidence in selecting RCT, these types of studies in the field of nutrition are often infeasible. Evidence-based clinical practice in nutrition and dietary intervention is generally based upon a broader range of clinical evidence. Therefore, we are concerned that the Cochrane review may not reflect the full range of clinical evidence on the use of ketogenic diet therapy in drug-resistant or complex epilepsy. We agree that further research	Thank you for your response. Please be assured the points raised were taken into consideration when discussing the evidence. Although there was some benefit seen for ketogenic diet, there was high risk of bias in the studies due to unclear methodological reporting, missing data, imprecision in the data for many outcomes and heterogeneity observed in data sets. Along with the high-cost implications, the committee could not strongly recommendation ketogenic diets. The committee have amended the recommendation to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is required to support ketogenic diet therapy in clinical practice, however we believe the current draft recommendation 8.1.1 will lead to limited patient access to ketogenic diet services and thereby limit future research.	
Danone	Guideline	113	22-25	There is a wide evidence base for ketogenic diet therapy as an option for the effective management of drug resistant or in certain genetically inherited epilepsies (Kossoff et al, 2018). Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the body of evidence to demonstrate that ketogenic diet therapy can be effective in a number of these patients, it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia is concerned that the proposed recommendation in 8.1.1. will unnecessarily scale back the use of ketogenic diet therapy as a management for drug resistant epilepsy, despite long-standing evidence that it is an effective treatment. Nutricia is also concerned that the change in recommendations in the guideline could lead to a reduction in offering ketogenic dietary therapy services and options for patients which will limit the ability to conduct further research in future as recommended on the	Thank you for your response. The recommendations are evidence-based and take into considering both the clinical and cost-effectiveness of the interventions. The committee further discussed the evidence and amended the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation. The committee acknowledge the need for further evidence in this area and have thus drafted a research recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				effectiveness and long-term tolerability of ketogenic diets. References:	
Danone	Guideline	113	26-28	<p>Since the introduction of NICE CG137 in 2012, patient numbers have increased from 101 in 2000 to 754 in 2017 (Whiteley et al, 2020), with an increase in centres accepting adult patients with a waiting list thereby showing the impact of the recommendation of the ketogenic diet therapy. Therefore, Nutricia is concerned that the changes to the NICE recommendations will have a significant impact on current clinical practice. Nutricia requests that NICE further examines any potential impact changes to the NICE guidelines will have on clinical practice. There remains strong evidence that ketogenic diet therapy is an essential tool in the effective management of epilepsy, particularly in those patients whose form of epilepsy is drug resistant or in certain genetically inherited epilepsies. Given that 36% of epilepsy patients have inadequate control of seizures with anti-seizure medication (Kwan et al, 2010), and the strong body of evidence to demonstrate that ketogenic diet therapy can be effective in these patients (Kossoff et al, 2018), it is important that NICE is cautious about any changes to relevant clinical guidance. Nutricia, in alignment with the British Specialist Nutrition</p>	<p>Thank you for your response. The committee have amended the recommendation for ketogenic diets to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Association (BSNA), proposes that the wording of section 8.1.1 is clarified and more reflective of the previous NICE recommendation (CG137 2012) which refers to consideration of the ketogenic diet as a management option for those whose seizures continue despite trying appropriate AED combinations. Proposed wording based on the previous NICE recommendation (CG137 2012): 'Refer children, young people and adults with epilepsy whose seizures have not responded to appropriate AEDs to a tertiary epilepsy specialist for consideration of the use of a ketogenic diet.' If this proposed wording is not considered acceptable, then BSNA requests that the wording of the guideline section 8.1.1 is clarified by amending to: 'Consider a ketogenic diet under the guidance of a tertiary epilepsy specialist, in people with	
Danone	Guideline	General	General	We request the committee clarify if Glut1 Deficiency Syndrome is included within the scope of the draft recommendations.	Thank you for your comment. The scope of this guideline covers diagnosing and managing epilepsy in children, young people and adults and therefore Glut1 deficiency syndrome is outside the scope.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Danone	Guideline	General	General	We request the committee clarify if the use of Cannabidiol (CBD) as a treatment of epilepsy is included within the scope of the draft guidelines and consultation. As NICE will be aware, there is a lack of substantiated, long-term data surrounding the use of CBD as a treatment for drug resistant epilepsy. We would be concerned if CBD was included as a preferred management option ahead of ketogenic diet therapy, which is supported by both robust clinical evidence, healthcare professionals and patients.	Thank you for your comment. In accordance with NICE process, the guideline must refer to any existing Technology Appraisals relating to the guideline. Therefore, the recommendations for Dravet syndrome and Lennox Gastaut syndrome must refer to TA614 and TA615 relating to cannabidiol and its place in the treatment pathway.
Danone	Evidence review 12	general	General	The disclaimer at the beginning of evidence review 12 should be repeated within the guideline itself to further clarify that the recommendations in the draft NICE guideline, including those related to the use of non-pharmacological treatments such as the ketogenic diet need to be considered alongside individual needs, preferences and values of patients or service users.	Thank you for your response. The disclaimer has been included at the start of each review chapter; however, it is not in the standard template of the guideline document. We will pass on your suggestion to the NICE editors.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Danone	R e g i s t e r o f i n t e r e s t s	General	General	Whilst we understand the need to avoid conflict of interest in the creation of guidelines, we note from the register of interests that certain committee members with expertise in ketogenic diet therapy were not actively involved in drafting the recommendations in this area. Given that clinical expertise in the use of the ketogenic diet is confined to a small group of clinicians, it would seem that relevant expertise and knowledge is potentially missing from the discussion on the benefit of the diet for patients in clinical practice. As a significant stakeholder we would like to understand more about the process used to reach the latest NICE position on the use of ketogenic diet therapy, and we would be grateful for clarity on how this decision was made to be shared with all interested parties.	Thank you for your response. As per the NICE conflict of interest policy, people with a direct interest in the topic of discussion were excluded. Other committee members with knowledge and experience of ketogenic diet but without a conflict of interest drafted the recommendations.
Dravet Syndrome UK	Evidence review K	012	009-018	These statements on caution around sodium valproate do not reflect the realities of living with Dravet Syndrome. While clinicians have a duty to explain the risks associated with sodium valproate in women and girls of child-bearing age, it is important to recognise that most girls and women with Dravet Syndrome are highly unlikely to bear children due to their overall	Thank you for your comment. The committee agreed that sodium valproate should be offered as a first line treatment and that pregnancy was rare for people with Dravet Syndrome. However, due to the risks associated with sodium valproate, the committee agreed that these risks must be fully understood by service users and carers before prescribing it, even if the likelihood of pregnancy is low. The committee

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				health and learning disabilities, while sodium valproate is one of the few available medications that can help with seizure control in Dravet Syndrome. Any prescribing decisions around sodium valproate should balance overall risks and benefits in the specific context of Dravet Syndrome, rather than generic advice around sodium valproate. We request that this statement is amended accordingly.	agreed that any decisions around prescribing sodium valproate should balance these risks and benefits (with the understanding that the benefits might regularly outweigh the risks for people with Dravet Syndrome). The committee have strengthened the wording of recommendation 6.1.2 to emphasise the potential benefits of sodium valproate in light of the lack of evidence to support other first-line treatments for Dravet Syndrome, and the committee's discussion of the evidence has been updated to reflect their understanding that the risks and benefits of sodium valproate for people with Dravet Syndrome are different. Additionally, 'likelihood of pregnancy' has been added to recommendation 4.1.1 as a factor to take into account when developing a treatment strategy. The committee agreed this would clarify the importance of this consideration for people who are unlikely to become pregnant, including people with neurodevelopmental disorders.
Dravet Syndrome UK	Evidence review K	012	027-028	<p>"Stiripentol is not licensed in the UK". We understand this statement to be factually incorrect. Stiripentol is licensed in the UK (see Summary of Product Characteristics and BNF entry). Also stiripentol is accepted for NHS use in Scotland and Wales.</p> <p>In addition, there is a common misperception that stiripentol is not indicated for us in adults.</p>	<p>Thank you for your comment. Confusion arose due to older nomenclature complicating understanding of the licensing of stiripentol. This statement has now been deleted from the committee's discussion of the evidence.</p> <p>The committee agreed that stiripentol should be considered for use in adults as a first-line add-on</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Please clarify that stiripentol can be continued to be prescribed in adults, as we know of numerous examples from our Dravet Syndrome community, where patients are refused continuation of stiripentol after turning 18, even when this has an adverse affect on seizure control. For a summary of some of the confusion around stiripentol prescribing and a clear statement supporting use in adults, please see an article from the Association of British Neurologists, entitled ' Stiripentol use in adults with Dravet Syndrome ', authored by Dr Simona Balestrini and Professor Sanjay Sisodiya for the Association of British Neurologists Epilepsy Advisory Group.	therapy and it is therefore recommended for people with Dravet Syndrome in recommendation 6.1.4. The article 'Stiripentol use in adults with Dravet Syndrome' would not have been included because it did not meet the inclusion criteria as set out in the protocol, due to the fact that it is an audit of 13 participants and not an RCT or a systematic review of an RCT.
Dravet Syndrome UK	Evidence review K	012	011	We were extremely concerned to see s factual error in the statement: "two-thirds of children outgrow this syndrome". This is factually incorrect. Dravet Syndrome is a genetic epilepsy caused by a mutation in the sodium ion channel gene. It is a life-long condition, affecting children and adults. Dravet Syndrome is increasingly recognised and newly diagnosed in adulthood, and around 85% of children with Dravet Syndrome survive to adulthood. Please remove this statement as its inclusion in these guidelines could lead to individuals with	Thank you for your comment. This statement was written in error and has been removed.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the condition being misdiagnosed and/or not given access to effective treatment, causing immeasurable harm to medically-vulnerable individuals.	
Dravet Syndrome UK	Guideline	004	002-017	<p>We appreciate this is general advice and that there are separate sections dealing with specific epilepsies. However, as prolonged febrile seizures occurring between 3-9 months are a key diagnostic sign of Dravet Syndrome, we suggest including the following:</p> <ul style="list-style-type: none"> • While febrile seizures in infancy are common (and not necessarily an indicator of epilepsy) be aware that prolonged febrile seizures in early infancy (e.g. 3-6 months) are less common. Consider investigating for Dravet Syndrome if infants present with prolonged febrile seizures but with a normal EEG and development. 	Thank you for allowing us to expand on this area. The committee have added a separate recommendation to try and cover complicated (complex) febrile seizures. While not specifying Dravet syndrome per se, the Committee have agreed a recommendation that all complicated febrile seizures are represent a risk for developing epilepsy. The consideration was to leave the recommendation as broad as possible to ensure that appropriate escalation of care is made for all children with complicated febrile seizures .
Dravet Syndrome UK	Guideline	008	006-020	<p>Although 1.4.2 talks about discussing the possible implications of genetic testing with the patient/family, we are concerned that the importance of genetic counselling is not emphasised clearly enough in this section. Genetic testing and eventual diagnosis of a genetic epilepsy can be extremely traumatic. We know from feedback from the Dravet Syndrome community that we support, that genetic</p>	Thank you for your comment, the recommendations have been amended to refer to the consent process of the NHS Genomic Medicine Service, part of which is the requirement for counselling.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				counselling is often absent when results are presented. We would request that genetic counselling always accompanies the process of genetic testing, particularly if the genetic test is confirmatory.	
Dravet Syndrome UK	Guideline	039	014	There is no mention here of Vagus Nerve Stimulation (VNS). VNS therapy may be a helpful option for some, although - like all treatments for Dravet Syndrome - not everyone with responds in the same way. We suggest including mention of VNS therapy in addition to ketogenic diet on this section on Further Treatment Option.	Thank you for your comment, section 8.3 recommends that VNS is considered where resective epilepsy surgery is not suitable for a person with drug-resistant seizures.
Dravet Syndrome UK	Guideline	042	007-018	Section on sodium valproate. We know some examples from our Dravet Syndrome community, where some parents/carers have had issues with the continuation of sodium valproate prescriptions when their daughter with DS reaches childbearing age. While clinicians have a duty to explain the risks, it is important to recognise that most girls and women with Dravet Syndrome are highly unlikely to bear children due to their overall health and learning disabilities. Any prescribing decisions around sodium valproate should balance overall risks and benefits in the specific context of Dravet Syndrome, rather than generic advice around sodium valproate.	Thank you for your comment. The committee were very aware of the issues you raise when discussing the draft recommendations. Due to the issues you raise, sodium valproate has been recommended as first line treatment for males and females for Dravet Syndrome and Lennox Gastaut Syndrome as recognition of this. For all other seizure and syndrome types where sodium valproate is recommended, an alternative is always tried for women and girls who are able to have children.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Dravet Syndrome UK	Guideline	042	003	<p>We appreciate that there is limited space available within the epilepsy guidelines to include detailed information on each syndrome/epilepsy type. However, given the severity of Dravet Syndrome and the fact that the syndrome is not limited to seizures, we would request some brief additions to this section on Dravet Syndrome to ensure clinicians are made aware of the severity of the condition. We feel strongly that including these points within the guidelines will help ensure individuals with this devastating condition, and their parents/carers, receive appropriate treatment, care and support. These points include the following:</p> <ul style="list-style-type: none"> • Dravet Syndrome is one of the most treatment-resistant epilepsies. Clinicians should be aware that treatment response is variable between individuals and that the pattern of seizures change over time and can be highly unpredictable. • Emergency care plan - it is essential that all individuals with Dravet Syndrome have an Emergency Care Plan as they are subject to severe, frequent and prolonged seizures; status epilepticus is common, especially in younger patients. Please include some guidance to 	<p>Thank you for your comment. The committee appreciate the complexities and additional needs of those with Dravet syndrome. However, they agreed that all the early onset epilepsies have similar issues to consider and therefore did not feel it appropriate to make these additional recommendations here. The recommendations made in this guideline should ensure that all those with these complex types of epilepsies will have a specialist neurologist involved in their care who will be aware of these complexities.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>ensure parents/carers have an emergency care plan in place.</p> <ul style="list-style-type: none"> • Dravet Syndrome is not limited to seizures. The condition also encompasses learning disability (severe to profound for the majority) and a spectrum of comorbidities. Left unmanaged and unsupported, these comorbidities can have a substantial negative impact on quality of life for the individual and their family. We suggest including a link to the section on p59 ('Psychological, neurodevelopmental, cognitive and behavioural comorbidities in epilepsy') to make clear the importance of providing coordinated multidisciplinary care. <p>Although SUDEP is mentioned elsewhere in the guidelines, we recommend including an additional note here to ensure that clinicians are aware of the high risk of SUDEP in individuals with Dravet Syndrome (up to 15 times higher than in other childhood epilepsies (see Cooper et al, 2016, and Shmueli et al, 2016) and encouraging them to make parents/carers aware of these risks and provide guidance on how these may be managed. We feel this is extremely important in helping to reduce the high levels of premature mortality in Dravet Syndrome (sadly</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				15% of individuals do not reach their 20th birthday).	
Dravet Syndrome UK	Guideline	042	003	We are concerned that the section on Dravet Syndrome is missing an 'Other Treatment Considerations' section (e.g. like the one on page 37, lines 4-12) with guidance to "not use any of the following antiseizure medications in people with 4 myoclonic seizures because they may exacerbate seizures [followed by list". There is no reason to omit this list from the Dravet Syndrome section, indeed it is essential to include, as use of these medicines in Dravet Syndrome can not only exacerbate seizures but long-term use may be associated with poorer intellectual outcomes (the underlying cause of Dravet Syndrome is a gene mutation in sodium ion channel, so sodium channel blockers should be used only with caution).	Thank you for your comment. This was an omission and this recommendation has now been added.
Dravet Syndrome UK	Guideline	043	012	Stiripentol use in adults is described as "off label". This seems inconsistent with the Summary of Product Characteristics for stiripentol, which states: "Patients aged ≥ 18 years of age. Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed" and https://bnf.nice.org.uk/drug/stiripentol.html ,	Thank you for your comment, this has been amended to specify that stiripentol is only off licence when initiated in adults, as per the MHRA guidance, to ensure it will not be deprescribed for young people that have been prescribed it in childhood when they reach 18.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>which states that “For Adult Doses of up to 50 mg/kg daily in 2–3 divided doses should be continued for as long as efficacy is observed”. Please correct, as we know of numerous examples from our Dravet Syndrome community, where patients are refused continuation of stiripentol after turning 18, even when this has an adverse affect on seizure control, as there is a misperception that it is not indicated for use in adults.</p> <p>Just for clarification, the indication for stiripentol is: “for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate”. To note, “severe myoclonic epilepsy in infancy” is an old term (no longer widely used) for Dravet Syndrome, it should not interpreted as stiripentol is only for use infancy. Dravet Syndrome is a genetic epilepsy and a life-long condition. Seizures remain throughout life and while the pattern of seizures may change, it is rare for adults to be seizure-free.</p> <p>For a summary of some of the confusion around stiripentol prescribing and a clear statement</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				supporting use in adults, please see an article from the Association of British Neurologists, entitled ' Stiripentol use in adults with Dravet Syndrome ', authored by Dr Simona Balestrini and Professor Sanjay Sisodiya for the Association of British Neurologists Epilepsy Advisory Group.	
Dravet Syndrome UK	Guideline	043	028	Please add Vagus Nerve Stimulation therapy as a potential further treatment option. For the efficacy/safety of VNS in Dravet Syndrome, see Dibué-Adjei et al, 2017.	Thank you for your comment, there is a specific section in the guideline (8.3) that makes recommendations for the appropriate use of VNS.
Eisai Limited	Evidence review F	047	005	There were 2 inconsistencies noted when compared with the source paper Nishida (2018) for this perampanel study for FOS. ITT population in Intervention group should be 529 (=174+175+180), instead of 531. ITT population in Control group should be 175, instead of 176.	Thank you for your comment. For these analyses the total number randomised was used as the denominator for the network and other meta-analyses as discussed in the methods. These figures as reported are consistent with Figure 1 in the source paper. No changes have therefore been made.
Eisai Limited	Evidence review F	048	005	There was an inconsistency noted when compared with the source paper Krauss 2012 (Study 208) for this perampanel study for FOS. ITT population in Control group should be 9, not 10. One patient (placebo group) was excluded from the ITT population due to an invalid baseline seizure diary.	Thank you for your comment. For the analyses the total number randomised was used as the denominator in the analyses and thus would have been 10 for this study. Whilst the study excluded one

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					<p>patient from the intention to treat analysis due to an invalid baseline seizure diary.</p> <p>Whilst it would be reasonable to exclude this person, to be consistent with how we handle other studies in the analysis we included them in our analysis.</p> <p>This is documented in the methods section of the document. Using either denominator would not change the conclusions of the analysis.</p>
Eisai Limited	Evidence review F	050	003	<p>There were 3 inconsistencies noted when compared with the source paper French (2015) for this perampanel study for GTCS.</p> <p>(1) 50% reduction in seizure frequency, full analysis set in Control group should be 32 ($=81 \times 0.395$), not 31.</p> <p>(2) Seizure freedom, full analysis set in Intervention group should be 19 ($=81 \times 0.235$), not 26.</p> <p>Seizure freedom, full analysis set in Control group should be 4 ($=81 \times 0.049$), not 10.</p>	<p>Thank you for your comment, the rounding error has been corrected in the control group to 32 in line with your comment. The values most consistent with our definition of seizure freedom are for those reported as placebo [12.3%] and perampanel [30.9%] in the results section of the source paper. These are consistent with the figures used.</p>
Eisai Limited	Evidence review F	107	002	<p>Correction to title in Figure 8, 'focal seizure' should be replaced with 'generalised tonic-clonic seizures'.</p>	<p>Thank you for your comment. The title of this network plot has been corrected.</p>
Eisai Limited	Guideline	028	004	<p>The guideline states that brivaracetam could be considered as a second-line add-on treatment option for people with generalised tonic-clonic</p>	<p>Thank you for your comment. Where treatments have been recommended off-label this has been stated below the recommendation with a link to NICE's</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>seizures, however, it is not indicated as per its Summary of Product Characteristics (SmPC).</p> <p>SmPC for Brivaracetam: Briviact is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. https://www.medicines.org.uk/emc/medicine/31452#INDICATIONS</p>	information on prescribing medicine which includes advice on prescribing off-label.
Eisai Limited	Guideline	028	008	<p>The guideline states that zonisamide could be considered as a second-line add-on treatment option for people with generalised tonic-clonic seizures, however, it is not indicated as per its Summary of Product Characteristics (SmPC).</p> <p>SmPC for Zonisamide: is indicated as</p> <ul style="list-style-type: none"> • monotherapy in the treatment of partial seizures, with or without secondary generalisation, in adults with newly diagnosed epilepsy; • adjunctive therapy in the treatment of partial seizures, with or without secondary generalisation, in adults, adolescents, and children aged 6 years and above. <p>https://www.medicines.org.uk/emc/product/2410/smpc#INDICATIONS</p>	Thank you for your comment. It has been acknowledged in the text below the recommendation that zonisamide is being recommended 'off-label' for adults and children with generalised tonic-clonic seizures. It also includes a link to NICE's information on prescribing medicine which includes advice on prescribing off-label.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Eisai Limited	Guideline	030	003	<p>The guideline states that perampanel could be considered as a second-line add-on treatment option for people with focal seizures, however, perampanel could be used as first-line add-on treatment as per its Summary of Product Characteristics (SmPC).</p> <p>SmPC for Perampanel: Fycompa (perampanel) is indicated for the adjunctive treatment of</p> <ul style="list-style-type: none"> - partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older. - primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE). <p>https://www.medicines.org.uk/emc/product/7877/smpc#INDICATIONS</p>	<p>Thank you for your comment. The committee based their recommendations on the presented evidence and their own clinical knowledge and experience. Antiseizure medicines could be recommended 'off-label' and where this has occurred it has been noted underneath the recommendation. Alongside this antiseizure medicines were not recommended either first or subsequent lines just because they were licensed as such. The committee was of the opinion that the evidence for the effectiveness of perampanel was weaker than that of other antiseizure therapies. This has been captured in the 'Committee's discussion of the evidence section' of the relevant evidence review.</p>
Eisai Limited	Guideline	090	024	<p>The sentence states '<i>The committee therefore recommended both brivaracetam and levetiracetam as well as phenobarbital, primidone and zonisamide, based on their experience and knowledge of current practice, as possible second-line add-on treatments.</i>' But this is inconsistent with the guidance in section 5.1.6, which considers brivaracetam, lacosamide, phenobarbital, primidone, and zonisamide as</p>	<p>Thank you for your comment, the recommendation was not correct and we have corrected the error.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<i>second-line add-on treatments</i> . Should it be lacosamide or levetiracetam?	
Eisai Limited	Guideline	092	012	Please include a comma after perampanel on line 12, as it currently reads as 'perampanel pregabalin' which is incorrect.	Thank you for your comment, a comma to separate them has now been added.
Epilepsy Action	Comments form Q1	General	General	<p>Given current limitations on resources in terms of funding and workforce in some areas, as well as the ongoing impact of the COVID pandemic, some of the timescales for referrals and reviews may be difficult to meet. While we support these measures, and strongly agree that these should be included, it should be recognised that in some areas meeting these timescales will require improvements in current provision, particularly referring children, young people and adults urgently (for an appointment within 2 weeks) and ensuring a wait of no longer than 6 weeks from referral for an MRI.</p> <p>In addition, offering epilepsy specialist nurse sessions at least twice a year for people with epilepsy who continue to have seizures and ensuring that all children, young people and adults with epilepsy have access to an epilepsy specialist nurse will require improvements in the numbers of epilepsy specialist nurses in some areas, or ensuring that well organised systems</p>	Thank you for your comments, the committee hope the guideline will help commissioners to identify the services that are necessary to deliver a high quality experience for all those with epilepsy, and encourage them to fund and commission services to do so.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				are in place to effectively and efficiently use the current epilepsy specialist nurses.	
Epilepsy Action	Comments form Q2	General	General	As above, the timescales around referrals and access to epilepsy specialist nurses may have cost implications in areas not currently meeting these targets. However, ensuring that well organised systems are in place to effectively and efficiently use the current resources available could mitigate the cost implications.	Thank you for your comment, the committee agree that these recommendations should help to maximise resources to best deliver services to people with epilepsy. The committee acknowledge that this may be challenging for some trusts that do not already have sufficient numbers of ESNs in place, however it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards. The economic modelling work conducted for this guideline also shows the evidence of cost savings both long-term and within the first year from implementing this and the committee hopes this will encourage commissioners to fund these roles to optimise service delivery.
Epilepsy Action	Comments form Q3	General	General	<p>Patient Initiated Follow Ups (PIFU) are an important tool to allow patients to refer themselves back to epilepsy services. Wider use of PIFU would also potentially relieve demands on other areas, though a clear framework for how patients can refer themselves is needed to ensure that this is successful.</p> <p>Providing EEG access through accident and emergency services would help to ensure quick access for patients. Improving the timescales of</p>	Thank you for your response. NICE guidelines do not usually make direct recommendations as to how services should be commissioned, as this will partly be down to local service configurations. However, the committee hope that the recommendations they have made will ensure that commissioners are able to recognise the services needed to deliver a high quality of care and commission them accordingly.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>access to EEG would also further speed up diagnosis and help better targeting of epilepsy medications.</p> <p>Video sharing facilities to allow people with epilepsy to share videos of their seizures would be beneficial to both clinicians and patients in relation to diagnosis.</p> <p>We are aware that some services have started providing Open Access to patients, where patients are able to contact a dedicated helpline with any questions or concerns they have about their health. Where used successfully this has reduced pressures on clinicians. We would also recommend enabling patients to email questions and get a response.</p>	
Epilepsy Action	Comments form Q4	General	General	During the coronavirus pandemic it has become necessary in some circumstances to avoid face-to-face appointments and instead carry out telephone or video assessments. In some cases telephone or video appointments may be sufficient, however we are aware that on occasion these appointments have not been useful and have ended in the patient being called in for a face-to-face appointment.	Thank you for your comment. Recommendation 2.1.2 encourages clinicians to tailor information and support to the individual's needs and circumstances, which the committee hope should reduce wasted appointments.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				While telephone or video appointments may continue to be used as alternatives in future, it is also important to acknowledge when face-to-face appointments are needed so as to avoid wasting clinician and patient time carrying out telephone or video appointments that do not prove to be useful.	
Epilepsy Action	Guideline	General	General	Overall we are concerned that the guidelines do not make enough reference to specific groups and comorbidities, such as older people, people with learning disabilities and people with mental health problems.	Thank you for your comment. The committee considered the needs of these groups when developing the guideline and made the decision to include these considerations as part of the overall recommendations, rather than having separate sections, so they are at the forefront of all professionals' minds when caring for these people. The committee make recommendations for those with learning disabilities in relation to: access to whole genome sequencing (1.4.6); their information needs (2.1.4); supporting them to access tertiary services (3.1.2); drug monitoring (4.5.1) and monitoring in pregnancy (4.6.5); provision of surgery (8.2.4); addressing their mental health and cognitive concerns (9.1.1 and 9.2.2) and planning for transition (11.2.3). On reflection, the committee agreed that more focus is needed on drug interactions and dosage for older people and so a recommendation was added to section 4.1 to reflect this. A recommendation was

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					also added in the Information and support section to ensure it meets the needs of older people.
Epilepsy Action	Guideline	004	003	It is not clear whether the intention is for this assessment to be carried out in A&E or by GPs. We have concerns as to whether A&E would be the appropriate setting, given the knowledge and tools needed to assess second seizure risk.	Thank you for your response. The committee believe this assessment can and should be carried out in A&E to initiate the treatment pathway as soon as possible.
Epilepsy Action	Guideline	005	001	Patients who have had a possible first seizure should be given essential information about how to recognise seizures, first aid and what to do if they have a further seizure while waiting for their first appointment, which was included in the 2012 guidelines. In addition, advice around stopping driving should also be provided.	Thank you for your comment. The committee agree and have added a recommendation to provide this information. Advice on driving is provided in the information and support section of the guideline.
Epilepsy Action	Guideline	005	003	We support the recommendation that patients should get an appointment within two weeks after a first seizure. We especially welcome the recommendation that people with seizure recurrence after remission should also get an appointment within two weeks. However, we are concerned that this may be missed as it is under the heading of referral for first seizure. We would therefore recommend a separate heading for urgent re-referral.	Thank you for your comment. This has been amended to separate seizure recurrence after remission from first seizure.
Epilepsy Action	Guideline	005	016	We are pleased that this has been included in the guidelines as the NASH audit found that witness	Thank you for your response.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				accounts were not being asked for and video footage of seizures is helpful in diagnosing.	
Epilepsy Action	Guideline	006	001	The previous guideline mentions referral to psychological or psychiatric services if NEAD is suspected and this should also be included here, especially as there is no separate guidance on NEAD.	Thank you for your comment. Non-epileptic seizures are not within the scope of this guideline.
Epilepsy Action	Guideline	006	006	We welcome this further clarity on the use of EEG, and it is important that an EEG is carried out quickly. However it is not clear from the guidelines who should be requesting the EEG. In addition the previous guidelines mentioned how diagnostic tests can be difficult for people with learning disabilities, and that facilities should be available for imaging under anesthesia if needed. This is missing from the proposed guidelines and we would ask for this information to be included here.	The person who arranges the EEG would be determined according to local service configuration. It would be anticipated that the person requesting the EEG would be aware of how the EEG is performed (to be able to explain to patients and carers) and the benefits/ limitations of this investigation. Consideration of individual patient needs would be applicable to all people when carrying out diagnostic tests therefore we do not agree this needs to be detailed within the recommendation.
Epilepsy Action	Guideline	008	002	We welcome the proposal to not carry out CT scans for people with established epilepsy presenting at an emergency department after a typical seizure, as the most recent NASH audit found that some people were having repeated scans and the risk was greater than the benefit	Thank you for your comment.
Epilepsy Action	Guideline	008	006	We welcome the inclusion of genetic testing as it would reduce variation in current practice	Thank you for your comment.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Epilepsy Action	Guideline	008	006	We are pleased that it is recommended that the implications and purpose of genetic testing is discussed with patients. We would also recommend that there should be access to genetic counselling	Thank you for your comment, the recommendations have been amended to refer to the consent process of the NHS Genomic Medicine Service, part of which is the requirement for counselling.
Epilepsy Action	Guideline	010	004	We support longer appointments to allow more time for discussion. However, there is not enough emphasis on the appropriate way to hold discussions with people with learning disabilities or other complex needs, particularly autism. More context is needed in this regard and was in the previous guidelines. In addition, throughout these guidelines there is no reference to specific populations, such as people with epilepsy and learning disabilities, older people with epilepsy and people with dementia and epilepsy	<p>Thank you for your response. The committee understands the need for more time and adequate resources to relay information based on the individual's needs, which is reflected in the recommendation 2.1.4.</p> <p>Cross reference has been made to the NICE guideline on challenging behaviour and learning disabilities, Patient experience in adult NHS services, and Babies, children and young people's experience of healthcare. All of these include recommendations on tailoring consultations, communication and information giving according to the needs of the individual.</p> <p>The scope for this guideline outlined the following groups of people that needed specific consideration during development; children and young people, girls and women who are able to get pregnant (including those who are pregnant or breastfeeding), older people and people with learning disabilities. Based on the evidence, where possible these subgroups of people were given special consideration and referred</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					to in recommendations and discussions sections of the guideline.
Epilepsy Action	Guideline	010	010	'Information about their syndrome and/or seizure types' should be added to this list. We speak to people who aren't sure what type of epilepsy they have or what their seizures are called, which can make it difficult for them to find relevant information or support	Thank you for your comment. This has been added.
Epilepsy Action	Guideline	011	001	While we support the idea of a framework, this should instead be a checklist. This would be good practice to ensure that the patient gets to think about all their possible questions. Epilepsy Action would be happy to produce the checklist with appropriate clinical input.	Thank you for your comment. The committee agreed discussions between health professionals and patients, families and carers should not be prescriptive and chose to recommend providing a framework of topics that were identified from the evidence and their own experience as issues commonly raised during appointments. The framework is intended as a tool to aid discussion between the person and the practitioner.
Epilepsy Action	Guideline	014	005	We support referring people with suspected or confirmed epilepsy and a learning disability, physical disability or mental health problem for additional specialist support to manage their epilepsy.	Thank you for your comment.
Epilepsy Action	Guideline	014	011	We support referring people to tertiary epilepsy services if there is uncertainty about the diagnosis or cause of epilepsy as this will help better identify people with epilepsy who would	Thank you for your comment.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				benefit from surgery as well as allowing better targeting of epilepsy medication.	
Epilepsy Action	Guideline	015	006	Sodium valproate and other AED use in pregnancy should be included in this list.	Thank you for your comment, the recommendation has been amended in line with your suggestion.
Epilepsy Action	Guideline	016	003	We support the inclusion of a review of the diagnosis of epilepsy if seizures continue despite an optimal dose of a first-line antiseizure medication. This is especially important given the high rates of misdiagnosis.	Thank you for your comment.
Epilepsy Action	Guideline	019	001	"European" needs clarification in this context. Which European countries does this refer to, and does it include people from the UK or Roma communities?	Thank you for your comment, 'European' is the term used by the MHRA and relates to ethnicity rather than specific country.
Epilepsy Action	Guideline	020	002	The suggestion of regular reviews is welcome, but it is not clear how often this should happen. Regular is too ambiguous and we would welcome greater clarity about how often this should happen	Thank you for your comment. It is not possible to specify a timeframe to review information and advice provided because the frequency would be dependent on individual needs and circumstances and would need to be tailored accordingly.
Epilepsy Action	Guideline	020	008	"Caring for children" is not specific to women with epilepsy and should be included in a more general list as this is an important issue for all people with parental responsibilities.	Thank you for your comment. We agree and have included caring for babies and children safely within the information and support recommendations.
Epilepsy Action	Guideline	021	019	We would welcome clarity about who should carry out the monitoring reviews, as if nobody knows whose responsibility it is it may not happen.	Thank for your response. The committee acknowledge that monitoring typically takes place in a GP practice, carried out by a GP or nurse. This has been detailed in review 7 section 1.1.9.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Epilepsy Action	Guideline	022	002	We would welcome the inclusion of more conditions as part of this serious comorbidity list or providing a link to a wider list of comorbidities.	Thank you for your comment. Examples of the type of comorbidities are given rather than a list because this would be variable and decisions on whether regular review of a patient is required would be dependent on individual circumstances and needs .
Epilepsy Action	Guideline	022	026	There should also be a formal framework for people with epilepsy to refer themselves back to epilepsy services.	Thank you for your comment. All people with epilepsy should be informed on how to access their epilepsy service when required. How this is organised and delivered would be determined locally.
Epilepsy Action	Guideline	025	003	The previous guideline stated that the individualised assessment should always be carried out by a specialist, and so we would ask for clarification about who should carry out the assessment to be included here.	Thank you for your comment, this has been amended to specify that the assessment should be carried out by an epilepsy specialist.
Epilepsy Action	Guideline	026	010	We would suggest adding in unlikely to have children to this list in order to include other considerations such as sexual preference and learning disabilities	Thank you for your comment. The committee discussed this suggestion, however it was agreed that it would be difficult to implement. It is a requirement for NICE guidelines to follow MHRA advice, and therefore the current wording is deemed appropriate.
Epilepsy Action	Guideline	030	011	The language here needs to be clarified to make it clear that this means try one of the first-line treatment options as an add-on.	Thank you for your comment. The guideline has been amended to clarify that if the first choice of drug is unsuccessful, other options in the list should be considered.
Epilepsy Action	Guideline	030	027	The language here needs to be clarified to confirm whether all first line add-on treatments should be tried or not, before considering second-line add-on treatment options.	Thank you for your comment. The guideline has been amended to clarify that if the first choice of drug is unsuccessful, other options in the list should be considered.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Epilepsy Action	Guideline	058	007	We support referring more people with drug-resistant epilepsy for surgery.	Thank you for your comment.
Epilepsy Action	Guideline	058	014	We support early referral for surgery, as it is counter-productive to keep trying medication when seizure reduction could happen sooner with surgery.	Thank you for your comment.
Epilepsy Action	Guideline	060	013	We are pleased that this has been included, however specific referral advice on cognitive function is not included in the guideline but should be.	Thank you for your response. This review was focussed on the prevalence and not referral criteria, therefore there is no evidence to make a referral recommendation.
Epilepsy Action	Guideline	060	016	We support assessing and providing mental health support and treatment for people with epilepsy and depression	Thank you for your response.
Epilepsy Action	Guideline	061	014	We are disappointed that the guidance does not acknowledge other causes of epilepsy-related death, such as suicide, injury and drowning.	Thank you for your response. The review does not exclude any epilepsy related death. The recommendation was based on the available clinical evidence.
Epilepsy Action	Guideline	062	015	We welcome the recommendation that all children, young people and adults with epilepsy have access to an epilepsy specialist nurse. The NGA evidence review O acknowledges the long term savings of ESN led intervention.	Thank you for your comments.
Epilepsy Action	Guideline	063	004	We note the absence of a suggested framework for providing this here, unlike in the section above. The role of epilepsy specialist nurses as educators is key to supporting people with epilepsy.	Thank you for your comment. There is currently a wide range of service provision across the country when it comes to ESNs. In some areas there are successful existing models of ESN involvement and the committee did not wish to over describe a framework

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					as it will be a matter of local implementation to suit the needs of the locality.
Epilepsy Action	Guideline	063	006	We welcome the commitment to ensuring that people who continue to have seizures have access to specialist nurse sessions at least twice a year.	Thank you for your comments.
Epilepsy Action	Guideline	064	009	We are pleased to see the inclusion of guidance on the range of topics that should be discussed with the young person and an acknowledgement that this needs to happen over time not just in a one off appointment	Thank you for your response.
Epilepsy Action	Guideline	067	010	We support the development of a risk prediction tool to detect all-cause mortality including SUDEP in people with a single seizure, however the language here needs to be changed to clarify why this is only suggested for SUDEP in people with a single seizure. The guidance rationale doesn't mention single seizure and indeed we would recommend that the tool be expanded to cover all people with epilepsy not just those who have had a single seizure.	Thank you for your comment. We have clarified the language used in the research recommendation. To summarise, we have suggested the development of a risk prediction tool to detect all-cause mortality including SUDEP in people with epilepsy or those who have had a single seizure and an external validation of a risk prediction tool to detect the probability of epilepsy-related death.
Epilepsy Action	Guideline	069	001	Cannabis Based Medicinal Products, and the use of AEDs in pregnancy, particularly for those AEDs where the CHM review identified there was not currently enough evidence of their safety, should also be included in the recommendations for research.	Thank you for your comment. In line with NICE guideline development methodology, we are unable to make research recommendations for areas we have not reviewed the evidence

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Epilepsy Action	Guideline	069	009	We welcome the development of this tool, but we would also welcome clarity on what should happen in these circumstances while the tool is being developed. Is this left to the judgement of individual clinicians?	Thank you for your comment. For guidance on assessment and risk factors for a second seizure see 1.1 entitled 'referral after a first seizure or remission and assessing risk of a second seizure. Until research is completed health professionals would need to use their clinical judgement and follow current practice.
Epilepsy Action	Guideline	070	002	The research into Digital Health Technologies is very important and we would argue that it should be included in the key recommendations for research. We need this evidence as there are many people with epilepsy looking for guidance and clinicians are currently not able to provide it.	Thank you for your response. The committee believe all the recommendations are important, the key recommendations have been chosen after careful consideration.
Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit	Guideline	General	General	Prep pandemic young persons SRH services were generally very available and accessible providing a full range of contraception but this has fallen off with the provision of services being affected by the pandemic and the challenge is to get these back up and running particularly LARC services and YP services.	Thank you for your response. The committee are mindful of the pandemic. NHS services have been and continue to be adapting to implement recommendations as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. Implementation of the recommendations should take the current context into account. Please see: https://www.nice.org.uk/guidance/ng179 also, for general COVID-19 advice.
Faculty of Sexual & Reproductive Healthcare	Guideline	020	General	4.4.1 – all methods of contraception should be discussed including IUCD's as there is no barrier to age/parity for use of these methods.	Thank you for your response. The recommendation does not specify specific contraception methods therefore all forms of contraception are included.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Clinical Effectiveness Unit					
Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit	Guideline	020	008-009	4.4.6 also that progesterone containing hormones e.g. desogestrel may increase levels of lamotrigine. Again see CEU document www.fsrh-guidance-drug-interactions-hormonal-contraception-jan-2019%20(2).pdf	Thank you for this comment. As will be appreciated, the committee did not think that they could comment on all potential interactions between contraceptive medications and anti-seizure medications. It was thought essential to highlight the common effect of oestrogen on lamotrigine as inadvertent co-prescription of such medications could result in breakthrough seizures. The committee felt that while the progesterone only pill could increase lamotrigine levels in some cases, significant increases resulting in lamotrigine toxicity were not widely observed in clinical practice.
Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit	Guideline	020	010	Consider document produced by CEU on drug interactions and consider referring girls/women using sodium valproate for specialist SRH advice. www.fsrh-guidance-drug-interactions-hormonal-contraception-jan-2019%20(2).pdf	Thank you for your comment and the reference to your resource, however we think the links provided to information from the MHRA are sufficient.
GW Pharmaceuticals	Guideline	014-066	017-016	Jazz are concerned that the wording of this recommendation "specialised treatments (for example, cannabidiol or a ketogenic diet)" may imply that cannabidiol is a specialised treatment	Thank you for your comment, the recommendation has been amended to remove cannabidiol as an example.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				and result in its alignment alongside invasive therapy rather than alongside other anti-seizure medicines. We would suggest the removal of reference to cannabidiol as an example of 'specialised treatments' in all instances where this is mentioned.	
GW Pharmaceuticals	Guideline	008	006-020	<p>Consistent with the UK Life Sciences Vision, genetic testing should be offered as a mandatory investigation to aid diagnosis unless it is clinically not recommended or there is no consent. According to the Life Sciences Vision as set out by the government, the aim is to "<i>Harness the UK's prior investments to fully integrate genomics into health service delivery through the Genomic Medicine Service, and deliver significant advancements in the understanding, diagnosis, and treatment of disease.</i>"</p> <p>Accordingly, genetic testing as a mandatory investigation will closely align epilepsy management with this vision. Given the debilitating nature of epilepsies, accurate diagnoses is important to ensure the right treatment is offered to the right patient at the right time.</p>	<p>Thank you for your comment, whilst the committee appreciate the UK Life Sciences Vision, it did not find the evidence to support mandatory genetic testing in all patient groups. It was noted that this is currently a vision and not a policy and therefore the committee felt the strength of the recommendations was sufficient. The recommendations have, however, been amended to state that tests should be commissioned in accordance with the National Genomic Test Directory.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Reference: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1013597/life-sciences-vision-2021.pdf	
GW Pharmaceuticals	Guideline	043	005-009	<p>As currently worded, recommendation 6.1.4 implies that there is only one potential option for triple therapy (namely adding stiripentol followed by clobazam as a first-line add-on therapy).</p> <p>In practice, clobazam can be used as an option in Dravet Syndrome independently of stiripentol and as such, there are other potential triple therapy options if sodium valproate alone is unsuccessful as first-line monotherapy (for example sodium valproate adding clobazam and cannabidiol). The guidelines should reflect this accordingly to allow clinician judgement on the most appropriate treatment combinations.</p> <p>Lastly, according to the label, cannabidiol can also be prescribed with clobazam within its licensed indication without the need of triple therapy.</p>	<p>Thank you for your comment, the recommendation has been amended so that it does not stipulate that stiripentol should be added before clobazam. Whilst cannabidiol can be prescribed with clobazam without the need of triple therapy according to its licence, the NICE TA614 states: <i>The committee concluded that the company's positioning of cannabidiol with clobazam after 2 treatments in the treatment pathway was appropriate.</i> Therefore the guideline committee also concluded that it was appropriate to recommend the use of cannabidiol with clobazam after two other drugs had been tried (sodium valproate and stiripentol).</p>
GW Pharmaceuticals	Guideline	045	014-023	Recommendation 6.2.4 positions lamotrigine as a second-line monotherapy or as an add-on therapy to sodium valproate for patients with	Thank you for your comment. NICE's technology appraisal on cannabidiol with clobazam for treating seizures associated with Lennox–Gastaut syndrome

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>LGS. The guidance does not refer to any other potential treatment options at this line of therapy. Cannabidiol and clobazam are also treatment options as adjunctive therapies therefore they are a treatment option in this second-line position. We would like the guidance to reflect this potential treatment option.</p> <p>In conjunction with our comment above about Recommendation 6.2.4, we agree with the cannabidiol with clobazam position in 6.2.5 but suggest the guidance should also mention that cannabidiol may be used earlier than third-line.</p>	describes that people with Lennox–Gastaut syndrome would have cannabidiol with clobazam if their drop seizures are not controlled well enough after trying 2 or more antiepileptic drugs, therefore the committee could not recommend these as second-line treatment.
GW Pharmaceuticals	Guideline	046	007-009	Recommendation 6.2.6 as currently presented may be incorrectly assumed to apply only to the treatments listed in 6.2.5, whereas we believe the intention is that this recommendation applies for all add-on therapies (e.g. including add on lamotrigine per 6.2.4). As such, we suggest that 6.2.6 is presented under a separate subtitle “e.g. Starting an add-on treatment in LGS”	Thank you for your comment, we have added the heading as suggested for clarity.
GW Pharmaceuticals	Guideline	084	005-009	This paragraph of text reflects on the switching guidance associated with anti-seizure medications. Although this makes specific reference to generic vs branded products, as currently phrased, Jazz feels this leaves the	Thank you for your comment. It is it is not possible to amend how the medication is referred to as the NICE Cannabis-based medicinal products: clarification of guidance - March 2021 states that: <i>3.1 The guideline made research recommendations for the use of unlicensed cannabis-based medicinal</i>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>guidance open to interpretation with regards to cannabidiol.</p> <p>There can be confusion between cannabidiol in the form of <i>Epidyolex</i>, which is a regulatory approved cannabis-based medicine, and unlicensed cannabis-based products that have not been the subject of randomised controlled trials nor strict manufacturing and quality control processes. We agree that anti-seizure medications differ in their characteristics and that the risk of switching needs to be considered. In the specific example of cannabidiol, we therefore request that wording is introduced to the guidelines that excludes unlicensed cannabis-based products.</p> <p>We also suggest that advice that switching between a licensed cannabidiol treatment and these unlicensed cannabis-based products is not recommended.</p>	<p><i>products for severe treatment-resistant epilepsy. The committee took the view, based on the evidence available at the time, that there was insufficient evidence of safety and effectiveness to support a population-wide practice recommendation (that is, a recommendation relating to the whole population of people with severe treatment-resistant epilepsy).</i></p> <p><i>3.2 The fact that NICE made no such population-wide recommendation should not however be interpreted by healthcare professionals as meaning that they are prevented from considering the use of unlicensed cannabis-based medicinal products where that is clinically appropriate in an individual case. Patients in this population can be prescribed cannabis-based medicinal products if the healthcare professional considers that that would be appropriate on a balance of benefit and risk, and in consultation with the patient, and their families and carers or guardian.</i></p>
Ketocarefoods Ltd and Ketogenic Dietitians	Guideline	General	General	<p>Recommendations</p> <p>KDRN suggest the following amendments to the Guidelines:</p> <ul style="list-style-type: none"> - The ketogenic diet should be considered for 	<p>Thank you for your response. The recommendation for ketogenic diets has been amended by the guideline committee to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy</p>

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Research Network	l i n e			<p>children who continue to have seizures despite appropriate standard and adjunctive treatments</p> <ul style="list-style-type: none"> - Teenagers at transition age that have responded to a ketogenic diet should be supported through transition to appropriate adult services - Suggest supporting adults who continue to have seizures despite trialling 2 ASMs and who wish to try a ketogenic diet as a non-pharmacological treatment option. - Consider use of a ketogenic diet as second- or third-line treatments in specific childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (see the section on treating childhood-onset epilepsies). 	and other treatments have been unsuccessful or are not appropriate, please see recommendation 8.1.1.
Ketocarefoods Ltd and Ketogenic Dietitians Research Network	G u i d e l i n e	113	14	<p>'potential long-term health drawbacks of ketogenic diets' Adverse effects of ketogenic diets (whilst following treatment) are most commonly gastrointestinal, not severe, and are transient. As detailed in the Cochrane Review, 'the most commonly reported adverse effects were vomiting, constipation and diarrhoea for both the intervention and usual care group'. Other potentially more serious reported adverse side effects are rare, with incidence rates generally $\leq 4\%$ in published prospective studies⁵. The Evidence review mentions 'one trial that</p>	Thank you for your response. The committee have discussed at length the points raised and taken them into consideration when determining the clinical and cost-effectiveness of ketogenic diets. The committee have amended the recommendation to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see section 8.1 of the guideline for the updated recommendation.

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>suggested increased adverse events with ketogenic diet'. We presume that this refers to Kim 20166, in which there was a higher incidence of hypercalcuria amongst children receiving a classical KD compared to a Modified Atkins Diet. Whilst an incidence rate of 33% in patients following a classical KD for 6 months certainly warrants close medical supervision, there is no comparison of incidence rates with care as usual (often another ASM) and it should be noted that incidence of renal stones (4%) and osteopenia (6%) 6 months after dietary treatment was much lower. Of note, pharmacological treatments for epilepsy are not free of adverse effects – for example, renal calculi have been shown to occur at an incidence rate of up to 4% in individuals taking carbonic anhydrase inhibitors⁷⁻⁹. As for potential long-term side effects of ketogenic diets, we would like to draw the committee's attention to studies that show normalisation of raised cholesterol and/or triglycerides over time and/or after stopping dietary treatment (usually considered after 2 years, with the exception of individuals with glucose transporter type 1 deficiency syndrome)¹⁰⁻¹³. In a similar vein, evidence for adverse impacted linear growth from dietary treatment is mixed, with more</p>	

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recent studies showing less of an impact in a small proportion of patients (Svedlund et al 2019 ¹⁴ : significant decrease in height SD at 6months but not at 12- or 24months; Armeno et al 2019 ¹⁵ : growth deceleration -1 SD observed in n=4 (9%)). Furthermore, any potential adverse impacts on linear growth in children who follow a ketogenic diet seem to normalise over time and/or after stopping dietary treatment (Kim et al 2013). Consider also potential long-term side effects from other treatments, for example, abnormal lipid levels with ASMs such as everolimus ¹⁶ , carbamazepine and valproic acid ¹⁷ , decreased bone mineral density from phenytoin and carbamazepine ¹⁸ , decreased vitamin D levels from valproic acid ¹⁹ , and abnormal liver function tests with cannabidiol with concomitant valproic acid ²⁰ . Of course, individuals following ketogenic diets must be under close medical and dietetic supervision and the risk/benefit ratio of continuing seizures, the possibility of achieving ≥50% seizure reduction and any (low) potential risks from initiating dietary treatment must be weighed up on an individual basis.	
Ketocarefoods Ltd and	Gu	133	15	'High-cost implications' Treatments such as ketogenic diets, which require intense input from	Thank you for your comment. We acknowledge that both studies were assessed as being partially

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Ketogenic Dietitians Research Network	i d e l i n e			a specialist multidisciplinary team, can often be costly. However, the statement 'ketogenic diet is not cost effective in children' (page 22, line 29) cannot be justified due to the limitations of the evidence available and the fact that it is not fully applicable to the UK. For example, as acknowledged by the committee, inclusion of the cost of a 5-day hospital admission when initiating a ketogenic diet is not reflective of UK current practice. The crucial sensitivity analyses displayed in Evidence review 12, undertaken with De Kinderen 201521, and De Kinderen 201622 and Wijnen 201723, with increased percentage of classical ketogenic diet users and assuming no hospitalisation (more realistic to UK clinical practice), resulted in a higher probability that ketogenic diet was cost effective. Other limitations of these studies, such as the lack of inclusion of all of the randomised controlled trials available, economic analysis based on trials without power to detect a change in quality of life, and not using EQ5D to estimate quality of life, are noted by the committee but seemingly treated as an afterthought.	<p>applicable with potentially serious limitations. However, they still meet the inclusion criteria of NICE to be included as health economic evidence and thus will be considered to help aid the committee consideration of cost effectiveness.</p> <p>As noted, in the committee's discussion of the evidence we have stipulated that the five-day hospital admission is not reflective of current practice. We have updated the evidence review and attempted to estimate the cost effectiveness of a ketogenic diet removing the cost of an inpatient stay (and assuming the benefits of ketogenic diet are the same without this admission). However, even when this cost is removed ketogenic does still not fall between NICE's £20,000 - £30,000 threshold. We have also updated the committee's discussion of the evidence, noting the details of the sensitivity analysis. However, the probability of a ketogenic diet being cost effective is still low and therefore does not provide sufficient evidence to make a strong recommendation for ketogenic diet.</p> <p>The other limitations of the studies were already mentioned in the committee's discussion of the evidence and detailed as reasons for the poor-quality grading of the health economic evidence. We have</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					also deleted the sentence on page 22, line 22 and rephrased this to note the committee could only make a consider recommendation due to the low quality clinical and health economic evidence.
Ketocarefoods Ltd and Ketogenic Dietitians Research Network	Guideline	133	15	'benefits are sometimes seen in clinical practice for a small number of people with drug-resistant epilepsy' There has been a dramatic increase in the use of KD over the last 10 years since the 2012 publication of the NICE epilepsy guidelines: between 2010 and 2017 there has been a 77% increase in the number of KD centres in the UK and Ireland, increasing patient numbers in that same time frame by 647% ²⁴ . This increase is likely in part to the NICE guidelines but must also reflect some level of effectiveness of the intervention in this refractory patient group, together with the development of modified ketogenic diets and medicinal foods to support patients by aiming to improve tolerability, adherence and reducing the risk of adverse effects.	Thank you for your response. This account refers to the specific clinical experience of the guideline committee which was discussed as part of the decision-making process. Please be assured this is not a summary for the general population.
Ketocarefoods Ltd and Ketogenic Dietitians	Guideline	133	027-028	'the recommendations are unlikely to have an impact on current practice' This statement is worrying, as we believe that the 2012 NICE guidelines have had a dramatic impact on accessibility and availability of KD services	Thank you for your response. The committee have amended the recommendation to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate. Please see

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Research Network	l i n e			nationwide (see comment 4) and the proposed changes could be detrimental to this.	section 8.1 of the guideline for the updated recommendation.
Ketocarefoods Ltd and Ketogenic Dietitians Research Network	G u i d e l i n e – G e n e r a l c o m m e	-	-	Recommendations KDRN suggest the following amendments to the Guidelines: The ketogenic diet should be considered for children who continue to have seizures despite appropriate standard and adjunctive treatments. Teenagers at transition age that have responded to a ketogenic diet should be supported through transition to appropriate adult services. Suggest supporting adults who continue to have seizures despite trialling 2 ASMs and who wish to try a ketogenic diet as a non-pharmacological treatment option. Consider use of a ketogenic diet as second- or third-line treatments in specific childhood epilepsy syndromes, for example, infantile spasms, myoclonic atonic epilepsy, Dravet syndrome and Lennox-Gastaut syndrome (see the section on treating childhood-onset epilepsies).	Thank you for your response. The recommendation for ketogenic diets has been amended by the guideline committee to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate, please see recommendation 8.1.1.

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
	n t				
LivaNova	Evidence Review 14 - VNS	General	General	<p>We note that the NCG NICE guideline methods supplement, page 44 (Lines 42-45) states: <i>"When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence."</i></p> <p>To align with the specified NCG methods supplement, we believe that only the clinical evidence and the relevant unit costs should be presented within the evidence review and that discussion regarding the <u>qualitative</u> judgement about cost effectiveness of VNS by considering the expected differences in resource use and unit costs should be outlined in the "The committee's discussion of the evidence" section. We believe this is appropriate to:</p> <ol style="list-style-type: none"> 1. ensure items presented as evidence are factual, 2. ensure there is transparency, in the absence of robust analysis, of the 	<p>Thank you for your comment. In a number of guidelines, we conduct additional calculations to aid the committee's consideration of cost effectiveness. In the absence of health economic evidence these calculations can help committee members develop a better understanding of the relationship between the costs and effects of the interventions being compared.</p> <p>When forming recommendations for guidelines the relationship between the costs and effects would be discussed with the committee in a similar way to how the threshold calculations are presented.</p> <p>This threshold calculation was conducted as part of the guideline development process and therefore omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making.</p> <p>The threshold calculations include evidence identified in the clinical review and quality of life weights which have been used in both economic models for this guideline. The maximum incremental cost was calculated using these two inputs and NICE's cost per QALY threshold, therefore the evidence presented is</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>qualitative judgements of the committee and thereby giving the audience a clear rationale of the recommendation.</p> <p>We believe that the presentation of a 'rough' estimation of a QALY gain in the VNS review as "evidence" is misleading and contrary to the spirit of the guideline. It is acknowledged within the committee discussion section that the uncertainty inherent in these simple calculations was sufficiently substantial for the committee to consider other factors in the formation of the recommendation in favour of VNS. Indeed, as NICE states in the introduction of the Evidence Review for Vagus Nerve Stimulation, 'VNS therapy is considered an option for selected people, with the aim of reducing seizure frequency and intensity and improving quality of life'.</p> <p>We would argue that the "rough calculation" as it is referred to in the draft guidance or 'back of envelope' analysis is not suitable to inform system-wide decision making and should be excluded from, and not presented within, the evidence review on account of serious limitations.</p>	<p>factual. We acknowledge there should be transparency on how these calculations were calculated, and therefore additional information has been added alongside the calculations to further explain the methodology and limitations associated with the analysis.</p> <p>The methodology and limitations of the threshold analysis have been discussed with the committee and this discussion has been updated in the committee discussion of the evidence section.</p> <p>In general, threshold calculations can be a useful addition to the guideline in the absence of health economic evidence when it is not possible to build a full health economic model to aid the committee's consideration of cost effectiveness. NICE fully acknowledge the serious limitations of threshold analyses, and alone these types of analyses would not be sufficient evidence to recommend or not recommend a given intervention. Whenever a threshold analysis is presented to the guideline committee, the costs and effects are qualitatively discussed with the committee and the final recommendations made are based on the clinical and health economic evidence, unit costs and committee opinion.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We would kindly ask for the calculations presented in the VNS review (14) to be removed as "evidence" as they are overly simplistic, do not assist informed decision making and do not provide additional clarity to the rationale of the recommendation.	
LivaNova	Evidence Review 14 - VNS	General	General	<p>As a general point, it appears that "back of envelope" calculations are not subject to the same rigour of analysis or critique which applies to analyses prioritised for economic modelling in the NICE guidance. Unlike other original analyses presented in the guideline, "back of envelope" calculations are not critically assessed nor reported within the evidence statements (i.e. please see Review 13, p24, lines 15-18 for an example of the assessment of the economic model for surgery, an assessment we believe should be undertaken for all de novo analyses – regardless of their simplicity).</p> <p>For example, we believe that "back of envelope" calculations presented for VNS (Review 14) would be critically assessed to have "serious limitations" in accordance with the NICE checklist for economic evidence, due to the over-</p>	<p>Thank you for your comment. We do not write evidence statements for calculations conducted within evidence reviews because these calculations are not pieces of published evidence or full economic analyses. However, the limitations of these are analyses are critically assessed in the committee discussion of the evidence. We acknowledge, that in this instance, the methodology and associated limitations of the threshold calculations were not sufficiently detailed in the committee discussion of the evidence so additional information has been provided in this section of the evidence review. The limitations of the analysis have also been noted in the section of the evidence review the calculations reside in.</p> <p>Evidence statements are provided for pieces of published economic evidence and economic analyses so the reader can easily interpret the quality of</p>

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>simplification of the decision problem, tenuous assumptions, lack of consideration of the relevant outcomes and costs, and lack of sensitivity analysis to evaluate uncertainty. It is not clear why, according to NICE methods, back of envelope calculations can be included within an evidence review without a statement about their quality (or limitations to avoid misinterpretation of their results). When such analyses are used, the committee appears to rely on qualitative judgements in any case considering the uncertainty introduced by the analysis (thus making the calculation redundant in decision making).</p> <p>Inclusion and presentation of 'back of envelope' analyses within an evidence review gives credibility and endorsement to the analyses and results presented – when in fact such results are at best highly uncertain, and at worst, misleading. This issue is compounded when the assumptions inherent in the calculation are not fully transparent and limitations of the analysis are divorced from their presentation (i.e. reported in the committee discussion section).</p>	<p>evidence that is used to inform the decisions of the recommendations. Threshold calculations do not directly inform the decisions of the recommendations but aid the committee's consideration of cost effectiveness.</p> <p>The format of evidence reviews is to present the evidence the committee considered in the main body of the report and a discussion of the evidence presented in the committee discussion of the evidence section. Therefore, the threshold calculations are presented under the unit costs section and discussed in detail in the committee discussion of the evidence. Additional text has been added under the calculations to highlight the uncertainties and provide context to the limitations of the analysis. Additional text has also been added to further explain this in the committee discussion of the evidence.</p> <p>The threshold calculations include evidence identified in the clinical review and quality of life weights which have been used in both economic models for this guideline. The maximum incremental cost was calculated using these two inputs and NICE's cost per QALY threshold, therefore the evidence presented is factual. De novo analyses are conducted to aid the</p>

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11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>In line with our understanding of NICE methodology and process, we believe that the evidence review should either pertain to factual information (such as unit costs) or, peer-reviewed and/or fully critiqued analyses. De novo analyses presented as 'evidence' should at least meet the same NICE quality inclusion criteria as that which applies to published economic evidence.</p> <p>We would strongly recommend that NICE, therefore, remove the "back of envelope" analyses from the evidence reviews presented in this guideline (if they would be assessed to have serious limitations by NICE criteria and therefore not suitable to guide decision making or taken out of context).</p>	<p>committee's consideration of cost effectiveness and used to help inform decisions based on additional evidence presented (for example, clinical and health economic evidence). A threshold analysis alone would not be considered robust evidence to inform a decision and therefore does not need to meet NICE's quality inclusion criteria. As mentioned above, we acknowledge the limitations of the analysis were not sufficiently explained in the section the calculations reside in or the committee discussion of the evidence. Therefore, we added additional information, so this is sufficiently explained.</p> <p>Because this threshold calculation was conducted as part of the guideline development process omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making. Therefore, the threshold calculations will remain within the evidence review. When forming the recommendation for this review question the committee considered the associated limitations of the analysis and due to these limitations and lack of additional evidence made a consider recommendation reflective of current practice. A research recommendation was also made with the hope that in future updates of the guideline more can be said on the cost effectiveness of VNS.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
LivaNova	Evidence Review 14 - VNS	013-014	013-015 014-023	<p>VNS increases in effectiveness in the longer-term, however, this is not represented in the over-simplified calculations presented in the review. This leads to a considerable underestimation of the maximum incremental cost of VNS which was presented to the committee and is presented to the reader.</p> <p>Relatedly, we also note that the trend for improvement in effectiveness outcomes (as demonstrated by the Englot et al. 2016 [1]) is not represented in the 'back of envelope' cost-effectiveness calculations, and therefore, the maximum incremental cost presented is no doubt considerably underestimated. We note that no consideration is given to this limitation (and the uncertainty it introduces) within the main evidence review. Given that only responder rates at 12 months are taken into consideration in the calculations and this may lead to erroneous conclusions about the maximum incremental cost, we ask that the calculations (on page 13, line 15 to page 14, line 23) are removed from the evidence review.</p> <p>1. Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and Predictors of Seizure</p>	<p>Thank you for your comment. Additional information has been added in the section of the evidence review the threshold calculations reside in and in the committee discussion of the evidence to explain that the QALY values used in our analysis are likely an underestimate of the true QALY gains observed from VNS.</p> <p>In these sections we have noted that the RCT used to inform the QALY gains had one-year time horizon and omits the outcome of seizure freedom. We have also provided an explanation of how this will impact the results, noting the effectiveness of VNS increases over time and also noting the limitations and uncertainties with the threshold calculations.</p> <p>Because this threshold calculation was conducted as part of the guideline development process omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making. Therefore, the threshold calculations will remain within the evidence review. When forming the recommendation for this review question the committee considered the associated limitations of the analysis. Overall, due to these limitations and lack of additional evidence the committee made a consider</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery. 2016 Sep;79(3):345-53	<p>recommendation reflective of current practice. A research recommendation was also made with the hope that in future updates of the guideline more can be said about the cost effectiveness of VNS.</p> <p>The protocol for this review was drafted to capture the best available evidence. Since RCT evidence was available there was no need to include other study types or datasets. Englot <i>et al</i>, 2016 was excluded from the review for this reason. We cannot at this stage include ad-hoc studies which deviate from the protocol.</p>
LivaNova	Evidence Review 14 - VNS	013	015	<p>For the non-technical reader (i.e. the clinical or patient audience) without prior training in health economics, the presentation of the calculations within the chapter may lead the reader to incorrectly conclude that the maximum incremental cost is equivalent to the maximum intervention cost (i.e. price).</p> <p>This is an inaccurate interpretation, as the incremental cost is a balance of all costs which may be traded off within the decision problem (i.e. the cost of the device and procedure as noted, but also the downstream cost savings which are realised via the intervention, as well as</p>	<p>Thank you for your comment. Under the presentation of the calculations, we have noted that the maximum incremental cost difference should not be directly compared to the cost presented in the evidence review. We have also highlighted the differences between threshold calculations and economic models to demonstrate that the results of the threshold calculations should be interpreted with caution.</p> <p>In a number of guidelines, we conduct additional calculations to aid the committee's consideration of cost effectiveness. In the absence of health economic evidence these calculations can help committee members develop a better understanding of the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>potential increases in cost in the comparator strategy in the longer term). The balance of such costs, in a decision problem as complicated as the one presented, can only be robustly evaluated within a full economic model.</p> <p>Positioning and presentation of the “back of envelope” analysis within the evidence review gives credibility to the findings and method of analysis, despite the fact that if this analysis was published, it would likely be excluded on the account of serious limitations. If it were included, a summary of the limitations and acknowledgement that it is without full exploration of uncertainty should be represented near the results, as well as a clear and accurate interpretation of what could be deduced from the analysis.</p> <p>We would kindly request that the analysis in this chapter is removed given the potential confusion in its interpretation and lack of critique. Through the removal of these calculations, emphasis can be placed on the qualitative consideration of drivers of cost-effectiveness in the narrative and important evidence gaps can be highlighted to</p>	<p>relationship between the costs and effects of the interventions being compared.</p> <p>We do not write evidence statements for back of the envelope calculations because these calculations are not pieces of published evidence or full economic analyses. However, the limitations of these analyses are critically assessed in the committee discussion of the evidence. We acknowledge, that in this instance, the methodology and associated limitations of the threshold calculations were not sufficiently detailed in the committee discussion of the evidence so additional information has been provided in this section of the evidence review. The limitations of the analysis have also been noted in the section of the evidence review the calculations reside in.</p> <p>Because this threshold calculation was conducted as part of the guideline development process omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making. Therefore, the threshold calculations will remain within the evidence review.</p> <p>Parts of the committee discussion of the evidence have been re-written to place more emphasis on the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>improve future research in this very important therapeutic field.</p> <p>If the calculation of incremental cost is to remain as evidence (and we do not believe it should), a caveat below the maximum incremental cost values should be added, such as: "Please note that the maximum incremental cost reported should not be directly compared with the VNS device and implantation unit costs listed in section 1.1.9. Such an approach would not account for any healthcare resource use savings due to seizures prevented, or minimised in severity or intensity, by VNS.</p>	<p>qualitative assessment of the cost effectiveness of VNS, highlighting the need for additional research. We have also noted that the maximum incremental cost reported should not be directly compared with the VNS device and implantation unit costs listed in section 1.1.9 (in evidence review 14).</p>
LivaNova	Evidence Review 14 - VNS	014	021-023	<p>We note that de novo economic modelling was not prioritised for the evaluation of VNS, and instead a simple "back of envelope" calculation was undertaken to estimate an expected maximum incremental cost to inform decision making and an unclear concluding statement followed (with no explanation of how the results in this concluding statement were derived). We would firstly argue these calculations should be removed from the evidence review. However, at a minimum, the detailed methodology of</p>	<p>Thank you for your comment. The threshold calculations were conducted as part of the guideline development process and therefore omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making.</p> <p>The methodology for the threshold calculations has been updated and a concluding statement has been added.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				obtaining results in the concluding statement should be clarified.	
LivaNova	Evidence Review 14 - VNS	016	006-009	We agree with the observation that benefit accrues and will be seen the longer VNS is used. However, we would argue that if benefit is observed in the shorter term (i.e. 3 or 6 months), the early benefit observed will only increase from this point (and not decrease), and therefore will represent the most conservative assessment of VNS's clinical benefit. That is to say, the incremental benefit observed between VNS+ASMs, and ASMs will only increase over time (especially for drug resistant patients where an increase in clinical benefit of ASMs over time is not likely to be observed). Please could the committee consider this reflection in their qualitative deliberation of the outcomes.	Thank you for your comment. Additional text has been added to the committee's discussion of the evidence noting, the total lifetime QALY gains used in the analysis are likely an underestimation of the true QALYs gains observed due to the effectiveness of VNS increasing over time (especially for those people who see a benefit within the first six months of treatment).
LivaNova	Evidence Review 14 - VNS	016	006-009	We agree with the committee's observation that the effectiveness of VNS is likely to improve over time. We believe, as per the suggested research recommendation, that RCT evidence is not necessarily a superior study type to case control studies or registry analysis to understand longer term outcomes of VNS. We would therefore ask the committee to consider the systematic review	Thank you for the response. The protocol for this review was drafted to capture the best available evidence. Since RCT evidence was available there was no need to include other study types or datasets. Englot <i>et al</i> , 2016 was excluded from the review for this reason. We cannot at this stage include ad-hoc studies which deviate from the protocol.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>and registry analysis by Englot et al. 2016 (1) as supplementary evidence that clearly demonstrates this trend of increased mean percentage reduction in seizure over time with VNS.</p> <p>1. Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery. 2016 Sep;79(3):345-53</p>	
LivaNova	Evidence Review 14 - VNS	017	004-017	<p>Although we agree that quality and uncertainty of the published evidence may mean a “consider” recommendation is appropriate, we do not believe that uncertain results from ‘rough’ calculations are also required to add to the poor evidence base. With the addition or indeed the removal of alternate data points, we have observed an extremely wide range of results, indicating a significant uncertainty in the methodology. The calculation of the maximum incremental cost is not an appropriate method of analysis to help reduce or quantify the uncertainty or assist in the articulation of the complicated and nuanced factors that may drive cost-effectiveness conclusions. This may only be</p>	<p>Thank you for your comment. In a number of guidelines, we conduct additional calculations to aid the committee’s consideration of cost effectiveness. In the absence of health economic evidence these calculations can help committee members develop a better understanding of the relationship between the costs and effects of the interventions being compared.</p> <p>The relationship between the costs and effects would be discussed with the committee in a similar way to how the threshold calculations are presented.</p> <p>Because this threshold calculation was conducted as part of the guideline development process and therefore omitting these calculations would not be</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>done in the context of an economic model, whereby the uncertainty can be quantified and explored via sensitivity analysis.</p> <p>We consider that the results of these scenarios should be removed. If the estimated maximum incremental cost(s) are to remain, they should be contextualised to be likely underestimated and as being highly uncertain due to the serious limitations of the threshold analyses undertaken.</p> <p>Furthermore, the statement that “the maximum cost difference between a strategy of VNS and no VNS in both scenarios was quite low compared to the costs of the device” leads the reader to believe that maximum cost of the device should be the equivalent or less than the incremental cost of two strategies to be considered cost-effective. However, this interpretation is inaccurate. If this section is to remain, please rephrase to make clear that the maximum incremental cost is that which needs to be achieved when all the costs and savings of both compared strategies are considered, and that no quantitative analysis of cost was undertaken as part of the guideline review.</p>	<p>transparent and in line with NICE's ethos for transparent decision making.</p> <p>We have added additional text alongside the calculations and in the committee's discussion of the evidence to highlight the limitations and uncertainties with analysis. In the committee's discussion of the evidence, we have also highlighted that the recommendations were made based on a qualitative discussion of the costs and benefits of VNS, noting the need for additional research in this area.</p> <p>We have also noted that the cost of the VNS device should not be compared to the costs presented in the evidence review. We have highlighted that resource use savings from VNS should also be considered when assessing the cost effectiveness of VNS.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
LivaNova	Evidence Review 14 - VNS	017	035-039	<p>We agree that costs of VNS have the potential to be offset by improvements in QoL observed for people with drug resistant epilepsy and, additionally, there may be cost savings associated with reduction in seizure frequency and/or severity in this group.</p> <p>People with drug resistant epilepsy (DRE) experience significantly more comorbidities, including depression, vascular disorders, seizure-related injuries, and neurological deficits, than those without epilepsy or with epilepsy that responds to treatment (1, 2). For people with DRE, the cost of seizure may be particularly high (especially if the seizure leads to other injuries or complications which, due to the comorbidity of epilepsy and comorbidities associated with epilepsy, may also be expensive to manage). While we acknowledge the reviewed evidence is insufficient to permit accurate calculation of the potential savings associated with seizure prevention, we would argue that this is an important qualitative consideration when discussing the offset of the cost of VNS as an adjunctive treatment to continued pharmacotherapy. Please could this benefit and cost saving be raised, considered, and</p>	<p>Thank you for your comment. We have added additional information to the committee discussion of the evidence on the potential cost savings observed from an improvement in comorbidities and complications associated with drug resistant epilepsy. We have also noted the potential QoL improvements associated with lower levels of depression which may be observed as a result of an improvement in seizure outcomes.</p> <p>The mentioned references were not included in this review as the inclusion of randomised controlled trials was prioritised, please see sections 1.1.2 and 1.1.3 of evidence review 14.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>acknowledged by the committee in their discussion.</p> <ol style="list-style-type: none"> 1. Strzelczyk A, Griebel C, Lux W, Rosenow F, Reese J-P. The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data. <i>Front Neurol.</i> 2017;8:712-. 2. Kantanen AM, Reinikainen M, Parviainen I, Kälviäinen R. Long-term outcome of refractory status epilepticus in adults: A retrospective population-based study. <i>Epilepsy research.</i> 2017;133:13-21. 	
LivaNova	Evidence Review 14 - VNS	017	018 - 021	<p>We find the committee discussion section confusing. Overall, we suggest that considerations regarding the economic trade-offs made would be clearer to the reader without reference to the analyses undertaken (or not undertaken). We believe that there is no need to present the 'back of envelope' calculations' and therefore this section should be revised.</p>	<p>Thank you for your comment. We have updated the committee's discussion of the evidence so the reader can better understand how the decisions for the recommendation were formed.</p> <p>We have discussed the results of threshold calculations at the beginning of the committee's discussion of the evidence and then gone on to qualitatively assess the costs and QALYs associated with VNS and no VNS. We have noted in the committee's discussion of the evidence that the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					<p>recommendations were based on a qualitative discussion of the costs and effects due to the associated limitations and uncertainties of the threshold calculations. We have also highlighted the need for additional research in this area.</p> <p>The threshold calculation was conducted as part of the guideline development process and therefore omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making. We have added additional text below the threshold calculations and in the committee discussion of the evidence to highlight the uncertainties and limitations of these calculations.</p>
LivaNova	Evidence Review 14 - VNS	017	033-034	The data source which informs the health-related quality of life (HRQoL) estimates used to estimate the maximum incremental cost has uncertain generalisability to the population of interest, and the relationship between the prevention of severe seizure and QALY gain is not fully explored. Subsequently, the committee should make a qualitative judgement and consider a research recommendation to improve future economic evaluations in this field.	Thank you for your comment. The estimate which informs HRQoL was also used in two of the health economic models developed for this guideline (the surgery model and ASM model). We appreciate that these estimates may have uncertain generalisability to the population of interest but no additional appropriate QoL estimates were available. We have made a research recommendation for this question. Therefore, hopefully future research in this area will

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>We agree with the committee's observation that people with "frequent disabling seizures may observe a significant improvement in their quality of life through a reduction in seizure frequency" when treated with VNS; however, note that this may not be adequately captured via the "back of envelope" calculations undertaken.</p> <p>We note that the source of the HRQoL data was from unpublished data from the UK SANAD study; however, this study is primarily concerned with the evaluation of first-line anti-seizure medications among patients with newly diagnosed epilepsy and not the management of drug resistant epilepsy. Because the HRQoL derivation and data are unpublished, it is unclear if the HRQoL study population is representative of the drug resistant population currently eligible for VNS (in terms of baseline seizure frequency or severity). We note there appears to be an evidence gap to robustly model the relationship between HRQoL and seizure severity and reduction. Relatedly, and pertinent to QALY estimation, there also appears to be an evidence gap to robustly model the relationship between seizure frequency and severity, and associated morbidity and mortality.</p>	<p>be able to provide more applicable EQ-5D estimates for a drug refractory population.</p> <p>When forming the recommendations for this review question the committee qualitatively discussed the costs and effects of VNS to assess the cost effectiveness of the two strategies being compared – the threshold calculations were provided to aid the committee's consideration of cost effectiveness but could not be used to inform the recommendations due to the uncertainties and limitations associated with the analysis.</p> <p>We have updated the committee's discussion of the evidence to highlight that the QoL weights may have uncertain generalisability to this population of interest.</p> <p>The threshold calculation was conducted as part of the guideline development process and therefore omitting these calculations would not be transparent and in line with NICE's ethos for transparent decision making. We have added additional text below the threshold calculations and in the committee discussion of the evidence to highlight the uncertainties and limitations of these calculations.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We would argue that the simple calculations using this source for HRQoL data are too simplistic to be useful to decision making and lead the reader to underestimate the maximum incremental cost. Furthermore, the limitations cited above (and uncertainty these limitations introduce) are not presented near the analysis. As such, we believe the calculations should be removed from the review. Instead, we would like to kindly ask the committee to acknowledge the evidence gap and consider a research recommendation for a study to evaluate the relationship between seizure severity and HRQoL to better inform future economic modelling and decision making.	
LivaNova	Evidence Review 14 - VNS	017	18-019	The direct comparison of incremental cost to the cost of the device misleads the reader that it is appropriate to compare the incremental cost between two strategies to only one component of the overall cost of the VNS strategy (without recognition of the savings made possible through reduction in seizure frequency or severity, e.g. via reduced hospitalisation). We would suggest removing this statement as it is misleading and suggest it is more simply put as:	Thank you for your comment. We have added additional text below the threshold calculation and in the committee discussion of the evidence noting the incremental cost should not be compared directly to the cost of the device. In the committee's discussion of the evidence, we have also added additional information on the potential cost savings and QALY gains associated with VNS.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<i>In the absence of a robust economic evaluation by NICE, a threshold analysis to obtain maximum incremental cost was presented. This was considered to contain lots of uncertainties, so instead the committee made qualitative judgements about the potential cost differences observed between the two strategies being compared.</i>	A sentence has been added to the committee's discussion of the evidence to illustrate the decisions made by the committee were based on a qualitative discussion due to lack of health economic evidence and the associated limitations and uncertainties with the threshold analysis.
LivaNova	Evidence Review 14 - VNS	067	General	We thank the committee for due consideration of VNS as a management strategy in the reduction in epileptic seizures and welcome the research recommendation to assess the effectiveness of VNS in people with drug resistant epilepsy, including people with learning disabilities as a subgroup. LivaNova is planning a real-world evidence comparative prospective study to help strengthen the evidence base regarding the longer-term outcomes of people treated with VNS and anti-seizure medication (ASMs) in comparison to best medical care with ASMs only.	Thank you for your response.
LivaNova	Evidence Review 14 - VNS	067	General	We welcome the research recommendation to assess the effectiveness of VNS in people with drug resistant epilepsy. We would like the committee to consider the following outcomes to	Thank you for your comment. We are pleased that you welcomed the research recommendation and agree that this is an important area for research. The role of the Guideline is to specify broad areas of

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>benefit future recommendations in this therapy area:</p> <ul style="list-style-type: none"> • Please consider health related quality of life (HRQoL) alongside wider quality of life measures. In particular, there appears to be an evidence gap to inform the relationship between seizure severity or frequency and HRQoL. • We welcome the inclusion of carer and family burden on quality of life. Please also consider the wider implications of caring for an epileptic patient (such as lost productive time or health care resource). • Please give careful consideration to how prevention of severe or disabling seizure, as well as seizure intensity, is a useful outcome. • Please consider absolute seizure frequency reduction and reduction in seizure severity, alongside relative percentage reduction in seizure frequency, as meaningful outcomes. • Please consider evaluation of the costs and healthcare resources associated with seizure prevention or reduction in severity, in the context that patients 	<p>potential research, but not to be didactic as to what is included in that research. That is the provenance of the potential researchers who will conduct the work. As such, the committee felt that 'effectiveness' was an appropriately broad term that could capture all of the outcomes highlighted.</p> <p>Absolute seizure reduction and seizure severity have been added as outcomes to the research recommendation.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with drug resistant epilepsy will have complex needs and comorbidities.	
LivaNova	Evidence Review 14 - VNS	068	002	<p>Use of the 50% reduction in seizure frequency does not capture all meaningful benefit of VNS. Indeed, the 50% reduction in seizure frequency, although commonly used in clinical studies in this therapeutic area, assumes that only a relative and not absolute reduction in seizure frequency is meaningful in terms of clinical benefit or cost reduction. For someone experiencing a high frequency of disabling seizures, a percentage reduction of less than 50 percent in seizure frequency may be meaningful (both from a clinical and economic viewpoint). We note that no consideration is given to this limitation (and the uncertainty it introduces) within the main evidence review.</p> <p>We would ask the committee to consider absolute seizure reduction and reduction in seizure severity as important outcomes to consider in their discussion of the cost-effectiveness of VNS, and in the research recommendation to enable future economic evaluations to demonstrate the value of VNS in patients with limited treatment options.</p>	<p>Thank you for your response. Along with 50% or greater reduction in seizure frequency, the guideline committee also included seizure freedom (100% reduction in seizure frequency) in the list of primary outcomes which would capture the absolute seizure reduction data. It is not possible to make ad hoc changes to the protocol once the review has been carried out, therefore we cannot add in reduction in seizure severity as an additional outcome at this stage.</p> <p>A sentence has been added to the committee's discussion of the evidence to illustrate the decisions made by the committee were based on a qualitative discussion due to lack of health economic evidence and the associated limitations and uncertainties with the threshold analysis.</p> <p>Absolute seizure reduction and seizure severity have been added as outcomes to the research recommendation.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
LivaNova	Guideline	059	005-010	We thank the committee for the review of vagus nerve stimulation and agree with the wording of the draft recommendations.	Thank you for your comment.
Matthews Friends	Evidence review 12	020	007-008	- The committee refers to 'cases in clinical practice where ketogenic diets have shown credible benefit for select individuals with respect to significant improvements in seizure control and improved quality of life'. It is many more than just cases, given there were 39 Ketogenic centres nationally in 2017 treating 754 patients (Whitely et al., 2020), a number which has no doubt grown further since.	Thank you for your response. This account refers to the specific clinical experience of the guideline committee which was discussed as part of the decision-making process. Please be assured this is not a summary for the general population.
Matthews Friends	Evidence Review 12	022	038-041	This will mean that doctors will want to try every drug and combinations of drugs, VNS and/or surgery on a patient before the diet. We agree that if a patient is a surgical candidate then this is the most important alternative treatment to drugs especially as this could also cure their epilepsy. However, the side effects of a cocktail of medications can severely impact the patient's quality of life and most consensus statements recommend trying Ketogenic therapy after the failure of 2 appropriate anti-seizure medications. VNS is invasive, expensive and can take a long	Thank you for your response. The concerns raised have been discussed and recommendation 8.1.1 has been amended to clarify that ketogenic diet may be considered if the person has drug resistant epilepsy and other treatments have been unsuccessful or are not appropriate Because the evidence was of low quality and shown to be not a cost-effective intervention the committee were unable to make a stronger recommendation. They have made a recommendation for more research to be carried out.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				time to get to therapeutic levels if it is going to work at all. A diet can be initiated and you will know within 3 months usually if it is going to work or not. The only reason we don't have more patients on the diet in this country is that we don't have enough Ketogenic Service for doctors to refer them to, therefore Ketogenic Diet is not an option for doctors when it should be available to them and their patients. We need MORE services and this guideline recommendation will definitely NOT help in this endeavour and therefore those patients with drug resistant epilepsy will have to suffer for longer and have hope taken away from them once again. This is hugely disappointing.	
Matthews Friends	Evidence Review 12	022	042-045	The reason why Ketogenic Diets are not routinely offered is because we don't have enough service available, especially not for adults. Many neurologists want to refer patients for a trial of the diet, but can't as there is no centre to refer them to. We actually need more NHS ketogenic services to be made available for drug resistant epilepsy patients and the recommendations in this guideline will certainly not help with this. Therefore, more patients will suffer with ineffective treatments and a cocktail of drugs and their side effects. We agree that more research	Thank you for your response. Although 13 randomised controlled trials were included in this review, they were of low to very low quality due to the presence of significant risks of bias i.e. unclear methodological reporting, missing data, imprecision in the data for many outcomes and heterogeneity observed in data sets. Consequently, the guideline committee could not be certain of the benefits seen in the evidence favouring ketogenic diets and were unable to recommend ketogenic diets routinely. In such instances a research recommendation is needed for better-quality trials which would provide

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				into the Ketogenic Diet is needed in specific areas, such as the reasons why the diet can cure some epilepsy patients and not others, so we can identify those patients quickly and target services more effectively. However, we disagree that there is limited clinical evidence and that protracted and expensive clinical trials are needed to prove the efficacy or short/long term effects of the diet, we have over a 100 years of studies available. The science IS already there.	more robust support in the future for the use of ketogenic diets.
Matthews Friends	Guideline	057	010 - 016	I wonder how much research is enough. The impact of refractory epilepsy on patients and their entire families health is relevant. To give no other option seems unethical. To deny a treatment that could at worst, be tried for 3 months and discontinued if ineffective, at best, result in a drug refractory patient becoming seizure free, be it child or adult, seems complete madness. How can keto be judged against standard care when standard care hasn't worked?	Thank you for your response. The committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.
Matthews Friends	Guideline	057	010-016	- this is a backward step that will take away families and adults choice to opt for Ketogenic diet therapy. It positions Ketogenic diet therapy as a 'try if all else fails'.	Thank you for your response. The committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Matthews Friends	Guideline	57	010 - 016	This is a massive step backwards, firmly placing Ketogenic diet as a last resort option.	Thank you for your response. The committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.
Matthews Friends	Guideline	57	010 - 016	As you have stated "people with epilepsy" and not just 'Children with epilepsy', I would to thank NICE for including adults along with children especially as there are many studies now for adults as well as children including a global consensus statement written by the world experts in this field.	Thank you for your response.
Matthews Friends	Guideline	57	010 - 016	I am disappointed that NICE used the term "if all other treatment options have been unsuccessful". Most guidelines say to try ketogenic diet therapy if 2 medications have failed (for epilepsy overall). Some "treatment options" such as surgery may be inappropriate for many forms of epilepsy. Neurostimulation (e.g. VNS or RNS) is invasive, requires a dedicated team, and is not available at all places. People with epilepsy have a right to decide and choose to do an approach that changes their diet and lifestyle rather than a medication (or surgery) if they and their doctor agree.	Thank you for your response. The committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.
Matthews Friends	Guideline	113	023 - 024	We do not agree that this is needed, There is a 100 years of clinical studies from many different	Thank you for your response. The committee noted that despite there being existing studies for ketogenic

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				centres and countries relating to the Ketogenic Diet being a treatment for both children and adults, proving the efficacy and long term safety of the diet, but apparently not the 'right kind' of research for NICE. Do we now have to waste hundreds of thousands of pounds and many more years, completing a study just for NICE? This is bureaucracy at its worst and not in the best interest of the patients. It is amazing that this is an excuse that is constantly used in relation to the Ketogenic diet, but doesn't seem to be the case when talking about drugs. We see CBD has jumped up to 2 nd line use in some epilepsy syndromes, even when it means adding in not one but 2 medications in some cases, but it is impossible to have long term data on CBD as it is a new drug and let's not forget the situation regarding Epilim which now has warnings for pregnant women many years after it was freely prescribed and had all the robust studies required by NICE. We are NOT 'anti-drugs' but this does seem very much like 'double standards' and on behalf of the families we serve, this reduces their treatment options and means there will be reduced services even though the majority of ketogenic services in this country has a waiting list of patients needing the diet.	diets, there was no high-quality evidence to strengthen a recommendation favouring the use of ketogenic diets. The committee made the current recommendation based on the latest clinical and cost effectiveness evidence, and in consideration of other recommended treatments. However, the committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medtronic	Guideline	058	001	<p>Section 8.2: Resective Epilepsy Surgery.</p> <p>Resective surgery is the standard-of-care;¹ however, while it is effective, the risk of permanent complications is high (3%-44%),²⁻⁷ it is often refused by patients,⁸ and eligibility is limited due to comorbidities.</p> <p>We ask the committee to consider providing guidance on minimally invasive surgical techniques, including LITT, as an alternative to traditional open surgery for people who are ineligible for, or refusing, open resective surgery. The clinical outcome in terms of seizure reduction and remission is comparable with that of open surgery but is associated with lower risks and a reduced length of hospital stay post-procedure. A further benefit related to minimally invasive surgery is the reduction or absence of neurocognitive functioning complications.</p> <p>From a resource utilization perspective, most patients are discharged from hospital after 1 day with LITT therapy compared with 5 days for resective surgery.⁹⁻¹²</p>	<p>Thank you for your comment. Minimally invasive surgical techniques, including LITT, were not included in the scope for this guideline and therefore we are unable to include evidence or make recommendations on these interventions.</p> <p>We will inform the NICE surveillance team of this to inform future guideline updates.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>NICE published IPG671: MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy in 2020. The IPG Committee recommended that “Evidence on the safety of MRI-guided laser interstitial thermal therapy for drug-resistant epilepsy shows there are serious but well-recognised safety concerns. Evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research”. This IP overview is based on 1,218 patients from 2 meta-analyses, 2 reviews, 1 retrospective case series and 2 case reports.</p> <p>The is an ongoing prospective study, the SLATE study NCT02844465 : designed to evaluate the safety and efficacy of the Visualase MRI-guided laser ablation system for drug resistant mesial temporal epilepsy (MTLE), single group assignment, n=150, completion date May 2022, location USA, follow up – 12 months, outcomes: freedom from seizures, health-related quality of life, adverse events and neuropsychological outcomes.</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>1. Marras CE, Canevini MP, Colicchio G, et al. Health Technology Assessment report on the presurgical evaluation and surgical treatment of drugresistant epilepsy. <i>Epilepsia</i>. 2013 Oct;54 Suppl 7:49-58.</p> <p>2. Tebo CC, Evins AI, Christos PJ, et al. Evolution of cranial epilepsy surgery complication rates: A 32-year systematic review and meta-analysis: a review. <i>Journal of Neurosurgery</i> (2014) 120:6 (1415-1427).</p> <p>3. Bjellvi J, Flink R, Rydenhag B, et al. Complications of epilepsy surgery in Sweden 1996-2010: a prospective, population-based study. <i>J Neurosurg</i>. 2015 Mar;122(3):519-25.</p> <p>4. Hader WJ, Tellez-Zenteno J, Metcalfe A, et al. Complications of epilepsysurgery: a systematic review of focal surgical resections and invasive EEG monitoring. <i>Epilepsia</i>. 2013 May;54(5):840-7.</p> <p>5. Spencer SS, Schramm J, Wyler A, et al. Multiple subpial transection for intractable partial epilepsy: An international meta-analysis <i>Epilepsia</i> (2002) 43:2 (141-145).</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>6. Rolston J D, Englot D J, Knowlton R C, et al. Rate and complications of adult epilepsy surgery in North America: Analysis of multiple databases. <i>Epilepsy Research</i> (2016) 124 (55-62).</p> <p>7. Koubeissi M Z, Syed T U, Syed I, et al. Hemispherectomy-associated complications from the Kids' Inpatient Database. <i>Epilepsy Research</i> (2009) 87:1 (47-53).</p> <p>8. Anderson CT, Noble E, Mani R, et al. Epilepsy Surgery: Factors That Affect Patient Decision-Making in Choosing or Deferring a Procedure. <i>Epilepsy Research and Treatment</i>. 2013;2013:309284. doi:10.1155/2013/309284.</p> <p>9. Lewis EC, Weil AG, Duchowny M, et al. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. <i>Epilepsia</i>. 2015 Oct;56(10):1590-8.</p> <p>10. Willie JT, Laxpati NG, Drane DL, et al. Realtime magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. <i>Neurosurgery</i>. 2014 Jun;74(6):569-84; discussion 584-5.</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>11. Wilfong AA, Curry DJ. Hypothalamic hamartomas: optimal approach to clinical evaluation and diagnosis. <i>Epilepsia</i>. 2013 Dec;54 Suppl 9:109-14.</p> <p>12. Kang JY, Wu C, Tracy J, et al. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. <i>Epilepsia</i>. 2016; 57:325–34</p>	
MHRA	Guideline	022	001	Could there be a link to information about SUDEP – predictive factors, monitoring?	Thank you for your comment. We have added a link to section 10 of the guideline.- reducing the risk of epilepsy related death.
MHRA	Guideline	022	006	We suggest a link could be provided directly to the Annual Risk Acknowledgment Form for valproate. Risk-acknowledgment.pdf (publishing.service.gov.uk)	Thank you for your suggestion. We have provided a link from the guideline to the MHRA safety guidance on epilepsy medicines and pregnancy which includes use of valproate and link to annual risk acknowledgement form.
MHRA	Guideline	024	018	The results of a study on best practices for switching valproate may be relevant for this section when available. https://www.ema.europa.eu/en/documents/agenda/agenda-prac-draft-agenda-meeting-11-14-february-2019_en.pdf	Thank you for your comment. The date for the final study report of the VALSE study - VALNAC09344 is 01/07/2022. We will pass this information on the NICE surveillance team who monitor guidelines to make sure they are up to date.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
MHRA	Guideline	028	013	Suggest wording changed from 'Consider sodium valproateonly if:' to 'Do not offer sodium valproateunless:'	Thank you for your comment, this has been amended throughout the guideline.
NHS England and NHS Improvement	Guideline	008	007	<p>The guidance for genetic testing should align with what is nationally commissioned on the Test Directory (which is updated annually). Suggested amends to align with current and future versions of the Test Directory:</p> <p>Discuss with a neurologist or geneticist if there are uncertainties about whether to offer genetic testing. Decisions about or which tests to offer to a person with epilepsy should be made with reference to the genetic tests that are nationally commissioned by the NHS in England as listed in the National Genomic Test Directory.</p>	Thank you for your comment, this has been amended in line with your suggestion.
NHS England and NHS Improvement	Guideline	008	013	Single gene testing for epilepsy is currently nationally commissioned (on the Test Directory) for POLG-related disorder only (including status epilepticus and other severe intractable epilepsy with other suggestive features), See rare disease Test Directory entry R315. Consider removing this sentence (and cover with the above addition for line 7) OR include reference to the single gene tests currently available on the Test Directory.	Thank you for your comment, the recommendation has been removed in line with your suggestion.
NHS England and NHS	Guideline	008	015	This sentence should align with what is nationally commissioned on the Test Directory (which	Thank you for your comment, this recommendation has been removed as this issue is now addressed in

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Improvement				<p>currently only includes whole genome sequencing (under Test Directory entry R59 for Early onset or syndromic epilepsy). No gene panel testing is currently commissioned nationally for epilepsy indications. Suggested amends:</p> <p>For people with a negative result from a single gene test, consider alternative genomic testing that is nationally commissioned by the NHS in England as detailed on the National Genomic Test Directory.</p>	the amendments to other recommendations in this section.
NHS England and NHS Improvement	Guideline	008	018	<p>This sentence should align with what is nationally commissioned on the Test Directory. Suggested amends:</p> <p>Consider gene panel genetic testing if the person has clinical features consistent with a specific epilepsy syndrome, for example, early age of onset, for which genetic testing is available via the NHS in England as detailed on the National Genomic Test Directory a suitable panel is available.</p>	Thank you for your comment, this recommendation has been removed as this issue is now addressed in the amendments to other recommendations in this section.
NHS England and NHS Improvement	Guideline	009	001	<p>The current eligibility criteria for genetic testing of Early onset or syndromic epilepsy (R59) on the National Genomic Test Directory is:</p>	Thank you for your comment, the wording has been amended in line with your suggestions.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>Unexplained epilepsy with clinical suspicion of a monogenic cause including:</p> <ol style="list-style-type: none"> 1. Onset under 2 years, OR 2. Clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome, OR 3. Additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital malformation), unexplained cognitive/memory decline <p>Please note that the next iteration of the Test Directory (expected publication April 2022) will include the following additional statement concerning eligibility for genetic testing under R59:</p> <p>"Testing may occasionally be appropriate where age of onset is between 2 and 3 years and following clinical agreement by a specialist MDT"</p> <p>Suggested amends:</p> <p>Consider whole genome sequencing for people with epilepsy of unknown cause who were aged under 3 2 years when epilepsy started or who have additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				malformation), unexplained cognitive/memory decline. Consider whole genome sequencing for people with epilepsy of unknown cause where age of onset is between 2 and 3 years following clinical agreement by a specialist MDT. See eligibility criteria for whole genome sequencing commissioned by the NHS in England as detailed on the National Genomic Test Directory learning disability.	
NHS England and NHS Improvement - Patient Safety Team	Guideline	General	General	<p>We, Valproate Safety Implementation group, (VSiG) are concerned that this recommendation implies that sodium valproate could still be considered as an option for people who can become pregnant where minimal treatment options may have been unsuccessful and not just for exceptional circumstances. We recommend the language is much stronger, for all new initiations to be exceptional and require two clinician authorisation. We recommend the committee revise the guidance for sodium valproate in people who can become pregnant for use only in generalised epilepsy & third-line for focal epilepsy.</p> <p>Supplementary to MHRA guidance referenced throughout we also recommend that sodium valproate is deprescribed for people who can</p>	Thank you for your comment. The recommendations for the use of sodium valproate are based on the best available evidence for each seizure type and syndrome it is recommended for. To limit the use of sodium valproate to only people with generalised epilepsy and third-line for focal epilepsy would be contrary to the evidence base. Each time it is recommended in the guideline the MHRA warnings are clearly referred to and links are given to indicate that it is a decision that should be carefully weighed against the risks. It was the view of the committee that the recommendations should be in line with the MHRA's advice on the use of this drug, which do not have a requirement for 2 clinicians to give authorisation. The committee also noted the MHRA warnings say that ' <i>All women and girls who are prescribed valproate should contact their GP and</i>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>become pregnant where safer alternatives exist. We recommend supporting people who can become pregnant understand the risks and benefits of remaining on valproate compared to switching to alternative treatments (including employing risk communication tools/decision support aids), as well as the impact of valproate exposure in pregnancy including age/ need appropriate information which may or may not have been highlighted when the medication was initiated.</p> <p>For further information please contact Deborah Baidoo – deborah.baidoo@nhs.net</p>	<p><i>arrange to have their treatment reviewed.'</i>, as well as giving a risk tool for clinicians to use.</p> <p>In addition the recommendations in the guideline have now been revised to use stronger language to state: <i>Do not offer sodium valproate monotherapy for xxx in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children) unless:</i></p> <ul style="list-style-type: none"> • <i>other treatment options are unsuccessful</i> • <i>the risks and benefits have been fully discussed, including the risks to an unborn child</i> • <i>the likelihood of pregnancy has been taken into account and a pregnancy prevention programme put in place, if appropriate.</i> <p><i>Follow the MHRA safety advice on valproate use by women and girls.</i></p> <p>Also, recommendation 4.4.1 states that age-specific information and advice should be given to women and girls and that this should be reviewed regularly to ensure it is relevant to their situation at that time. Recommendation 4.4.3 says that the risks and benefits of antiseizure medications for women and girls should be considered for those who are able to have children, now or in the future.</p>
Royal College of	General	General	General	Please could the committee consider creating an infographic or summary table for the preferred	Thank you for your comment. The committee did consider this and explore how it could be done.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
General Practitioners				medication required for each age group/ situation/ subset of epilepsy to ensure the information is easily accessible and not misunderstood when clinicians review the guidance looking for the best medication to prescribe.	However, due to the complexity of the condition and the number of variables that need to be taken into account when deciding on the most appropriate drug for an individual the committee did not think it feasible within the development time of the guideline.
Royal College of Midwives	Guideline	004 -071	014 007	Following, ‘second afebrile seizure’ we recommend the committee consider adding the following: with the exception of complex febrile seizures. These seizures are focal, prolonged, or multiple within the first 24 hours. Evidence indicates that complex febrile seizures are a more heterogeneous group and as such, associated with an increased risk of future afebrile convulsions during early childhood. Reference: Millichap, J.J. and Millichap, J., 2019. Clinical features and evaluation of febrile seizures. Up To Date. Waltham, MA Publisher. Re above, it would be helpful to define the difference between a simple and complex febrile convulsion	Thank you for your comment. Typically, simple febrile seizures are the ones that are generalised in nature, usually single seizure in the same 24 hours of illness, no focal features, and duration less than 10 minutes. Complicated (previously called complex febrile seizures) febrile seizures are the ones that are longer in duration over 10 min, have a focal component either at the onset or during the seizure and can recur within 24 hours or within the same febrile illness.
Royal College of Midwives	Guideline	004	015	In view of above, please consider adding, after a first episode of a complex febrile seizure or a first afebrile seizure in children.....	Thank you for your comment. A separate recommendation on complicated febrile seizures has been formulated. Please see recommendation 1.1.6.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Midwives	Guideline	006	017	Please could the committee make it clear this is a sleep recording and not a sleep deprived recording	Thank you for this comment. There was some uncertainty on this as the main purpose of sleep deprivation is to capture sleep. The committee were referring to a sleep deprived EEG to capture sleep rather than, for example, a sleep induced EEG
Royal College of Midwives	Guideline	007	008	If claustrophobic and CT does not complete clinical picture, would the committee consider suggesting referral for open MRI scanner	Thank you for your comment, this would be a matter for local implementation and the needs of the individual as the risks of a lower quality MRI would need to be weighed against the benefits to the patient of not using an MRI/an MRI being carried out under general anaesthetic or sedation.
Royal College of Midwives	Guideline	020	005	The committee have not added a recommendation for folic acid supplementation or the reason why the committee are no longer recommending this. Particularly as the recommendation in the BNF and RCOG epilepsy in pregnancy guidelines is for folic acid 5 mg once daily (preconception or risk of pregnancy and for first 12 weeks)	Thank you for your comment. This has been added to the recommendation.
Royal College of Midwives	Guideline	022	009	To optimise safety, women at risk of or planning pregnancy and pregnant women, should be counselled by an epilepsy specialist about the importance of adherence with recommended treatment and provided information about possible risks associated with uncontrolled or poorly controlled seizures (particularly tonic clonic) versus risks to fetus associated with	Thank you for your response. Please see recommendations made in section 4.6, especially 4.6.1 and 4.6.3 which ensure women that are planning pregnancy/ are pregnant receive the specialist referral, support and information they need.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				antiseizure medicines when prescribed in pregnancy and whilst breast feeding.	
Royal College of Midwives	Guideline	022	012	Would the committee consider a flexible approach to care to meet individualised needs of patients who are self-managing and not in a vulnerable category. We can see this has been discussed by the team.	The committee believe the frequency of monitoring reviews reflects current practice; however, they agree the frequency should be tailored to the needs of the individual and have amended the recommendation to reflect this.
Royal College of Midwives	Guideline	023	006-007	Would the committee include: Review of their diagnosis and anti seizure treatment and future options	Thank you for this comment. In discussing this topic, the committee were more focussed on women with epilepsy through pregnancy. There is considerable attention to medications and options although reconsideration of diagnosis is not mentioned. The committee were generally minded that re-evaluation of diagnosis should occur iteratively and at most clinical encounters. This is, for example, specifically the case at transition although there was not a sense that conception and pregnancy would similarly trigger a more specific re-evaluation.
Royal College of Midwives	Guideline	023	022	<p>Would the committee include the following in these bullet points, the analysis of these risks arising from the MBRRACE report referenced below.</p> <ul style="list-style-type: none"> • Have seizures arising from sleep • Live alone • Poor or non-adherence with antiseizure medicines 	Thank you for this comment. The current recommendation 4.6.5 does include anyone who has had a seizure within the past 12 months which will capture those with sleep seizures and seizures from wakefulness. Recommendation 4.6.6 was designed to capture women who may be poorly adherent to medication and suggests formal monitoring of levels in that group.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Have complex physical, mental or social co-morbidities (Knight et al, 2020)	That being said, the committee were very keen to ensure that the current guideline tries to mitigate epilepsy-related risk as far as possible. As such we have cross linked recommendation 4.6.5 to 10.1.2 which covers the specific bullet points raised.
Royal College of Midwives	Guideline	024	006 - 009	Note to the committee> In many secondary care centres, these results can take 3-4 weeks to return therefore a combination of therapeutic and vigilant clinical monitoring is required. As an example, delay in waiting for a antiseizure serum level and a specialist opinion participated to a delay in a treatment decision with one of the vignettes reviewed in the MBRRACE report: <i>(Marian Knight, Adrian Wills, Sreeman Andole, Kathryn Bunch, Samantha Holden, Sebastian Lucas, Kim Morley, Catherine Nelson-Piercy, Judy Shakespeare, Esther Youd on behalf of the MBRRACE-UK neurology chapter-writing group In Knight M, Bunch K, Tuffnell D, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2020: p36-42</i>	Thank you for your comment. We agree vigilant monitoring would be required in these circumstances, and the committee have recommended that management of medication is undertaken by a specialist epilepsy team. Awareness of epilepsy related risk factors including SUDEP is important, and the committee have added discussion of this within the information and support section of the guideline. The committee acknowledge monitoring in pregnancy is not just about ASM but consider wider issues to support and care for women and girls are addressed within the information and support, ASMs for women and girls, and support and monitoring for women planning pregnancy or who are pregnant sections of the guideline. We agree the wording is unclear in the recommendation on returning to preconception dosages and have amended this.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
		024	014	<p><i>Page 25 Knight et al, 2020 vignette-‘A woman with a history of poorly controlled epilepsy on lamotrigine was referred to a neurologist urgently after her booking visit as her seizures had increased. Her dose of lamotrigine was increased twice over the next three months. She attended in the third trimester with reduced fetal movements following a seizure. The obstetric registrar discussed her seizures with the medical registrar who was reluctant to change her medication as she was under the care of a neurologist and awaiting a follow up appointment. The local neurology service was in a different hospital. The obstetric registrar tried unsuccessfully to expedite the neurology appointment by telephone. Letters requesting a further neurology appointment were sent by both the obstetric registrar and the woman’s GP. She was seen in the neurology clinic three weeks later after a further admission to the maternity unit following a seizure. Her lamotrigine dose was increased again and levels were due to be checked ten days later. She died</i></p>	
		024	015		

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p><i>from SUDEP the following week.' (Knight et al, 2020).</i></p> <p>Note the following recommendation from the report page 24: <i>Develop guidance to ensure SUDEP awareness, risk assessment and risk minimisation is standard care for women with epilepsy before, during and after pregnancy</i> and ensure this is embedded in pathways of care. Clinicians need to talk to women and their partners or carers about the risk of SUDEP and how to minimise it (Knight et al, 2020).</p> <p>Important to note monitoring in pregnancy is not just about antiseizure treatment levels but also the aetiology, history (including previous pregnancies), clinical picture, comorbidities and lifestyle issues.</p> <p><i>'If dosing of antiseizure medications has changed during pregnancy, discuss and make a plan with the woman or girl to return their medications to pre-conception dosages before the baby is born.'</i></p> <p>We are concerned the wording above is misleading. The way it is worded makes it sound like the recommendation is to return their</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				medications to preconception dosages before the baby is born rather than writing a plan antenatally for postnatal management of medications to gradually return to preconception dosages with support from the epilepsy specialist team after the baby is born.	
Royal College of Midwives	Guideline	029	006	The recommendation did not include lamotrigine exacerbating myoclonus in some people with JME particularly in higher doses.	Thank you for your comment, this has been amended.
Royal College of Midwives	Guideline	033	009	Please add phenobarbital	Thank you for your comment, this has been amended in line with your suggestion.
Royal College of Midwives	Guideline	034	023	Please add phenobarbital	Thank you for your comment, this has been amended in line with your suggestion.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Midwives	Guideline	051	010	Also important to consider in children affected by benign epilepsy with centrotemporal spikes evidence suggests they should receive a complete neuropsychological evaluation at seizure due to the associated high rate of comorbidity with ADHD. See recommendations from: Aricò, M., Arigliani, E., Giannotti, F. and Romani, M., 2020. ADHD and ADHD-related neuro in benign epilepsy with centrotemporal spikes: A systematic review. <i>Epilepsy & Behavior</i> , p.107448. Zanaboni, M.P., Varesio, C., Pasca, L., Foti, A., Totaro, M., Celario, M., Provenzi, L. and D V., 2021. Systematic review of executive functions in children with self-limited epilepsy with centrotemporal spikes. <i>Epilepsy & Behavior</i> , 123, p.108254.	Thank you for your comment. Recommendation 9.2.2 states that all people with epilepsy should have a review of their neurodevelopment, cognitive function, mental health and social and emotional well-being. In addition, recommendation 6.4.6 recommends that if there is any concern that a child or young person with self-limited epilepsy with centrotemporal spikes shows decline in cognitive function they should be given a neuropsychology assessment and/or EEG.
	Guideline	108	025	Would the committee also consider that the above could be elaborated at this point of the guidance, too because initial baseline neuropsychological screening and monitoring is always going to be more proactive than waiting for a child to start failing in school.	
Royal College of Midwives	Guideline	060	022	We can see that the committee have considered the evidence from Abraham et al (2019) meta-analysis but as it was clearly demonstrated there was a positive association between epilepsy and suicide attempts, with there being a threefold increase in the risk of attempting suicide among patients with epilepsy compared with those	Thank you for this comment. The committee are aware of the tragic associations between epilepsy and dying from suicide. Suicide was, though, specifically excluded from the scope of this guideline and, as the SH will be aware, high grade evidence in this area can be difficult to obtain. The committee have, though, now added the risk of suicide to recommendations 9.1.1 and 9.2.4 to ensure that clinicians are aware of

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>without the condition we feel, part of the points mentioned should include this.</p> <p>Acknowledgement and recognition of suicide risk in people with epilepsy particularly those prescribed a non-mood stabilising ASM such as levetiracetam is imperative in prompting professionals who support people with epilepsy to at least do a routine assessment in order prevention strategies are instigated at the earliest opportunity. This is imperative too in general practice in order to monitor the efficacy of the ASM.</p> <p>A recommendation re suicidal ideation following or during prescribing of ASM: we recommend this should prompt a MHRA yellow card in order to have a picture of the true extent of this; we understand the FDA has collated data on suicidal ideation and suicide with antiseizure medicines and this will not be isolated to the epilepsy community due to the other licensed and off-licensed use.</p>	<p>this risk in people with epilepsy. The current guideline does also cross refer to multiple NICE guidelines on mental health difficulties to help holistic improvements in the care of people with epilepsy.</p>
Royal College of Midwives	Guideline	061	013	<p>Please can the committee include</p> <ul style="list-style-type: none"> • Alcohol and substance misuse <p>The reason for this is it is often associated with all the bullet points you have mentioned, it is</p>	<p>Thank you for your response. This was an error and the substance abuse/alcohol dependence outcome has now been included in the review. The committee have revised the recommendation to</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
		119	015	<p>potentially modifiable and SUDEP in this population is often under-diagnosed as the confounder is an alcohol/substance misuse related death.</p> <p>Sveinsson, O., Andersson, T., Mattsson, P., Carlsson, S. and Tomson, T., 2020. Clinical risk factors in SUDEP: a nationwide population-based case-control study. <i>Neurology</i>, 94(4), pp.e419-e429.</p> <p>The above could be mentioned here, too.</p>	include alcohol misuse and substance abuse in the recommendation..
Royal College of Midwives	Guideline	061	020	<p>In these bullet points please include:</p> <ul style="list-style-type: none"> pregnancy and the postnatal year <p>Marian Knight, Adrian Wills, Sreeman Andole, Kathryn Bunch, Samantha Holden, Sebastian Lucas, Kim Morley, Catherine Nelson-Piercy, Judy Shakespeare, Esther Youd on behalf of the MBRRACE-UK neurology chapter-writing group In Knight M, Bunch K, Tuffnell D, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and</p>	<p>Thank you for your response.</p> <p>Pregnancy and the postnatal year was not a prognostic risk factor identified by the committee to be included in the review question. We are therefore unable to include this in the recommendation. Details of the evidence included can be found i in evidence review 18.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>Morbidity 2016-18. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2020: p36-42</p> <p>Knight M, Bunch K, Tuffnell D, Patel R, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2017-19. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2021.</p>	
Royal College of Midwives	Guideline	062	021	Medicines management support from ESN qualified in non medical prescribing	Thank you for your comment, the committee agree that if ESNs are qualified in non-medical prescribing then they will be able to do this.
Royal College of Midwives	Guideline	064	011	Add: and support available from the epilepsy charities about education, examination support, work support, employment and benefit support including medical exemption for prescriptions from age 18 years.	Thank you for your response. Links to epilepsy charities and organisations will be provided via the epilepsy guideline on the NICE website 'information for the public' page.
Royal College of Midwives	Guideline	084	016	Please can the committee add: <i>particularly if the focal epilepsy is secondary to conditions such as neurocysticercosis and other antiseizure treatments have failed to control the seizures.</i>	Thank you for your comment, this section has edited heavily in response to other comments. The sentence for which this was suggested as an adjunct is no longer in the guideline and consequently the suggested text has not been added.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Midwives	Guideline	085	004	<p>Please can the committee consider further guidance/recommendations for women who are:</p> <ol style="list-style-type: none"> 1. perimenopause and menopause in addition to bone health and the impact of hormone replacement therapy (HRT). In clinical practice this can be a marker of change in women' usual seizure control, co-morbidities and tolerance of antiseizure medicines. Also dilemma's regarding contraception in women during the menopause who have epilepsy and co-morbidities including mental health issues. 2. Have catamenial epilepsy (even if it is only to mention seizures with a hormonal cyclic pattern are often difficult to treat or antiseizure medicine resistant). <p>There needs to be further research into both of these points mentioned above, would the committee consider this as a suggestion?</p> <p>Joshi, S. and Kapur, J., 2019. Neurosteroid regulation of GABAA receptors: a role in catamenial epilepsy. <i>Brain research</i>, 1703, pp.31-40.</p>	<p>Thank you for your response. The subgroups of people with epilepsy that needed to be given special consideration were identified by stakeholders at the start of the guideline development process and incorporated in the guideline scope. This cannot be amended at this stage. The study cited was not relevant to the evidence review question and was not included.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Midwives	Guideline	086	032	Have the committee considered that postnatal lamotrigine dosage reduction has to often start taking place within 3 days of birth therefore the advice re lamotrigine plasma levels after the birth is going to hinder medicines changes in units such as ours where the wait is 3-4 weeks for a serum level and in NHS Trusts where there is not a specialist to provide advice based on the normal physiological process that occurs following birth and impact on lamotrigine serum levels and other antiseizure medicines. The only levels we can get back within 24 hours are a carbamazepine and phenytoin plasma level.	Thank you for this comment. The committee were aware of the variability in being able to check drug levels and sought to address this by highlighting 'on site testing is often available at tertiary epilepsy centres for some antiseizure medications (ASMs) including carbamazepine, phenobarbitone and phenytoin'. This underscores that such testing may not be available everywhere and even tertiary centres may not be able to perform other ASM levels. The current rationale does not specify that clinicians should wait for post-natal drug levels to be available to begin to adjust lamotrigine dosing post-delivery.
Royal College of Midwives	Guideline	087	019	This recommendation for oxcarbazepine plasma levels will be a challenging in practice because in our NHS Trust we do not have any way of ordering this on our electronic system however, minimal women come through pregnancy taking this antiseizure medicine.	Thank you for your response. Guidance for monitoring women planning pregnancy or who are pregnant is in line with MHRA safety advice. Implementation of guidance would need to be planned and organised by service providers.
Royal College of Midwives	Guideline	087	028	In order to reduce the possibility of this plasma level being inaccurate, please may the committee consider adding: If the woman is taking the combined oral contraceptive, a pre-conception plasma serum level should be taken after the COC has been discontinued. Also important to state whether	Thank you for your comment. We have considered your suggestion but do not think this level of detail is required because we have recommended that women and girls who are pregnant or planning pregnancy are referred to a specialist epilepsy team.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				antiseizure plasma levels should be taken as a trough level (difficult when women have to get to a specialist centre to have this done) or how many hours following dosing. Also the need for whichever method used to be consistent.	
Royal College of Midwives	Guideline	091	019	Simple and complex partial is dated terminology. We recommend the committee use ILAE classification for focal seizures: Fisher, R.S., Cross, J.H., French, J.A., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshé, S.L., Peltola, J., Roulet Perez, E. and Scheffer, I.E., 2017. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. <i>Epilepsia</i> , 58(4), pp.522-530.	Thank you for your comment. These terms were mistakenly included in a small section of the guideline. This has now been removed.
Royal College of Midwives	Guideline	112	11	Did the committee discuss status epilepticus in pregnant women, differential diagnosis and recommend treatment and management including joint working with obstetrics? If not, we recommend this is included in the recommendations.	Thank you for your response. Pregnant women were not excluded from the review which took into account status epilepticus. The recommendations made were based on available evidence which matched the review protocol requirements for inclusion.
Royal College of Nursing	Guideline	General	General	No mention of school nursing provision and role of school nursing services in supporting management	Thank you for your comments, the recommendations for epilepsy specialist nurses have now been amended to ensure they support professionals working in education.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Nursing	Guideline	General	General	What is meant by community provision? Does that require expanding, and to include the roles and responsibilities of the wider multi-Disciplinary teams in primary and community nursing services?	Thank you for your comment. Other community and multi-agency services include roles such as Occupational Therapists that the Epilepsy specialist nurse can facilitate access to. The committee decided that it would not be helpful to list these services in the recommendation as it would vary for each person and local area.
Royal College of Nursing	Guideline	012	General	Topics to discuss with carers – should include rescue medication / its use and how to administer	- Thank you for your comment. We have cross referred to the NICE guideline on supporting adult carers. This includes recommendations on training for carers in the management of medicines.
Royal College of Paediatrics and Child Health	Guideline	General	General	No real change in initial assessment which is pretty consistent with practices.	Thank you for your response.
Royal College of Paediatrics and Child Health	Guideline	General	General	Drug Management guidance is more thorough than previously which allows for variation based on parental choice, side effect profile and child comorbidities.	Thank you for your comment. The drugs recommended are based on the best available evidence, and warnings from the MHRA to ensure the most effective treatment is given to the person.
Royal College of Paediatrics and Child Health	Guideline	General	General	Regarding epilepsy, there is a considerable heterogeneity in disease burden in terms of social status, culture, ethnicity, beliefs and genetics which widen the treatment gaps and knowledge gaps which ultimately become big challenges.	Thank you for your comment, the committee hopes that the recommendations re Information and Support (section 2) will ensure that people with epilepsy are given the tools to be informed and

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Thus, the treatment gaps and knowledge gaps should be addressed in this guideline.	knowledgeable about their condition and any concerns about it they may have.
Royal College of Paediatrics and Child Health	Guideline	General	General	Nearly 80% of people with epilepsy live in developing countries. The taboos, stigma, and misconceptions attached to this condition are significant which prevents a person from accessing appropriate medical care, even when they migrate from their country of origin to a well-developed country such as the UK. This should be addressed in the guideline.	Thank you for your comment. Misconceptions surrounding epilepsy and the stigmatisation of people were themes that emerged from the information and support review. The committee have included this as a topic for discussion in the information and support recommendations.
Royal College of Paediatrics and Child Health	Guideline	General	General	Strategies related to "Prevention, promotion and protection" along with early detection of the condition and ensuring a steady supply of medications is important.	Thank you for your comment. Early detection and access to medication are important issues and have been addressed within the diagnosis and anti-seizure medication recommendations.
Royal College of Paediatrics and Child Health	Guideline	General	General	Considering the deployment of Artificial Intelligence (A.I.) can cause a paradigm shift in the delivery of Health care related to epilepsy.	Thank you for your comment. AI was included in the digital health technologies question protocol, but no evidence was found.
Royal College of Paediatrics and Child Health	Guideline	General	General	Schools can be places of early identification and detection of Neurological Disorders such as epilepsy especially of that with onset during childhood and adolescence.	Thank you for your response. . Early identification may take place within educational settings, and whilst the guideline is developed for the NHS, families and carers other sectors may find the guidance helpful.
Royal College of	Guideline	General	General	The five points above would help achieve the goal of "no deaths due to epilepsy", to an extent.	Thank you for your comments.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Paediatrics and Child Health					
Royal College of Paediatrics and Child Health	Guideline	General	General	Overall a detailed guidance.	Thank you for your comments.
Royal College of Paediatrics and Child Health	Guideline	General	General	The reviewer is happy with this well researched draft guideline.	Thank you for your comments.
Royal College of Paediatrics and Child Health	Guideline	Transition	General	<p>In terms of transition arrangements, it is excellent to see that the guidance recommends early transition planning but would be better if it included a latest by age (years) in the text in line with the NICE Transition (NG43) guidelines and NICE Transition quality standards.</p> <p>Although the guidelines highlight the importance of joint working between paediatric and adult teams during transition, greater clarity and emphasis would be very welcome as in some tertiary centres, young people with epilepsy transfer care from paediatric to adult services by a letter and there are no joint clinics or MDT's</p>	<p>Thank you for your comment.</p> <p>The guideline recommends that when planning transition to adult epilepsy services the NICE guideline on transition from children to adult services for young people using health or social care services should be followed along with the recommendations made specifically for young people with epilepsy. Both guidelines recommend that adult and children's services work together in reviewing the person's needs and planning for transfer of care.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				that would enable the required joint working during transition. Meeting the adult team prior to transfer of care is a NICE quality standard for transition and would be met with joint clinic working. Joint clinics could be face to face or virtual and are deserving of emphasis in the guidelines.	
Royal College of Paediatrics and Child Health	Guideline	010 - 011	001 - 004	It would be useful to consider virtual appointments here and offer guidance on how to ensure patients are aware of and have access to information via online platforms. Additionally, it will be important to maintain confidentiality when using virtual appointments (e.g., Can patients speak freely without fear or others overhearing in the house?)	Thank you for your response. Appointments are currently more likely to be held virtually. Cross reference has been made to the patient experience guideline which includes recommendations on ensuring effective communication with patients and consideration of the environment where consultations take place.
Royal College of Paediatrics and Child Health	Guideline	004	015	Is the 'appropriate safety advice' to be provided in A+E, or will there be an urgent referral to the Epilepsy Team, especially Epilepsy Specialist Nurse to provide the advice?	Thank you for your comment. Safety advice can be provided in A/E and referral to ENS is not needed.
Royal College of Paediatrics and Child Health	Guideline	005	020	Consider rephrasing 'first suspected seizure' as 'first convulsive seizure'. Otherwise, this may imply that an ECG is required for absence seizures etc.	Thank you for your comment. The committee disagree with your suggestion. All first suspected seizures should be evaluated with an ECG.
Royal College of	Guideline	006	006	If NICE are changing the advice to suggest children should be given an EEG after a first	Thank you for your comment. We have edited the recommendation to reflect usual practice and

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Paediatrics and Child Health				epileptic seizure, this statement needs more clarity to confirm this as this would be a substantial change in practice. Currently, an EEG is recommended to be performed in children after a second epileptic seizure, and sometimes after a first where a specific syndrome is being considered.	expanded on this in the discussion of evidence section within the evidence review.
Royal College of Paediatrics and Child Health	Guideline	006	009	This should refer to 'standard EEG', as other types of EEG can be useful in excluding epilepsy in some circumstances.	Thank you for your comment. This has been amended to clarify the type of EEG.
Royal College of Paediatrics and Child Health	Guideline	006	010	The 72-hour target stated here may be too ambitious and difficult to achieve. Is there a specific group where early standard EEG is recommended? The reviewer noted that their team struggle to achieve this even where it is indicated, e.g., infantile spasms, and a generic recommendation like this, risks compromising those who really do need an early EEG. This together with a recommendation for an EEG after a first epileptic seizure would have a profound impact on total numbers of EEGs requested and their timeliness.	Thank you for your response. The committee acknowledge this can't always be achieved but the time-frame of 'within 72 hours' has been added to encourage a quicker ECG and ideally bring about a restructure where ECGs are offered sooner.
Royal College of Paediatrics	Guideline	007	002	Not all people with epilepsy will choose or need to start on anti-seizure medication.	Thank you for your comment, the committee recognise this, and state in recommendation 4.1.1 that as part of an individualised treatment strategy it

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
and Child Health					should be discussed whether treatment is needed or not.
Royal College of Paediatrics and Child Health	Guideline	007	003	Are the timescales for a Child receiving an MRI Scan realistic, particularly in a young child, who may need a General Anaesthetic?	Thank you for your comment, the committee acknowledge that this timescale may be challenging for some trusts, however it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards. A 6 week wait for an MRI is also in line with the pledge on waiting times in the NHS Constitution for England.
Royal College of Paediatrics and Child Health	Guideline	007	020	Add 'self-limited epilepsy with centrotemporal spikes' to the third bullet point: 'they have idiopathic generalised epilepsy that has not responded to 24 first-line treatment'. There are also other indications other than epilepsy for an MRI.	Thank you for your comment, this has been amended in line with your suggestion.
Royal College of Paediatrics and Child Health	Guideline	012	Box 1	Box 1 describes safety issues for epilepsy rather than first seizure. Epilepsy safety information is not always suitable for patients who do not have epilepsy as it can imply that they have epilepsy when they might not have epilepsy. Therefore, safety advice may not always be given in practice. The RCPCH first seizure safety net leaflet has been designed as a safety issues resource specifically for this group in response to a request from NHS improvement. This overcomes this	Thank you for your response. The advice given is specifically for those individuals with Epilepsy.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				issue and ensures that early pathway safety advice is given.	
Royal College of Paediatrics and Child Health	Guideline	014	021	<p>More detail on these criteria for referring children to tertiary paediatric epilepsy services would be useful:</p> <ul style="list-style-type: none"> • <i>are aged under 3 years</i> <ul style="list-style-type: none"> ○ When they had their first epileptic seizure • <i>are aged under 4 years and have myoclonic seizures (see 24 recommendation 5.4.1 in the section on myoclonic seizures) 25</i> <ul style="list-style-type: none"> ○ had myoclonic seizures commencing before 4 years of age • <i>have a unilateral structural lesion 26</i> <ul style="list-style-type: none"> ○ Have a unilateral structural brain lesion • are showing signs of behavioural or developmental regression. <p>Replace 'signs' with 'features'.</p>	Thank you for your comment, the recommendation has been amended to add more detail about what signs or features clinicians should look out for.
Royal College of Paediatrics and Child Health	Guideline	014	021	<p>Although this does seem sensible are there enough Tertiary Paediatric Neurologists to allow this to happen? Most regional clinics are four times per year and that would have to be expanded.</p>	Thank you for your comment, it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards, and encourage commissioners to fund.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health	Guideline	015	006	Does this include the method of delivery of the medication, especially whether liquid would be available, particularly for young children, those with significant additional needs, those with gastrostomy/jejunostomy in situ.	Thank you for your comment, the final bullet 'how and when antiseizure medicines need to be taken' includes the method of delivery.
Royal College of Paediatrics and Child Health	Guideline	016	005	This phrasing implies that monotherapy might be tried where epilepsy is not confirmed. Consider removing 'and epilepsy diagnosis confirmed' and inserting 'continue to review the person's seizure and epilepsy type and try monotherapy with another antiseizure medication'.	Thank you for your comment, the recommendation has been amended to clarify that this is if the epilepsy diagnosis remains confirmed.
Royal College of Paediatrics and Child Health	Guideline	017	004	The term 'unprovoked' can be confusing and is not frequently used in paediatric practice. Consider rephrasing to 'after a first epileptic seizure'.	Thank you for your comment, a definition of 'unprovoked' has been added to the guideline.
Royal College of Paediatrics and Child Health	Guideline	019	001	The descriptor 'European' needs more definition here – UK citizens remain European. Is this referring to the specific group of patients requiring HLA screening? If so, this needs better characterisation.	Thank you for your comment. This recommendation has been revised so that it does not restrict prescribing of these drugs and the requirement for HLA screening has been removed. The recommendation now focuses on raising awareness that there can be a risk of serious skin reactions.
Royal College of Paediatrics and Child Health	Guideline	020	001	Although the ARAF has changed there is still the issue of women and girls with very significant learning disabilities/profound multiple learning disabilities. These are women who due to their very severe learning needs will never be able to	Thank you for your response. The recommendation has been edited to tailor the information to age specific and developmental needs. These needs would need to be determined by the health professional and

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				consent to a sexual relationship, and any sexual relationship would be non-consensual/highly abusive. However, their carers are still required to sign a form every year highlighting this or they would be unable to access an effective medication that would/could be beneficial to their care.	the necessary adjustments made based on the requirements of each individual patient.
Royal College of Paediatrics and Child Health	Guideline	020	002	Advice needs to be tailored to their age-specific and developmental needs.	Thank you for your response. This has been incorporated.
Royal College of Paediatrics and Child Health	Guideline	020	010	The phrase 'able to have children' is potentially confusing; 'able to become pregnant' may be more suitable. There is a balance of risk, as there are also risks to the mother and baby of untreated seizures. This consideration of balance needs to be reflected in the recommendation.	Thank you for your comment. The committee considered this but think the current wording is clear.. The committee agree there is a balance of risks that need to be considered but think this is adequately conveyed in the recommendations.
Royal College of Paediatrics and Child Health	Guideline	021	003	Can all references to BNF also cite 'BNF for children'?	Thank you for your response. BNF for children has been cited where appropriate in the recommendations.
Royal College of Paediatrics	Guideline	021	020	Is the first bullet point referring to learning difficulty or disability, or both?	Thank you for your comment. This has been amended to learning disability

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
and Child Health					
Royal College of Paediatrics and Child Health	Guideline	022	012	Would suggest rephrasing to 'Arrange regular monitoring reviews at least every 12 months for children and young people with epilepsy.' (this is because some will need monitoring more frequently than six months). It would be better to express this as 12 months rather than a 6-12 month range.	The committee believe the frequency of monitoring reviews recommended reflects current practice; however, they agree the frequency should be tailored to the needs of the individual and have amended the recommendation as suggested.
Royal College of Paediatrics and Child Health	Guideline	047	009	<p>Consider avoiding the term 'baby/babies' here, as some children are not technically babies when they get spasms.</p> <p>Referrals should usually be via secondary service in the first instance, rather than directly to neurology. Referrals should occur when there is suspicion. The wording here should reflect that children present generally to GP/ED/health visitor in the first instance.</p> <p>If a child has suspected infantile spasms, health professionals should immediately seek advice or refer to an acute paediatric service. Acute assessment should then include discussion with tertiary paediatric neurology to ensure rapid investigation, including a sleep EEG, and rapid treatment to stop the spasms.</p>	Thank you for your comments. The term 'babies' has been revised throughout to 'child under 2 years' for clarity. The recommendation has also been amended to include when spasms are suspected, and 'immediately' has been clarified as 'within 24hrs'.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health	Guideline	054	015	<p>There is good evidence that buccal midazolam is superior to rectal diazepam in children in the ED setting: (Lancet 2005 Jul 16-22;366(9481):205-10. doi: 10.1016/S0140-6736(05)66909-7. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial)</p> <p>Where is this evidence reflected in this guidance as buccal midazolam should be the recommended non-IV route where possible?</p>	Please see evidence review 9 for the evidence considered when making the recommendation 7.1.3. In that evidence review, section 1.4 summarises the committee's discussion and considerations when forming the recommendation.
Royal College of Paediatrics and Child Health	Guideline	055	016	<p>Spelling mistake: replace 'fewer adverse effects that the alternative options' with 'fewer adverse effects than the alternative options.'</p>	Thank you, this has been amended.
Royal College of Paediatrics and Child Health	Guideline	056	022	<p>Rephrase to 'manage prolonged convulsive seizures.'</p> <p>There would be operational difficulties with this new definition of prolonged seizures both in clinical practice and in the Epilepsy12 audit. If their previous usual seizures are prolonged then it is still an emergency, without it needing to be longer than usual for them.</p>	The committee noted this comment with thanks. As the SH is aware, seizures lasting longer than 5 minutes are now classified as status epilepticus and there is cross referral to that part of the guideline. The committee agreed that it was reasonable to differentiate prolonged convulsive seizures from prolonged non-convulsive seizures and this has now been done with the previous recommendations relating to prolonged convulsive seizures and a new

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>Consider using the definition of prolonged as 5 minutes and state that it is a medical emergency if convulsive seizure is prolonged or 2 minutes longer than the usual seizure</p> <p>Or</p> <p>Consider using the definition of prolonged as 5 minutes or 2 minutes longer than the usual seizure and then state that it is a medical emergency if convulsive seizure is prolonged</p>	recommendation on prolonged non-convulsive seizures
Royal College of Paediatrics and Child Health	Guideline	062	001 - 005	Rephrase to 'Discuss with 'young people and adults', as we wouldn't necessarily recommend discussion of this issue with young children but would with their parents.	Thank you for your comment. We have amended the recommendation as suggested.
Royal College of Paediatrics and Child Health	Guideline	062	015	Is it correct to reference the first function of ESNs as supporting professionals here? It may be better to state their primary role as supporting people with epilepsy.	Thank you for your comment, the order of the bullet points has been revised in line with your suggestion.
Royal College of Paediatrics and Child Health	Guideline	062	015	Very important and useful that it is in the NICE Guidance.	Thank you for your comments.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health	Guideline	063	020	Important Guidance and one that has been difficult to arrange.	Thank you for your comment.
Royal College of Paediatrics and Child Health	Guideline	121	001	Was the following paper included in the review: <i>2018 Dec;63:71-78. doi: 10.1016/j.seizure.2018.11.002. Evaluation of a questionnaire to measure parent/carer and child/young person experience of NHS epilepsy services.</i> This study found profound evidence of improved experience associated with service 'contact-ability'.	Thank you for your comment. The main aim of the review was to determine whether having an epilepsy nurse specialist as part of the epilepsy care management strategy is effective in improving the outcomes of people with epilepsy, therefore studies validating questionnaires were not eligible for inclusion. For further details regarding inclusion criteria, please see appendix A in evidence review O.
Royal College of Paediatrics and Child Health	Guideline	121	001	We cannot see that the following paper was included in the review: <i>(Lancet, VOLUME 3, ISSUE 9, P627-635, SEPTEMBER 01, 2019 Association of quality of paediatric epilepsy care with mortality and unplanned hospital admissions among children and young people with epilepsy in England: a national longitudinal data linkage study)</i> This study showed evidence linking ESN provision with admission rates and specialist provision with subsequent adult death rate reduction.	Thank you for your comment. This study does not meet inclusion criteria because it does not have a comparison group. For further details regarding inclusion criteria, please see appendix A in evidence review O.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				This paper wouldn't suggest a change in any recommendations but would strengthen and add to the evidence behind the recommendations being made.	
Royal College of Speech and Language Therapists	Guideline	009	008	We suggest the recently published NICE guideline on Babies, children and young people's experience of healthcare could also be linked to here.	Thank you for your suggestion. This has been added.
Royal College of Speech and Language Therapists	Guideline	010	001	<p>Given the prevalence of communication needs in people with learning disabilities, we suggest that the person's communication needs and preferences should be explicitly included here (See wording below in bold): "Take into account the information, communication needs and preferences and support needs of people with epilepsy who have a learning disability or other complex needs"</p> <p>This could link more explicitly to Speech & Language Therapy service support in relation to accessible information and the Accessible Communication Standard.</p>	<p>Thank you for your suggestion.</p> <p>We have cross referred to both the adult and babies, children and young people's experience of healthcare guidelines both of which include recommendations on taking into account an individual's communication needs and preferences.</p>
Royal College of Speech and	Guideline	010	004	It would be helpful to include other strategies which support communication. We suggest expanding recommendation 2.1.4 to include the following:	<p>Thank you for your suggestion.</p> <p>We have cross referred to both the adult and babies, children and young people's experience of healthcare guidelines both of which include recommendations on</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Language Therapists				<ul style="list-style-type: none"> Give people plenty of time to absorb and reflect on information they are given. Check they have understood it, and how it applies to them, as is appropriate for their age and developmental level. Additional resources may be required (for example, foreign language or sign language interpreters, picture boards, computer-based systems) <p>Individuals with additional communication needs might need more time and specialist support for alternative forms of communication (for example, speech and language therapist support for augmentative and alternative communication).</p>	taking into account an individual's communication needs, different formats that may be required and other specialist support
Royal College of Speech and Language Therapists	Guideline	012	Box 1	RCSLT suggests that safety issues should also include advice about mealtimes to reduce risk of choking (particularly for children with learning disabilities and/or dysphagia)	Thank you for your comment. The framework of topics included is intended as an aid for discussion based on issues identified by the evidence and committee experience, and is not meant as a prescriptive list. The committee are aware there are many other important areas, but it is not possible to include them all, and people should be encouraged to discuss any other issues that are of concern to them.
Royal College of Speech and	Guideline	012	Box 1 Medication	Add risk of medications causing dysphagia: Johnson, P. R. (2001). Professional Practice: The Effects of Medication on Dysphagia in the Pediatric Population. <i>Perspectives on Swallowing</i>	Thank you for your comment. The framework of topics included is intended as an aid for discussion based on issues identified by the evidence and committee experience, and is not meant as a

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Language Therapists				<i>and Swallowing Disorders (Dysphagia)</i> , 10(2), 23-26.	prescriptive list. The committee are aware there are many other important areas, but it is not possible to include them all, and people should be encouraged to discuss any other issues that are of concern to them.
Royal College of Speech and Language Therapists	Guideline	021	023	Change learning difficulty to 'learning disability' to reflect terminology throughout	Thank you for your response. This has been amended to learning disability.
Royal College of Speech and Language Therapists	Guideline	042	002	Include information on Landau Kleffner syndrome within the section on Treating childhood-onset epilepsies See: Mikati, M. A., & Shamseddine, A. N. (2005). Management of Landau-Kleffner syndrome. <i>Pediatric Drugs</i> , 7(6), 377-389.	Thank you for your comment. The committee acknowledge that there are many types of syndromes and were not able to cover each one in detail. Rather they focused on seizure types, which should be followed regardless of the syndrome, in addition to some of the more common childhood onset epilepsies. However, in light of your comment the committee have amended recommendation 3.1.3 to ensure those with a diagnosis of an epilepsy syndrome that is likely to be drug resistant, such as Landau Kleffner syndrome, are referred to a tertiary epilepsy service.
Royal College of Speech and Language Therapists	Guideline	059	014	Speech and language difficulties are more common in people with epilepsy, and have a significant impact on quality life. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5826845/ ,	Thank you for your response. The subgroups of people with epilepsy that needed to be given special consideration were identified by stakeholders at the start of the guideline development process and incorporated in the guideline scope. This cannot be amended at this stage.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.410380412 We suggest adding 'speech and language difficulties' as one of the comorbidities (see wording below in bold): "Be aware that the prevalence of mental health difficulties, learning disabilities, speech and language difficulties and dementia is higher in people with epilepsy."	
Royal College of Speech and Language Therapists	Guideline	059	016	Coordinated care should be provided for people with all comorbidities, not just those with mental health conditions – we suggest clarifying this (see wording below in bold): "Provide coordinated care for people with epilepsy who have a mental health condition, learning disability, speech and language difficulties or dementia using a multidisciplinary team approach."	Thank you for your response. The additional comorbidities mentioned are captured by recommendation 9.1.3.
Royal College of Speech and Language Therapists	Guideline	064	003	This could link more explicitly to Speech & Language Therapy service support in relation to accessible information, the Accessible Communication Standard and use the terminology of the Equality Act i.e. 'reasonable adjustments'.	Thank you for your suggestion. The committee do not agree speech and language therapy service support would be required in most instances and think the importance of ensuring accessibility is clear within the recommendation.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal Pharmaceutical Society	Guideline	031	004	Pregabalin is recommended as 2 nd line add-on for focal seizures in the draft guideline; such use is off-label in children but this is not stated in the guidance. This may imply that it is licensed in children.	Thank you for your comment, this has been amended.
Royal Pharmaceutical Society	Guideline	039	002	Use of topiramate for tonic or atonic seizures is off-label in all age groups; however the draft guidance states that it is off-label only in children under 2 years of age.	Thank you for your comment, this was an error and has been amended in line with your suggestion.
Royal Pharmaceutical Society	Guideline	043	015-022	Cannabidiol in combination with clobazam is recommended in the draft guideline as a second-line add-on treatment option in line with NICE TA614. The unlicensed statement underneath the recommendation states that this is off-label in children under 6 months of age, but both the SPC and TA614 describe use from 2 years of age	Thank you for your comment, this was an error and has been amended in line with your suggestion.
Royal Pharmaceutical Society	Guideline	055	019	Use of levetiracetam for status epilepticus is off-label: because this is not stated in the draft guidance we are concerned that this may imply that use is licensed.	Thank you for this comment. We have included the drug information in the recommendation.
SUDEP Action	Guideline	Commissioners	General	National guidelines since 2004 and Government Action plans and national initiatives in response to the National Audit of Epilepsy Deaths 2002 and other inquiries and reports have not had included any system wide enablement.	Thank you for your comment. Thank you for your comment. The committee agree that this is a tragic case, and that it is important that lessons are learnt from it. As a clinical guideline it is not possible to address all the concerns you raise however the committee hope that the new guideline

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>Some of the evidence from surveillance and research that we have included in this response points to a system before the pandemic that failed to protect people with epilepsy from systemic inequalities in access not only to services but to essential information necessary for a person-centred approach to the safeguarding of life.</p> <p>This guideline is intended for commissioners as well as clinicians and we would strongly recommend that the guideline development group include recommendations from the Clive Treacy Report below. We would particularly recommend that there must be an identified lead at place (and at ICS) who has responsibility for including epilepsy and epilepsy and learning disability as part of any strategy or action plan to tackle inequalities and that local training and audit include tackling under-reporting of epilepsy related deaths so that missed opportunities to put in place measures that could greatly reduce sudden death are not repeated.</p> <p>We particularly prioritise the report's recommendation 2g) Commissioners of care for people with a learning disability and epilepsy</p>	<p>will help commissioners to identify the services that are necessary to deliver a high-quality experience for all those with epilepsy, and encourage them to fund and commission services to do so.</p> <p>Recommendation 3.1.2 addresses the need for professionals working with people with epilepsy and learning disabilities to give extra support to access tertiary epilepsy services.</p> <p>It is outside the scope of this guideline to make recommendations about training, however the recommendations on Epilepsy Specialist Nurses (11.1.1-11.1.4) will increase the support people are given, and improve liaison between all the services included in a person's care.</p> <p>We recognise the importance of auditing local epilepsy services and ensuring procedures are in place to mitigate risk of epilepsy related death. Risk factors and interventions to reduce the risk of epilepsy related death have been included in the guideline and the committee have made what they hope are clear recommendations for recognising and managing risk. Evidence for risk prediction tools for epilepsy related mortality including SUDEP was reviewed in the guideline, but the evidence was not strong enough to recommend any specific tool. The committee</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>must ensure that care and service providers take a risk management approach to epilepsy related death, as recommended in the NHS Right Care Epilepsy Toolkit. This should specifically include application of a standard risk template for people living with epilepsy that crosses organisational boundaries, such as the SUDEP and Seizure Safety Checklist tool as an opportunity to enable the implementation of the main recommendation of the National Sentinel Audit of 2002 and subsequent inquiries which have repeated this key recommendation. If NICE were to adopt this it would not only give hope to the family of Clive Treacey but thousands of suddenly bereaved families that do not feel they are listened to or that evidence from surveillance of deaths is used to transform care.</p> <p>Clive Treacy report recommendations on commissioning</p> <p>2a) In commissioning care provision (specialist hospital or community) for people with a learning disability and epilepsy, commissioners at a local level (health and social care) should actively assure themselves that care providers are delivering a standard of epilepsy care that is compliant with NICE standards.</p>	<p>recognised the value of having such a tool and decided to make a research recommendation to develop and validate a risk prediction tool for all-cause mortality including SUDEP.</p> <p>The committee agree audit and monitoring of care provided for people with a learning disability and epilepsy is important. The NICE epilepsy quality standards will be updated once the guideline is published.</p> <p>The recommendations in the NICE guidelines Challenging behaviour and learning disabilities and Mental health problems in people with learning disabilities were reviewed by the committee who agreed this provided valuable guidance for health professionals, families and carers in relation to managing the care and supporting people with epilepsy with learning disabilities or with mental health difficulties. Links to the recommendations in these guidelines are provided in the current epilepsy guideline.</p> <p>People with epilepsy and learning disabilities were a group identified for special consideration early on during the scoping of the guideline and where evidence was found it was reviewed by the committee. The particular needs of this group of people were raised and discussed throughout the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>2b) Commissioning organisations at a local level (health and social care) should ensure commissioners of care provision for people with a learning disability are equipped with or able to access specialist epilepsy expertise to commission safe and effective care for people with a learning disability and epilepsy.</p> <p>2c) Regional NHSE/I Learning Disability and Autism Programmes should undertake a capacity and training needs audit to review the capacity and skills of staff to commission safe care for people with learning disabilities who have complex needs including epilepsy. Epilepsy care coordination and management: Management and oversight of Clive's epilepsy care was often fragmented, and it was not always clear who was responsible overall. People with a learning disability and epilepsy are more likely to have complex needs and multiple co-morbidities. Often there are many professionals involved in their health and social care, and research shows that this is often fragmented affecting the quality of care received.</p> <p>2d) Commissioners of care for people with a</p>	<p>development of the guideline and where there was a lack of evidence the committee considered making consensus recommendations. This includes within the following sections of the guideline: 2 information and support, 3 referral to specialist services, 4.5 monitoring and review, 9.1 providing co-ordinated care, 9.2 support and treatment and 11.2 transition from child to adult epilepsy services.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>learning disability at a local level (health and social care) must take action to assure themselves that there is effective coordination between the full network of professionals in primary, secondary and community care supporting an individual necessary to provide holistic person-centred care for people with complex needs with a clearly identified lead.</p> <p>2e) Commissioners responsible for epilepsy care at a local level should undertake an audit of the effectiveness of local epilepsy services and support for people with a learning disability drawing on the NHS Right Care Epilepsy Toolkit and NICE standards to ensure they are meeting the needs of people with a learning disability and epilepsy, and that they are compliant with NICE standards of care. Care quality and safety: The standard of epilepsy care Clive received in specialist hospital and community residential care settings was often poor and his high risk of epilepsy-related death and sudden death was not always effectively recognised and mitigated. The learning from this review clearly identifies that the management of day-to day epilepsy care is critical to the safety of people with a learning disability and epilepsy. The standard of epilepsy</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>care provided in specialist hospital and community care settings, in Clive's case, was often poor. The level of training and awareness of epilepsy amongst care staff was sometimes very limited and they were not sufficiently equipped to manage complex and drug-resistant epilepsy. The high risk of epilepsy related death and sudden death was not systematically and comprehensively understood or mitigated.</p> <p>2f) Care providers (specialist hospital and community) must ensure that the care they provide for people with a learning disability and epilepsy is compliant with NICE epilepsy care standards and that all staff are trained in full to meet these standards.</p> <p>2g) Commissioners of care for people with a learning disability and epilepsy must ensure that care and service providers take a risk management approach to epilepsy related death, as recommended in the NHS Right Care Epilepsy Toolkit. This should specifically include application of a standard risk template for people living with epilepsy that crosses organisational boundaries, such as the SUDEP and Seizure Safety Checklist tool. Epilepsy and challenging behaviour: The link between Clive's epilepsy and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>challenging behaviour was overstated and disproportionately impacted on the generally held view that Clive required a hospital setting, depriving him of the opportunity to better manage his behaviours Care providers can struggle to understand the relationship between epilepsy and behaviour that is deemed to be challenging, which can lead to inadequate management and support, deterioration in physical and mental health,</p> <p>2h) With a view to providing better guidance for clinicians, carers and care professionals in relation to epilepsy and challenging behaviour linked to epilepsy and its management, the National Institute for Health and Care Excellence (NICE) should consider reviewing current guidelines in relation to: NHS RightCare: Epilepsy Toolkit (2020), SUDEP Action: SUDEP and Seizure Safety Checklist, . diagnostic overshadowing and poor decision-making, epilepsy and special consideration for people with a learning disability, challenging behaviour and learning disabilities.</p>	
SUDEP Action	Guideline	General	General	Since July 2020 there have been significant, concerning, national publications and inquiries which highlight the urgent need for improved	Thank you for your comments.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>epilepsy-mortality risk communication, epilepsy risk management and support for the bereaved following an epilepsy related death:</p> <ol style="list-style-type: none"> 1. Population based research in England using General Practice Data showing a 69% increase in epilepsy-related deaths in the lead up to the pandemic; 2. MBRRACE report finding a doubling of maternal deaths 2016-2018; 3. The LeDeR reports finding epilepsy as the second most common cause of death in adult learning disability and the first in children; 4- The findings of the Clive Treacey national review (December 2021), which included very poor risk assessment, poor communication of epilepsy situation, lack of recognition of response to risk, failure to monitor care quality; failure to investigate death as epilepsy-related. <p>We would in the light of these very stark and concerning findings urge that very serious consideration is given to:</p> <ol style="list-style-type: none"> 1. A separate section on Learning Disability and on Women with epilepsy, to give visibility to the needs of these vulnerable cohorts, and improved access to services to help reduce their risks. The 2004 guideline had separate 	<p>The committee have considered your suggestion for a separate section on learning disability but have decided against this because it may result in recommendations applicable to the wider epilepsy population including those with learning disabilities might be overlooked, and it is more helpful for all the recommendations on a particular topic together. For areas that are applicable for a specific population such as medication for women and girls who are planning pregnancy or are pregnant these are grouped together.</p> <p>The committee consider that they have highlighted epilepsy related mortality risk including SUDEP extensively within the guideline and have conducted several reviews in this area (17- tools to predicting death, including SUDEP, 18 -modifiable risk factors for epilepsy-related mortality, including SUDEP,19 - interventions in reducing the risk of seizure-related mortality, including SUDEP) and have made recommendations on this and for groups with special needs including people with learning disabilities wherever possible. Please refer to sections: 2 information and support,3 referral to tertiary epilepsy services, 4.5 monitoring and review, 9.1 providing co-ordinated care, 9.2 support and treatment, 10 reducing the risk of epilepsy related mortality</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>sections & they are likewise recognised as requiring extra focus in the NHS Rightcare Epilepsy toolkit. We would also suggest that specific guidance is given regarding the information provision (particularly on epilepsy risks and SUDEP) for parents and carers of people with epilepsy and Learning Disabilities.</p> <p>2. Ensuring epilepsy-mortality risk management is a thread running throughout the guideline – repeating key information so it is embedded in the patient pathway/shared care decision making (which is especially important as the guideline will be dipped in and out of over time).</p> <p>3. SUDEP & Epilepsy Deaths - Since 2002, national surveillance and individual inquiries have taken a precautionary approach to SUDEP/Epilepsy mortality, using 'potential avoidability' as a clearly stated focus for epilepsy-mortality risk communication and management practices. Ensuring existing knowledge, information and interventions are recommended as best practice, in the absence of a proven solution, given the</p>	<p>including SUDEP and 11.2 transition from children's to adults' epilepsy services.</p> <p>Unfortunately, little evidence for interventions to reduce epilepsy related mortality risk was found and therefore the committee were limited in the recommendations they could make. The committee consider the communication of risk to patients and their families and carers has been addressed within the guideline, however they agreed to add a consensus recommendation to stress the importance of supporting people in adhering to the medication prescribed as a key intervention to reduce risk.</p> <p>We agree support following SUDEP is vital and the committee have included providing information about SUDEP counselling within the topics to discuss with people in the information and support recommendations.</p> <p>We acknowledge the support provided by specialist epilepsy organisations and charities. NICE will provide links to other sources of information and support from the epilepsy guideline on the NICE website.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>urgency of preventing deaths by taking actions to do so e.g. standard checklists to support better understanding and communication. Such an approach also ensures there is a focus on learning lessons following epilepsy deaths, to improve future practice.</p> <p>This focus on the potential avoidability of many epilepsy deaths, and the significant opportunities to save lives is currently missing from this guideline, but is an important aspect for the clinical and epilepsy community to be made aware of. Taking a risk management approach to epilepsy mortality, where the preventability of many deaths is at the forefront, helps frame the importance of risk-management as an integral part of their care, treatment and decision making.</p> <p>During a pandemic when access is more limited than ever, people need to be able to self-advocate, and they cannot do that if they are not aware that they are at risk. Whilst monitors are given some prominence in this draft guideline, the management and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>communication of epilepsy risk is not – with the need for these reviews downplayed or separated out for certain 'high risk' groups. A holistic and regular check in on epilepsy risk with view to mitigating risk of SUDEP or other epilepsy mortality is good practice recommended by NHS RightCare and should be a standard part of epilepsy management for all people with epilepsy, regardless of current perceived risk level.</p> <p>4. Nocturnal seizures are given greater recognition in the SUDEP section but optimisation of seizure control which was identified as key in the guideline in 2004 appears diluted e.g. in respect of medications but without reference to consideration and communication of risks as part of decision-making.</p> <p>5. Commissioners - It is essential that there is a series of strong recommendations to Commissioners. Previous guidelines have not been supported by any system-wide levers. Key recommendations from the 2002 National Audit of Epilepsy Deaths focusing on epilepsy risk management and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>communication were not supported at a national, or in many local levels. The Treacey national review findings illustrate how failed implementation of this recommendation during life contributed to the harm Clive faced, and also the harm to the family (as well as to the investigation following his death).</p> <p>6. Bereavement – there is significant harm and public burden from epilepsy mortality. The 2004 guideline included recognition of this (1.3.14) although the evidence was far weaker of harm at that time. NHS RightCare and Royal College of Pathologists guidelines into investigating epilepsy deaths both recognise SUDEP Action as uniquely providing specialist services in this field and recognise the Epilepsy Deaths Register as a cathartic way to involve families in research following a death, which helps ensure lessons can be learnt to save future lives. The removal of this guidance for after an epilepsy death takes these guidelines backwards and leave those bereaved by epilepsy more vulnerable and at risk of not being able to access</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>specialist support and services. Specialist services SUDEP Action provide include:</p> <ul style="list-style-type: none"> Supporting families with an expert pathology review of the post-mortem with regard to the RCPATH Guidelines and support engaging with the Coroner Counselling Supported involvement in research, including informing the bereaved that there is no systemic information provided to clinical teams that one of their patients has died suddenly and that the Epilepsy Deaths Register team can facilitate this communication. https://doi.org/10.1016/j.yebeh.2019.07.017 https://doi.org/10.1016/j.yebeh.2019.106454 <p>Given generic bereavement services have significant waiting lists or closed books, and are overwhelmed by the impact of the COVID-19 pandemic, it is imperative those bereaved by epilepsy are signposted to a specialist service such as ours which can</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>provide this support both immediately after a death, and ongoing into the future.</p> <p>7. We would like to see the audience widened for the guidelines – good to see commissioners as audience but would like to see professionals widened to include social workers, community learning disability teams and voluntary sector advocacy teams.</p> <p>The NICE methodology may have constrained the development of the draft. This was not our experience in 2004 and as evidence has strengthened since then of systemic inequalities contributing to deaths, we hope our representations on behalf of many thousands of bereaved families will be considered.</p>	
SUDEP Action	Guideline	004	012-017	<p>We welcome the inclusion of afebrile seizures. We would also welcome reference to NICE guideline on Febrile Seizures. We have suddenly bereaved families of children less than 18 months reporting recurrent febrile seizures where the death is being investigated as a sudden unexplained death of childhood and differential diagnosis not yet under consideration</p>	<p>Thank you for enabling the Committee to comment on this. The Committee agreed that there can be a risk from seizures, even in very early life. The specific risk, though, relates to those children with complicated (complex) febrile seizures. It was, therefore, not thought appropriate to associate simple febrile seizures with epilepsy and associated risk. Rather, and mindful of the comments from other stakeholders, the Committee have formulated a separate</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					recommendation for complicated febrile seizures to try and ensure that those children receive appropriate and prompt escalation of care.
SUDEP Action	Guideline	009	007	<p>In this section/the guideline there is no reference to what information should be provided to those experiencing seizures who are on the diagnosis pathway. In the previous guidelines this was included:</p> <p>4.4.7 Essential information on how to recognise a seizure, first aid, and the importance of reporting further attacks should be provided to a person who has experienced a possible first seizure and their family/carer/parent as appropriate. This information should be provided while the individual is awaiting a diagnosis and should also be provided to family and/or carers.</p> <p>This previous information was helpful, though does not go far enough given a proportion of those undiagnosed will be at risk of premature epilepsy mortality while awaiting diagnosis. This information is particularly important in the current climate given the significant delays facing many epilepsy services across the country due to the COVID-19 pandemic, which is likely to continue for some time to come:</p> <p>https://sudep.org/sites/default/files/lives_cut_sh</p>	<p>Thank you for your comment.</p> <p>A recommendation on information for people who have not yet had a diagnosis of epilepsy has been added.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				ort - final.pdf https://www.neural.org.uk/wp-content/uploads/2021/07/20200703-Final-Restarting-Services-for-People-with-Neurological-conditions-v3.pdf During the pandemic, SUDEP Action have received increased contact from bereaved families whose loved one has died while awaiting diagnosis and experiencing delays in accessing these services, and there xx% of deaths reported to the Epilepsy Deaths Register are in those undiagnosed – so inclusion of information on risk is important.	
SUDEP Action	Guideline	010	001-007	This section should be strengthened to ensure that healthcare professionals are aware this is needed because of the higher risks of mortality for people with learning disabilities and epilepsy, and to include that all individuals with epilepsy and learning disabilities should have a risk assessment. This was included in the previous guidelines but in light of the recent NHS England commissioned independent review into Clive Treacey (can be found here) we feel this needs further strengthening.	Thank you for your comment. We agree health professionals need to be alert to the needs and support of people with epilepsy and learning disabilities. The committee have considered this throughout the guideline and have recommended additional specialist support for this population including regular monitoring reviews and the provision of co-ordinated care by MDTs. Cross reference has also been made to other NICE guidance on learning disabilities, that provide recommendations on risk assessment.
SUDEP Action	Guideline	010	015	As this is the first time using the acronym SUDEP in the main document (excluding the reference in	Thank you for your response. The guideline has been amended.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				the contents), it may be worth spelling out what the acronym stands for on this bullet point.	
SUDEP Action	Guideline	010	026	Are 'information and care planning appointments' a standard which people with epilepsy should expect? Are they only available to people with epilepsy who are under the care of an epilepsy specialist nurse, or can those being managed in primary care also gain access to this valuable type of appointment? It is important to be clear on whether people with epilepsy can expect/request these as a standard part of their care, or whether it is a geographically dependent service they may receive.	Thank you for your comment. The guideline committee has recommended that all people with epilepsy have access an epilepsy specialist nurse and are offered an information and care planning session.
SUDEP Action	Guideline	012	016-37	These are welcome new additions to draw out more specific areas of concern and importance for people with epilepsy and their carers.	Thank you for your response.
SUDEP Action	Guideline	012	027	Could this be made more explicit on why this is an important conversation? "Adherence to antiseizure medication (including its importance in reducing epilepsy mortality/SUDEP risks), and how to improve this"	Thank you for your comment. The committee agree this is a very important topic and think this has been addressed by the recommendation to discuss the importance of adherence to medication and reducing epilepsy related risks including SUDEP at the first appointment.
SUDEP Action	Guideline	013	007-014	It is important the bullet points noted in this 'sexual health and pregnancy' section are discussed with women with epilepsy in the wider context of epilepsy mortality risks, so they can	Thank you for your comment. Epilepsy related risks have been added to the list.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				make informed choices about their care. Could a note to that effect be added here to make this explicit – as it is feared (& beginning to become evident via the MBRRACE maternal death reports which showed a doubling of deaths in women with epilepsy between 2016-2018), particularly in relation to the PREVENT programme, that this is not always occurring, and women are making decisions about their medication/care without knowing about SUDEP/potential risks of premature mortality to themselves and any unborn child.	
SUDEP Action	Guideline	013	019-023	<p>It is good to see further detail added here compared to the previous guidelines, given the importance of the topic, and the gaps still prevalent in always discussing this with people with epilepsy. The Clive Treacy national review is just latest example of this of non-implementation between 2002 and his death in 2016.</p> <p>What is 'SUDEP Counselling'? What is evidence of any SUDEP Counselling Service reducing risks of sudden deaths and the costs of the service? Who would normally provide this service? Would non-epilepsy specialists know where to signpost people with epilepsy to receive this?</p>	<p>Thank you for your comment. SUDEP counselling is a service by trained health professionals to support people who have been bereaved by a sudden epilepsy death. The evidence review aimed to explore patients' and carer's perceptions, views, opinions and experiences in relation to information, education or support that will help people with epilepsy. The evidence highlighted the lack of understanding or awareness of SUDEP, including access to SUDEP counselling. The committee therefore recommended information about SUDEP including risk factors and how to mitigate risk, and the availability of counselling support be included within the framework as a topic for discussion between health professionals and patients, families and carers.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is also important to widen discussions of SUDEP to sit in a context of epilepsy-mortality in general (eg: accidents, suicide, status epilepticus and drowning) – as would happen if clinicians used the SUDEP and Seizure Safety Checklist to discuss epilepsy mortality risks in positive context of risk reduction with their patients.	The committee agree the wider context of epilepsy related mortality is important and safety issues and medication are also included.
SUDEP Action	Guideline	015	006-022	Again, it is important this discussion takes place with the person with epilepsy/their carer being aware of SUDEP and wider epilepsy mortality risks so they are able to make informed choices about the best medication/treatment route for them. Could a more explicit note to this effect be put in this section? Perhaps on the end of the bullet on line 14 eg: risks and benefits of antiseizure medication (including its importance in reducing epilepsy mortality/SUDEP risks)	Thank you for your comment, the recommendation has been amended in line with your suggestion.
SUDEP Action	Guideline	020	002-023	Again, it is important in this section to make sure this information is discussed with women with epilepsy in the wider context of epilepsy mortality risks, so they can make informed choices about their care. Could a note to that effect be added here to make this explicit – as it is feared (& beginning to become evident with doubling of deaths in pregnant women between 2016 and 2018 via the MBRRACE maternal death	Thank you for your comment. Epilepsy related risks have been added to the list.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				reports), particularly in relation to the PREVENT programme, that this is not always occurring, and women are making decisions about their medication/care without knowing about SUDEP/potential risks of premature mortality to themselves and any unborn child.	
SUDEP Action	Guideline	022	026-029	<p>Is 'if appropriate' needed here as it could be interpreted as something optional for clinicians to mention to their patients, rather than something they should say to them (unless a plan is already in place to review periodically). Could this be made more explicit in the case of if their epilepsy/epilepsy risks changes? We know people with epilepsy avoid burdening health professionals, or may not know when they should seek additional help. So giving some examples of when they should get in contact, could not only improve their self-management, but also help reduce burden on services (ie: if they don't seek help and end up in crisis), and potentially help avoid deaths.</p> <p>Eg: Explain to people with epilepsy, and their families and carers if appropriate, that they can ask for a review of their care if they have concerns (eg: over seizure control, medication/side effects, changing epilepsy-</p>	<p>The committee agree that all people with epilepsy need to know how to ask for a review of their care. The recommendation explains that what is optional is whether to explain this to families and carers. In those who cannot advocate for themselves, it would seem always appropriate to involve family and carers, but this may not apply universally. The committee think the wording is clear and already includes examples of the kind of issues this might include.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				mortality risks), need advice or their care needs change, for example, to support medicines withdrawal, advice on pregnancy planning or to review	
SUDEP Action	Guideline	022	001	<p>How will clinicians know who is 'high risk' of SUDEP if they are only seeing them yearly? Research has shown risk factors can change to become worse/fatal in as little as 3-6 months? (https://doi.org/10.1016/j.seizure.2014.02.005) Should all people with epilepsy not have access to an annual review of their epilepsy and medication, in case their risks change? Evidence from the Epilepsy Deaths Register highlights that it is not those 'at high risk' who are dying prematurely: https://epilepsydeathsregister.org/wp-content/uploads/the_adult_profile_of_sudep_using_the_epilepsy_deaths_register_abn.pdf</p> <p>The National Audit of Epilepsy-Related Deaths – epilepsy deaths in the shadows (2002), was the last time there was national surveillance across UK on epilepsy-related deaths. It found 47% of people who died had no recording of frequency of seizures, 21% had between once a month and once a year; 11% between once a week and once</p>	<p>Thank you for your comment. This would include the people described in recommendation 10.1.2 and 10.1.3 within section of the guideline entitled 'reducing the risk of epilepsy related death including SUDEP'. The committee considered that people whose epilepsy is well managed may not require a timetabled appointment but could access epilepsy services when required as in recommendation 4.5.4</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>a year; 9% once a week or more. 42% of deaths were potentially avoidable.</p> <p>Research on deaths between 2004 and 2014 with data from the General Practice Research Base Epilepsy and mortality: a retrospective cohort analysis with a nested case-control study identifying causes and risk factors from primary care and linkage-derived data found that:</p> <ul style="list-style-type: none"> • While the number of people with epilepsy registered in the GP database decreased by 22% over an 8-year period, the number of deaths in people with epilepsy increased by 69%. • The average age of death increased over time, and the data showed increased risk linked with emergency visits and/or emergency admissions, prescription of more than one anti-epileptic drug (which indicates someone has more complex, tricky to control epilepsy) and status epilepticus. • For the younger group of people with epilepsy included in the research, emergency visit or emergency admissions, number of medications, and 	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>injury were linked with higher risk of death.</p> <ul style="list-style-type: none"> For all age-groups, seizure freedom was linked to a lower risk of death. 	
SUDEP Action	Guideline	023	003-022	<p>There is no explicit mention here of the need for care to be managed by an MDT, with shared decision making, in the context of wider epilepsy mortality risks. Given the MBRRACE report showing a doubling of maternal deaths (pre-pandemic), and how many of these deaths were avoidable with improved risk communication/management, it is important this is clearly and specifically mentioned in this section.</p>	<p>Thank you for your comment. The committee agree communication between staff delivering care is very important and have recommended that care should be managed by an epilepsy specialist team in liaison with a specialist obstetric team and primary care (please see recommendation 4.6.2).</p>
SUDEP Action	Guideline	023	017-022	<p>Add another bullet for those with medication adherence issues? Would they also not benefit from closer monitoring?</p> <p>The MBRRACE reports also flag that many of the deaths in women are in those where English is not their first language, or they are from a minority group – should additional consideration of these challenges also be given here as they could be equally vulnerable groups requiring additional support?</p>	<p>Thank you for your comment.</p> <p>We think adherence to medication is addressed by the recommendation that women and girls who are pregnant or planning pregnancy are referred to an epilepsy specialist team who are able to review and monitor epilepsy medication and provide advice such as not stopping treatment. Information and support should be given that meets the need of individuals including those whose first language is not English, or they are from a minority group. This is addressed within the Information and support section, please see recommendation 2.1.2 and the patient experience</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					guideline which we have cross-referred to in recommendation 2.1.1.
SUDEP Action	Guideline	023	011-013	Again, could an explicit mention be added here of why they shouldn't stop medication? Eg: due to risk of premature epilepsy-mortality/SUDEP. It is important to be clear here on specifically why this is important, so phrases like 'could cause you and your baby harm' are not used by clinicians– which doesn't get across the potentially devastating consequences of medication non-adherence.	Thank you for your response. We think the recommendation is clear. The committee have drawn on the advice provided by the MHRA safety guidance on epilepsy medicines and pregnancy. Further information on this issue has been detailed in review 8 section 1.1.10.
SUDEP Action	Guideline	024	018-024	Again, could an explicit mention be added here of how these discussions should take place in the context of wider epilepsy-mortality risks and how they apply to that individual person with epilepsy at that moment in time? While seizure freedom reduces SUDEP risk significantly, it does not mean they are at zero risk from premature mortality, so it is important this is discussed as part of any withdrawal conversation, particularly if withdrawal is being managed by a non-epilepsy specialist who may not be as familiar with SUDEP/Epilepsy mortality risks.	Thank you for your comment, the recommendation has been revised to include the risk of SUDEP.
SUDEP Action	Guideline	027	008-009	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	028	018-019	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	031	024-025	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	033	027-008	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	036	023-024	More explicit mention here about preventing epilepsy mortality/SUDEP:	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	039	008-009	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	041	024-025	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	042	017-018	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child – particularly important given those with Dravet are often at increased risk of SUDEP/premature mortality.	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
SUDEP Action	Guideline	045	007-008	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child - particularly important given those with Lennox-Gastaut are often at increased risk of SUDEP/premature mortality.	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	052	015-016	More explicit mention here about preventing epilepsy mortality/SUDEP: "the risks and benefits have been fully discussed (including the importance of medication in reducing epilepsy mortality/SUDEP risks), including the risks to an unborn child	Thank you for your comment. The importance of considering SUDEP has been added to recommendation 4.1.1 in the 'Treatment with antiseizure medications' section, and 4.7.1 in the 'Discontinuing antiseizure medications' section so it is considered every time drugs are prescribed or withdrawn.
SUDEP Action	Guideline	054	015-020	If a person with status epilepticus does not have an emergency care plan in place, should this be agreed with their epilepsy professional as a matter of priority if they are having active seizures? A note to state the importance of this would be helpful in this section (as well as the line on this on pg 56), so clinicians, people with epilepsy and their carers are aware that this is something they should expect to help them manage their condition and reduce their risks.	Thank you for your comment We think this is addressed by Recommendation 7.1.12 which states to agree an emergency management plan if the person doesn't already have one.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
SUDEP Action	Guideline	055	004-005	Would it be worth adding a line in here for if this is the case, a discussion about the importance of medication adherence would be beneficial eg: If this is the case, discuss the risks and benefits of antiseizure medication (including its importance in reducing epilepsy mortality/SUDEP risks).	Thank you for your comment. Adherence to medication is very important and the committee have made recommendations on this throughout the guideline. Please see information and support monitoring and review, support and monitoring for women, reducing the risk of epilepsy related mortality and transition from child to adult epilepsy services.
SUDEP Action	Guideline	058	005-006	Ditto above comments about clinicians having this discussion in the context of wider epilepsy mortality risks.	Thank you for your comment. One of the benefits would be reducing risk of epilepsy mortality as you describe. The benefits and harms are discussed in the resective epilepsy surgery rationale and impact section of the guideline
SUDEP Action	Guideline	059	009-010	Ditto above comments about clinicians having this discussion in the context of wider epilepsy mortality risks.	Thank you for your comment. The evidence is much weaker for the committee agreed that the benefits and harms should be discussed with the person because the intervention does not work in all people and is not a risk-free procedure. This is described in the VNS rationale and impact section of the guideline.
SUDEP Action	Guideline	059	016-017	In the previous guidelines, it was stated that for those with learning disabilities, the management and treatment of their epilepsy should be undertaken by a specialist, working within a multi-disciplinary team. Can 9.1.2 therefore be strengthened to ensure it is explicit that those with learning disabilities should be provided with	Thank you for your comment. We have amended the recommendation as suggested. Learning disabilities was a group identified as requiring specific consideration during the scoping of this guideline, and included as a subgroup in all evidence reviews. Unfortunately, little evidence was found for this population, but when found it was

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>coordinated care using a multidisciplinary approach.</p> <p>We also suggest that more should be added for those with learning disabilities and epilepsy given the vulnerability of this group regarding premature epilepsy mortality and the effective management of associated risks:</p> <p>In making a management plan for an individual with learning disabilities and epilepsy, particular attention should be paid to any adverse cognitive and behavioural effects.</p> <p>Healthcare professionals should also be aware of the higher risks of mortality for people with learning disabilities and epilepsy, and discuss these with individuals, their families and/or carers. All individuals with epilepsy and learning disabilities should have a risk assessment.</p> <p>The recent NHS England commissioned independent review into Clive Treacey (can be found here) found neither Clive or his family or the carers around him understood his person-centred risks of SUDEP or other fatality. Too frequently he was moved from residential</p>	<p>included and considered by the committee and recommendations made where relevant. The committee also made consensus recommendations for areas of the guideline where no evidence was found but they considered it important to provide guidance specifically for this population. Cross reference has been made to other relevant NICE guidelines including 'Challenging behaviour and learning disabilities' and 'Mental health problems in people with learning disabilities'.</p> <p>Recommendations on the care and support for people with learning disabilities are included within : information and support needs, referral to specialist services, monitoring and review, epilepsy surgery, psychological. Neuro-behavioural, cognitive and developmental comorbidities, and transition of young people to adult services sections of the guideline.</p> <p>We agree it is important to raise awareness of epilepsy related risk and SUDEP and this has been highlighted throughout the guideline. A review of accurate tools to predict death, including SUDEP was carried out, but the evidence was not sufficient to recommend the use of any particular SUDEP or all-cause mortality risk tool. The committee have made a</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>settings for non-clinical reasons or moved very suddenly without any check on his risk. The Treacy report recommends that there is a holistic check on fatality risk including physical and mental risk factors including changes to anxiety and depression, e.g. using the SUDEP and Seizure Safety Checklist (www.sudep.org/checklist). Use of the SUDEP and Seizure Safety Checklist as part of a management plan is recognised by NHS RightCare 2021 and by LEDR national reviews 2019/20 as good practice.</p> <p>https://www.england.nhs.uk/rightcare/products/pathways/epilepsy-toolkit/</p> <p>http://www.bristol.ac.uk/media-library/sites/sps/leder/LeDeR_2019_annual_report_FINAL2.pdf</p> <p>Placed based planning and ICS planning on tackling inequalities should include a plan for people with learning disability and epilepsy with a designated champion responsible.</p> <p>Existing tools, e.g. SUDEP and Seizure Safety Checklist and EpSMon App (www.sudep.org/epsmon), are supported by research and development to contribute to person-centred communication and enablement regardless of whether someone is living with</p>	<p>recommendation for further research on the development and validation of a risk prediction tool for all cause epilepsy related death.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				their family or in community based supported living or a specialist setting.	
SUDEP Action	Guideline	060	013-015	The clinical SUDEP and Seizure Safety Checklist (and patient version, the EpSMon app), provide a framework to have these important discussions in the wider context of epilepsy risks, epilepsy management and wellbeing.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
SUDEP Action	Guideline	061	008-016	<p>It is good to see a more detailed section focusing specifically on SUDEP than in the previous guideline.</p> <p>The section title however says it focuses on epilepsy mortality generally, yet the information in the section mostly focuses on SUDEP. This viewpoint should be widened to cover other causes of death alongside the SUDEP information provided to acknowledge the wider epilepsy mortality risks people with epilepsy may face, and the role clinicians play in discussing and helping to mitigate them.</p> <p>Will other modifiable epilepsy mortality risk factors be mentioned elsewhere in this section though as it currently narrows in solely on SUDEP rather than also covering wider epilepsy mortality risks, despite the title for the section saying it covers mortality more generally eg: alcohol and/or substance abuse, depression or other</p>	Thank you for your response. The aim of the review was to capture evidence for any epilepsy related death as well as SUDEP. The review summarises all the available clinical evidence which matched the review protocol criteria for inclusion.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>psychiatric disorder, status epilepticus/prolonged seizures.</p> <p>In the previous guideline it stressed the important of medication in minimising risk of SUDEP and optimising seizure control (as part of shared decision making), which would be a worthwhile addition here for clarity. There are also other parts of the guideline where an emphasis on monotherapy does not take into consideration shared decision making around reducing risks of avoidable mortality and the potential benefits of polytherapy for some individuals.</p>	
SUDEP Action	Guideline	062	014-020	<p>Does this mean all people with epilepsy (even if they are currently managed in primary care), are/should be able to have access to an epilepsy specialist nurse to support them with their epilepsy? Or will some only receive this service if they meet certain criteria/dependent on where they live/early on in their epilepsy diagnosis? It isn't clear, but is something which would be very beneficial to people with epilepsy, as the ESN can act as a main point of contact for people with epilepsy throughout their care, helping to coordinate any step up, down or across which</p>	<p>Thank you for your comment. The recommendation states that all people with epilepsy should have access to an epilepsy specialist nurse. It is the hope of the committee that they will be able to facilitate better care, acting as support, a point of contact and giving information to those with epilepsy should they wish to access this help.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				may be needed to help them better self-manage their epilepsy.	
SUDEP Action	Guideline	062	008-012	<p>Again, should caution be taken of using the phrase 'high risk' given research has shown risk factors can change to become worse/fatal in as little as 3-6 months? (https://doi.org/10.1016/j.seizure.2014.02.005)</p> <p>Should all people with epilepsy having seizures during sleep not have the option to discuss this with their clinician, in case their risks change? Evidence from the Epilepsy Deaths Register highlights that it is not those 'at high risk' who are dying prematurely: https://epilepsydeathsregister.org/wp-content/uploads/the_adult_profile_of_sudep_using_the_epilepsy_deaths_register_abn.pdf There is also evidence in the Epilepsy Deaths Register of premature deaths in people who have the support of monitors – so it is important there is recognition here that any discussion of monitors is one part of a wider epilepsy mortality risk care plan, taken alongside other actions to reduce any other epilepsy risks which may be prevalent for that specific individual.</p>	<p>Thank you for your comment.</p> <p>This would include the people described in recommendation 10.1.2 and 10.1.3 within the reducing risk of epilepsy related death and SUDEP section of the guideline. The recommendation gives the example of people at higher risk and does not preclude having a discussion with others if the person with epilepsy or their clinician think it appropriate. The committee wished to ensure that this recommendation was kept broad such that anyone with tonic clonic seizures from sleep, for example, should have the relevant discussions about reducing risk as all such individuals would be classified as being at higher risk.</p>
SUDEP Action	Guideline	062	001-004	It is welcomed to see the importance of discussing SUDEP with people with epilepsy and their carers mentioned clearly here. As well as	<p>Thank you for your comment.</p> <p>The wording has been amended to clarify.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>the need for this to be a repeated conversation where an action plan to tackle risks is identified together (the SUDEP and Seizure Safety Checklist is a tool already in existence to support and help facilitate this discussion and has been proved to help reduce risks in people with epilepsy previously known to be at risk).</p> <p>Is 'if appropriate' needed here as it could be interpreted as something optional for clinicians to mention to their patients, rather than something they should say to them. The lack of guidance on what would constitute a good reason not to inform and the need for a plan to mitigate risk of not sharing risk is concerning especially against a context of people experiencing long waits to access services for diagnosis and treatment and if put on medication without a full understanding of the benefits and risks of medications.</p>	
SUDEP Action	Guideline	062	005-007	<p>Is there a reason why those experiencing seizures while asleep are being singled out here? While this does increase risk in this cohort, there is a concern that by focusing on this group, some clinicians may focus their attentions exclusively/more heavily on this group of</p>	<p>Thank you for your response. this recommendation was based on the evidence available for the review (please see review 19).</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				individuals, rather than having a SUDEP/epilepsy risk conversation with all their epilepsy patients.	
SUDEP Action	Guideline	063	004-007	This is a significant improvement for people with epilepsy and would help provide them with continuity of care with a specialist. However, is there the ESN capacity around the country for this to feasibly work? If not, what service provision should people with epilepsy expect instead, or will local health services be expected to provide a local ESN for their epilepsy population?	Thank you for your comment, the committee acknowledge that this may be challenging for some trusts that do not already have sufficient numbers of ESNs in place, however it is the role of NICE guidelines to set the standards of care that should be aspired to and worked towards. The economic modelling work conducted for this guideline also shows the evidence of cost savings both long-term and within the first year from implementing this and the committee hopes this will encourage commissioners to fund these roles to optimise service delivery.
SUDEP Action	Guideline	064	009-010	In section 2.1 it discusses the importance of repeating conversations about key information – should a note to that effect also be put here? Eg: Offer the young person with epilepsy, and their families and carers if appropriate, opportunities at each appointment to discuss issues that concern them including, but not limited to, the topics listed below.	Thank you for your suggestion. The committee consider the recommendation is clear and provides an opportunity for the young person to have an independent and open discussion with a health professional. This was a theme identified within the evidence. They agree the topics for discussion should not be limited to those listed and have amended the recommendation.
SUDEP Action	Guideline	067	010-013	We welcome the recommendation that better prediction of SUDEP/epilepsy mortality is needed as discussing and taking action against risks is a vital mechanism for preventing future deaths. This is long overdue given evidence of this need	Thank you for your response. The committee considered the currently available risk tools for predicting epilepsy-related mortality (including SUDEP) have inadequate levels of predictive accuracy to allow reliable and safe prediction . They

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>has been prevalent since the original epilepsy guidelines were created in 2004 following the National Sentinel Clinical Audit of 2002. The Lancet editorial in 2002 was clear that although more research was needed, that if existing research was used in the meantime many lives would be saved,.</p> <p>It is imperative however that this recommendation is followed through on, so in years to come it has been achieved, rather than re-repeated in a new guideline update. The lack of systemic support to identifying barriers and enabling solutions following the original guideline in 2004 and the cutting of the QOF annual review in 2013 which was a potential enabler has contributed to rising deaths (see Lives Cut Short Report).</p> <p>To fill this gap SUDEP Action codesigned a standardised approach developed in a local population across learning disability and general community settings which has raised rates of communication and reduced risk. The tool does not separate out SUDEP from other risk of fatality but takes a holistic approach to enable one communication which can enable where</p>	<p>therefore decided to make a research recommendation for a new risk tool to be developed, ideally based on a large-scale cohort study. The committee were aware of the SUDEP and Seizure Safety Checklist and existing tools would be factored in when designing new research.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>enablement is likely to be most positive e.g. this might be mental health.</p> <p>It includes balanced information to women of child-bearing age.</p> <p>While this recommendation is welcomed, it is important to note that an epilepsy mortality/SUDEP communication tool is already in existence and is widely used by over 1300 clinicians across the UK to discuss, monitor and reduce epilepsy mortality risks – it was, and remains funded by families bereaved by epilepsy to help prevent future deaths despite the lack of national support for preventing epilepsy deaths. The SUDEP and Seizure Safety Checklist (www.sudep.org/checklist) is underpinned by a significant body of research, and has been proven to help reduce risk in those previously known to be at risk: https://doi.org/10.1111/ene.13651. It has also been adopted in Australia as a way to help tackle epilepsy mortality when no other tool is currently available to do this.</p> <p>The SUDEP and Seizure Safety Checklist is recommended to be used as good practice by the NHS RightCare Epilepsy Toolkit (see here), and in a recent NHS England commissioned</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>independent review into Clive Treacey (can be found here)</p> <p>Any creation of a new tool, rather than working to further develop and enhance what already exists, would be a reinvention of the wheel, a waste of public funds, and an insult to the bereaved families who have provided this tool when no national service was willing or able to. We would urge NICE, or whoever plans to take this recommendation forward, that they coordinate with SUDEP Action and the experts involved in the Checklist project on this before any action is taken.</p>	
SUDEP Action	Guideline	069	002-004	<p>We agree that further research into, and support for digital technologies can play an important role in better supporting people with epilepsy with their self-management and risk reduction. It is a shame that no existing solutions available (for example the Epilepsy Self Monitoring app, EpSMon) are able to be signposted to at present though, as in the absence of having anything recognised by NICE's review process, it could leave people with epilepsy unsure what is available to support them, and once again leaves it to the patient organisations to provide this vital signposting.</p>	<p>Thank you for your comment.</p> <p>No evidence was found for EpSMon and therefore under NICE guideline development methods we are unable to make a research recommendation for this topic.</p> <p>In the discussion of the digital health technologies evidence review the committee have referred to sources (such as Epilepsy Action) that provide information on digital technologies available.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The EpSMon app is recommended to be used as good practice by the NHS RightCare Epilepsy Toolkit (see here). We would urge NICE to give recognition to this tool that already exists.	
SUDEP Action	Guideline	061	003	<p>There is no mention in this section about what clinicians should do if one of their patients dies due to their epilepsy/SUDEP (which was included in the previous guidelines in the SUDEP section 1.3.14).</p> <p>The National Sentinel Clinical Audit of Epilepsy Deaths 2002 found that good practice in making contact with families after a sudden death was very rare and noted that although it is possible that some specialists were not aware of the deaths of patients, it is of concern that an invitation to meet the bereaved family was rarely recorded. Frameworks of care for patients with epilepsy should include details of post-mortem processes for contact with bereaved carers/families in the event of an epilepsy related death so that there is an open sharing of information and understanding of the events leading up to and the circumstances of death.</p>	<p>Thank you for your comment and the useful links to other sources of information and support. We agree support for families and carers following SUDEP is very important and the committee have included providing information about SUDEP counselling within the topics to discuss with people in the information and support recommendations.</p> <p>We acknowledge the support provided by specialist epilepsy organisations and charities. NICE will provide links to other sources of information and support from the epilepsy guideline on the NICE website</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>This is particularly important when the death is sudden and unexpected because families experience bewilderment, isolation and prolonged distress (Nashef et al., 1998). A government action plan included development of national epilepsy and pathology guidelines.</p> <p>Sadly, the experience today is that wide-ranging systemic problems in the aftermath of a sudden death that prevented implementation of guidelines have exacerbated these inequalities with worsening of harm of bereaved families during the pandemic. In these cases, there is too often a systemic failure to consider epilepsy as a contributor to/cause of death or to recognise learnings to prevent future deaths.</p> <p>The recent NHS England commissioned independent review into Clive Treacey (can be found here) illustrates the harm of delayed signposting of a family to a specialist service able to provide specialist support and enablement in a highly complex multi-disciplinary environment in the immediate aftermath and the years following a sudden death. Evidence also from over 900 bereaved families from the Epilepsy Deaths Register finds access to specialist support and</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>enablement in research is partially cathartic. Early intervention through referral to a specialist service can be helpful to support and enable the family. In the Treacey case the intervention of SUDEP Action four years after the inquest enabled recognition for the first time that SUDEP had not been considered in line with Royal College of Pathologist guidelines at the inquest into his death (https://www.rcpath.org/uploads/assets/15a26420-ce7b-4858-ad538b210328d973/G175-Guidelines-on-autopsy-practice-Deaths-in-patients-with-epilepsy-including-sudden-deaths.pdf). Through the pandemic SUDEP Action has supported and enabled 70 families to bring this knowledge into investigations into sudden deaths in people with epilepsy.</p> <p>Early signposting to specialist epilepsy bereavement services is vital to those suddenly bereaved by epilepsy, and these guidelines can play a significant role in helping bereaved families access this help by alerting clinicians to its importance and the existence of such services (which in turn can help alleviate the burden on health services, and help avoid legal cases being</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>brought in the case of avoidable epilepsy deaths): https://doi.org/10.1016/j.yebeh.2019.07.017</p> <p>With increasing after a death reviews/inquiries flagging the importance of learning from epilepsy deaths (MBRRACE, LeDeR, CDOP), this signposting is increasing in importance, and can help both the bereaved, and researchers to ensure lessons are learnt should an epilepsy death occur: https://doi.org/10.1016/j.yebeh.2019.106454</p> <p>Many of the main generic bereavement services (Cruise) also currently have long waiting lists for support, or are not able to take on any additional clients (Sudden) and are not services that have expertise in sudden medical deaths or able to support enablement through family navigation of the system for the aftermath of complex processes.</p> <p>Specifically, the Royal College of Pathologist's Guidelines on deaths in patients with epilepsy (see here) and the NHS RightCare Epilepsy Toolkit (see here) recognises signposting to SUDEP Action and the Epilepsy Deaths Register (EDR) after an epilepsy related death.</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>It is vital that bereaved families are not excluded from the new guideline and that the previous guideline 1.3.14 (which used evidence from Kennelly, C. and Riesel, J. Sudden death and epilepsy. The views and experiences of bereaved relatives and carers. 2002. London, College of Health, and Nashef 1998 see here) is strengthened in recognition of what can help families and systemic learning from deaths.</p> <p>Suggested wording to add to this guideline could be:</p> <p>Where families and/or carers have been affected by SUDEP or an epilepsy-related death, professionals who are aware of the death should contact families and/or carers to offer their condolences, offer them a meeting and offer referral to a specialist service for families recognised by NHS RightCare and the Royal College of Pathologists guidelines as offering relevant services for families affected by SUDEP and epilepsy-related deaths.</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
The Breastfeeding Network	Guideline	021	010-018	We are pleased to see that breastfeeding is considered and encouraged in mothers with epilepsy. However, in addition to the SPC and BNF, we would recommend that prescribers should refer to the UK Drugs in Lactation Advisory Service, provided by the NHS specialist pharmacy service (UKDILAS, UK Drugs in Lactation Advisory Service (UKDILAS) – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice), LACTMED (Drugs and Lactation Database (LactMed) - NCBI Bookshelf (nih.gov)) and The Breastfeeding Network Drugs in Breastmilk service (DiBM, Drugs In Breastmilk - Is It Safe? - The Breastfeeding Network), as the SPC and BNF can take an overly conservative stance on taking medication whilst breastfeeding. Reference to these alone could lead mothers taking the unnecessary decision to terminate breastfeeding prematurely, not to breastfeed at all, or to discontinue a necessary medication in order to breastfeed, putting the health and safety of themselves and their child at risk. For example, in the cases of topiramate and Levetiracetam, the SPC and BNF both advise that breastfeeding is not compatible with these medications. However, UKDILAS and LACTMED both advise that	Thank you for your comment and the list of resources. We are unable to refer to these directly however your comments will be considered by NICE where relevant support activity is being planned'.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>breastfeeding can continue with the correct monitoring in place.</p> <p>These recommendations have been discussed within the Safer Medicines in Pregnancy and Breastfeeding Consortium to enable women and professionals to make evidence based decisions.</p> <p>https://www.gov.uk/government/publications/safer-medicines-in-pregnancy-and-breastfeeding-consortium</p>	
The Daisy Garland Charity	Guideline	General	General	<p>The Daisy Garland, as a key charity stakeholder, wish to register our strong objection to the draft proposal of the new NICE Guidelines restricting the availability of the ketogenic diet for children with difficult to control epilepsy.</p> <p>The ketogenic diet is a well-recognised medical-led diet with proven efficacy. Strong scientific research clearly demonstrates the positive impact the ketogenic diet has on the lives of children with drug-resistant epilepsy. Research shows:</p> <ul style="list-style-type: none"> ▪ half the children on the ketogenic diet will see a 50% seizure improvement ▪ one third will see more than 90% improvement 	<p>Thank you for your response.</p> <p>The 2012 guidance recommends referral of children and young people who have not responded to appropriate anti-seizure medication to a tertiary paediatric specialist for consideration of a ketogenic diet.</p> <p>The committee made the current recommendation based on the latest clinical and cost effectiveness evidence, and in consideration of other recommended treatments such as resective surgery or VNS. However, the committee have reviewed the wording of the recommendation and have amended this to clarify that not every treatment option has to be tried before a ketogenic diet can be considered.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<ul style="list-style-type: none"> around 10-15% will be seizure-free <p>The proposal to impose restrictions on the use of the ketogenic diet will have catastrophic effects on the lives of over 18,000 children living in the UK with drug-resistant epilepsy and their families.</p> <p>As a charity and ketogenic service provider we have first-hand experience of the positive impact the ketogenic diet has on seizure control, quality of life and improved mental health.</p> <p>The present guidelines of offering the ketogenic diet to children with complex epilepsy when two appropriate anticonvulsant medications fail, are reasonable, proportionate and should remain.</p>	
Tuberous Sclerosis Association	Guideline	042	002	We would like to suggest that section 6 on 'Treating childhood onset epilepsies' should also include a new section on Tuberous Sclerosis Complex (TSC). There is a specific treatment pathway for TSC that should be included in this clinical guideline to raise awareness among health professionals.	Thank you for your comment. The committee acknowledge that there are many types of syndromes and were not able to cover each one in detail. Rather they focused on seizure types, which should be followed regardless of the syndrome, in addition to some of the more common childhood onset epilepsies.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>TSC is a rare genetic condition estimated by NHS England to affect around 3,200 people living in England. Around 8 out of 10 people living with TSC have refractory epilepsy which is hard to treat with anti-epilepsy drugs.</p> <p>NHS England has developed a clinical commissioning policy recommending the use of everolimus for TSC-related refractory epilepsy. You can find their guidance here: https://www.england.nhs.uk/wp-content/uploads/2018/12/Everolimus-for-refractory-focal-onset-seizures-associated-with-TSC.pdf.</p> <p>We would also like to draw your attention to the recommendations relating to epilepsy set out in the UK consensus guideline on diagnosing and managing TSC. You can find the details here: https://tuberous-sclerosis.org/wp-content/uploads/2019/10/TSA_TSC-UK-clinical-guidelines-summary.pdf.</p> <p>Finally, we would like to flag up that NICE is expected to start a technology appraisal on cannabidiol for TSC-related refractory seizures in January 2022. We appreciate that guidance on</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cannabidiol will be issued too late for inclusion in this version of the updated clinical guideline, but it would be helpful to note this appraisal for future updates of the guideline.	
UCB Pharma Ltd	Guideline	General	General	UCB welcomes the comprehensive review of CG137. We welcome the analysis and the focus on the individualised care strategies tailored to each patients' needs.	Thank you for your comments.
UK Infantile Spasms Trust	Comments form Q1	General	General	The section Infantile Spasms- we have been trying to raise awareness that suspected IS (Infantile Spasms) needs immediate/emergency assessment. Now this is potentially in the NICE guidelines we feel it should make this much more likely and really change practice for the better. This will be challenging to implement unless GPs/A+E departments are aware of the new guidance and have access to same day paediatric assessment and urgent EEGs. The updated guidance to recommend that dual therapy with Vigabatrin and Prednisolone combined should be used first line if appropriate, will also likely have a significant positive difference on outcomes.	Thank you for your comment. Recommendation 6.3.1 has been amended to state that any child under 2 years with suspected or confirmed infantile spasms should be referred to a tertiary paediatric neurologist within 24 hours for assessment, including a sleep EEG.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
UK Infantile Spasms Trust	Comments form Q2	General	General	Unable to comment except on area related to Infantile Spasms. We do not foresee significant cost implications as a result of this	Thank you for your comment.
UK Infantile Spasms Trust	Comments form Q3	General	General	Expansion of digital technology systems to allow parents/GPs to send in videos of potential Infantile Spasms to specialists for review. Increased access to paediatric neurologists/paediatricians with a specialist interest in epilepsy. Increased access to on the day/urgent EEG including at the weekends or bank holidays	Thank you for your comment. The committee agree that rapid access to a paediatric neurologist is very important, particularly for children with infantile spasms. Recommendation 6.3.1. has been amended to specify that these children should be referred within 24 hours to be seen urgently. Recommendation 1.2.7 states that anyone with epilepsy should ideally have an EEG within 72 hours of a first seizure, and recommendations 6.3.2 and 6.3.3 specify that EEG monitoring should continue.
UK Infantile Spasms Trust	Comments form Q4	General	General	We have found access to support services e.g. physio/OT to have been negatively impacted by the pandemic. Children on steroid treatment are immunocompromised and this has meant that some IS patients were not treated with prednisolone	Thank you for your comment. The committee hope that the recommendations for the Epilepsy Specialist Nurses will facilitate access to support services.
UK Infantile Spasms Trust	Guideline	005	003	We are concerned that the recommendation to refer all seizures/recurrence of seizures urgently (within 2 weeks) does not correlate with the recommendation for 'immediate' assessment in suspected Infantile Spasms as cited in the section of the draft guidelines pertaining to Infantile Spasms directly. We were wondering if a caveat	Thank you for highlighting this. We have amended the recommendation by linking to the recommendation for immediate referral if infantile spasm is suspected.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				could be introduced for suspected IS/link to the IS section?	
University Hospitals Birmingham NHS Foundation Trust	Guideline	022	012	4.5.2 We are concerned that this recommendation is unrealistic given current capacity within the epilepsy service. The recommendation could be modified to suggest 6 to 12 month review in those patients whose seizures are uncontrolled.	Thank you for your comment. The committee believe the frequency of monitoring reviews reflects current practice; however, they agree the frequency should be tailored to the needs of the individual and have amended the recommendation to reflect this.
Young Epilepsy	Guideline	General	General	<p>Young Epilepsy has shared the following survey reports with the guideline committee, highlighting young people's views and experiences of epilepsy care and the impact of living with epilepsy on their mental wellbeing:</p> <ul style="list-style-type: none"> • Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings • Young Epilepsy (2021) Young people's experiences of epilepsy and mental wellbeing: Summary of survey findings 	Thank you for your comment, the group considered this report when revising the draft guideline.
Young Epilepsy	Guideline	001	007	In the section 'Who is it for?', the guideline should indicate that it may also be relevant for education professionals. For example, education staff who assume caring responsibilities for children whilst they are at school.	Thank you for your comment. Unless explicitly stated in the scope, NICE guidelines are for health and social care professionals. However, the recommendations for epilepsy specialist nurses have now been amended

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					to ensure they support professionals working in education.
Young Epilepsy	Guideline	009	015	<p>We welcome the recommendation to include children and young people in discussions about their information and support needs and provide information appropriate to their developmental age.</p> <p>This section should also include a recommendation that appointments should allow sufficient time for discussion with children and young people, including asking about any questions or concerns they may have and checking they have understood all the relevant information.</p> <p>A Young Epilepsy survey [1] found that only 57.6% of young people (aged 11 to 25) felt listened to by their epilepsy doctor and 59.9% said their epilepsy doctor explained things clearly.</p> <p>1) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings</p>	<p>Thank you for your response. Recommendation 2.1.3 states 'Include children and young people in discussions about their information and support needs and provide information appropriate to their developmental age'. This was drafted to ensure a direct dialogue between children with epilepsy and their epilepsy healthcare provider which would take into consideration their concerns and information needs.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Young Epilepsy	Guideline	010	010	<p>Mental wellbeing should be included in the issues to be discussed during a first appointment and at each subsequent appointment. A Young Epilepsy survey [1] found that 77% of young people said living with epilepsy has had a significant impact on their mental wellbeing, including their thoughts, feelings and how they are able to cope with everyday life.</p> <p>Despite the increased risk of experiencing mental health problems, a further Young Epilepsy survey [2] found that only 45.2% of young people (aged 11 to 25) said their epilepsy doctor or nurse had spoken to them about how epilepsy might impact on their mental health.</p> <ol style="list-style-type: none"> 1) Young Epilepsy (2021) Young people's experiences of epilepsy and mental wellbeing: Summary of survey findings 2) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings 	Thank you for your comment. The committee considered these were the key issues that should be covered at a first appointment, but it would not preclude discussion of other topics if deemed appropriate. The committee agree mental health is very important and included emotional and psychological wellbeing within the framework of topics commonly raised for discussion at all appointments.
Young Epilepsy	Guideline	012	General	In 'Activities of daily living', public transport should be included alongside driving. For example, access to disability travel passes and	Thank you for your comment. The framework of topics included is intended as an aid for discussion based on issues identified by the evidence and committee experience, and is not meant as a

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				safety considerations when using public transport.	prescriptive list. The committee are aware there are many other important areas, but it is not possible to include them all, and people should be encouraged to discuss any other issues that are of concern to them.
Young Epilepsy	Guideline	059	016	<p>We welcome the recommendation to provide coordinated care for people with epilepsy who have a mental health condition. Mental health screening and support should be an integrated part of children and young people's epilepsy care.</p> <p>A Young Epilepsy survey [1] found that 77% of young people said living with epilepsy has had a significant impact on their mental wellbeing, including their thoughts, feelings and how they are able to cope with everyday life.</p> <p>Despite the increased risk of experiencing mental health problems, a further Young Epilepsy survey [2] found that only 45.2% of young people (aged 11 to 25) said their epilepsy doctor or nurse had spoken to them about how epilepsy might impact on their mental health.</p> <p>1) Young Epilepsy (2021) Young people's experiences of epilepsy and mental wellbeing: Summary of survey findings</p>	Thank you for your response and for sharing the results of your survey

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Young Epilepsy	Guideline	060	009	<p>The section on 'Support and treatment' for psychological, neurodevelopmental, cognitive and behavioural comorbidities in epilepsy should include a recommendation to communicate with parents and education settings about how these comorbidities may affect a child or young person's education.</p> <p>These comorbidities have a significant impact on children and young people's experiences at school, including their wellbeing and attainment. Education staff need sufficient information to effectively support the children and young people with epilepsy in their care.</p> <p>State schools in England have a legal duty to support pupils with medical conditions [1] and are expected to have individual healthcare plans (IHPs) in place. IHPs should include key information such as what to do in an emergency, but also support for the child's educational, social and emotional needs.</p> <p>In a study of the school experiences of children with epilepsy [2], parental interviews highlighted difficulties accessing educational and therapeutic supports. Parents often felt that they had to drive</p>	Thank you for your response. Please see recommendation 9.2.4 which links to other relevant guidance for support as well as section 2 on specific recommendations for information and support.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>the process to gain supports themselves. They also reported limited professional support, and inadequate communication between school staff and medical/therapeutic professionals regarding their child's needs. Parents would like more school staff to recognise the impacts of epilepsy on learning and behaviour and to support their child more holistically.</p> <ol style="list-style-type: none"> 1) Children and Families Act 2014, section 100 2) Johnson et al (2021) Epilepsy in schools: Views on educational and therapeutic provision, understanding of epilepsy and seizure management 	
Young Epilepsy	Guideline	060	013	<p>We welcome regular review of the emotional wellbeing and mental health of people living with epilepsy. The guideline should specify that mental wellbeing should be discussed at the point of diagnosis and at each subsequent appointment.</p> <p>A Young Epilepsy survey [1] found that 77% of young people said living with epilepsy has had a significant impact on their mental wellbeing,</p>	<p>Thank you for your response.</p> <p>A recommendation has been made to discuss mental health at the first assessment before a diagnosis is made.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>including their thoughts, feelings and how they are able to cope with everyday life.</p> <p>Despite the increased risk of experiencing mental health problems, a further Young Epilepsy survey [2] found that only 45.2% of young people (aged 11 to 25) said their epilepsy doctor or nurse had spoken to them about how epilepsy might impact on their mental health.</p> <ol style="list-style-type: none"> 1) Young Epilepsy (2021) Young people's experiences of epilepsy and mental wellbeing: Summary of survey findings 2) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings 	
Young Epilepsy	Guideline	062	020	<p>We welcome the recommendation that all children and young people should have access to an epilepsy specialist nurse. The recommendation on providing information, education and support should specify that (in addition to the young person and their family) this should be offered to others who have responsibility for a child's wellbeing, including staff in education and childcare settings.</p>	<p>Thank you for your comment, the recommendation has been amended to state that the Epilepsy Specialist Nurse should also support professionals in education settings and facilitates communication with multi-agency services.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>In a study on the inclusion and participation of children with epilepsy in school [1], the majority of children (64%) and parents (56%) agreed that the child with epilepsy was restricted from doing things their peers could do because of their epilepsy.</p> <p>1) Johnson et al (2021) Inclusion and participation of children with epilepsy in schools: Views of young people, school staff and parents</p>	
Young Epilepsy	Guideline	063	001	<p>We welcome the recommendation to offer people with epilepsy an information and care-planning session with an epilepsy specialist nurse (ESN).</p> <p>The guideline committee have also 'noted the importance of an agreed, individualised emergency care plan for people with epilepsy', which should include 'details of any emergency medicine that has been prescribed, who is trained to use it and when to give it' (p. 111, line 4).</p> <p>It is important that any care plans for children are effectively shared with education and childcare</p>	<p>Thank you for your comment, whilst we are unable to make recommendations for the training that educational staff should receive, the recommendation has been amended to state that the Epilepsy Specialist Nurse should also support professionals in education settings and facilitates communication with multi-agency services.</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>settings. Training should also be provided to staff at these settings, where they support children who have been prescribed emergency medicine.</p> <p>There should be effective communication between the ESN, the family and the school or childcare setting to ensure consistency in care plans. Schools, for example, are required to put in place individual healthcare plans (IHPs), outlining the support needs for a child with medical conditions, including any emergency protocols [1].</p> <p>1) Department for Education (2015) Supporting pupils at school with medical conditions</p>	
Young Epilepsy	Guideline	063	017	<p>The guideline should state that transition planning should begin early for all young people with epilepsy and that this is particularly important for the specific groups listed here ('young people who have complex or additional health and social care needs, for example young people whose seizures are not yet controlled or those with learning disabilities').</p>	<p>Thank you for your comment. Planning for transition should begin at the appropriate time to meet the needs of the young person, as stated in the recommendation 11.2.2. The evidence showed that for some young people with complex needs including those with learning disabilities, transition to adult services may need more planning and involve other specialties, such as a learning disabilities MDT and child and adolescent mental health services and the</p>

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>A Young Epilepsy survey [1] found that for those young people who transferred to adult epilepsy care at 16, only 45.1% said their epilepsy doctor or nurse started talking to them about their transition before the age of 16.</p> <p>1) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings</p>	committee agreed planning would need to start earlier (see recommendation 11.2.3).
Young Epilepsy	Guideline	063	020	<p>We welcome the recommendation on paediatric and adult epilepsy services jointly reviewing diagnosis and management with the young person.</p> <p>A Young Epilepsy survey [1] found significant disparities in how many joint appointments young people with epilepsy received as part of the transition process. The largest proportion of young people who had transitioned to adult epilepsy care said they had no joint appointments with children's and adults' epilepsy services (39.5%). However, 26.7% had more than three joint appointments.</p> <p>Around 1 in 3 young people (32.3%) said their experience of moving from children's to adults'</p>	Thank you for your response and for sharing the results of your survey. The committee agree it is important both paediatric and adult epilepsy services work together to ensure a smooth transition.

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>epilepsy services had a negative impact on their mental health.</p> <p>The survey also found that nearly half of the young people (45.3%) said their treatment or diagnosis changed when they moved to adults' epilepsy services.</p> <p>1) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings</p>	
Young Epilepsy	Guideline	064	009	<p>We welcome the recommendation to discuss these topics with young people with epilepsy. However, these discussions should be a regular part of young people's care and not limited to the transition process. Young people should be encouraged to play an active role in their epilepsy management, including through questions and discussion. This should develop throughout paediatric care and into adult care.</p> <p>A Young Epilepsy survey [1] found that:</p> <ul style="list-style-type: none"> Only 39.4% of young people said their paediatric epilepsy doctor or nurse spent 	<p>Thank you for your response and for sharing the results of your survey. The committee agree and believe the points you raise have been addressed in recommendation 2.1.3.</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>more time talking to them directly as they got older.</p> <ul style="list-style-type: none"> Nearly 1 in 3 young people (29.7%) said their paediatric epilepsy doctor or nurse did not speak to them about how epilepsy might impact on a range of life issues. Only 1 in 2 young people (51%) said their epilepsy doctor or nurse (in paediatric or adult care) helped them to understand and self-manage their epilepsy more as they got older. <p>The guideline should also note the importance of providing young people an opportunity to speak with their epilepsy healthcare professional confidentially. Our survey found that only 1 in 3 young people (29.0%) said they had more opportunities to speak with their paediatric epilepsy doctor or nurse on their own as they got older.</p> <p>1) Young Epilepsy (2021) Young people's changing experiences of epilepsy care: Summary of survey findings</p>	

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Epilepsies in children, young people and adults

Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Zogenix International Ltd	Evidence review K	042 - 048	003 - 007	Grade tables include a comparison of fenfluramine 0.2mg/kg/day vs placebo and of fenfluramine 0.7mg/kg/day vs fenfluramine 0.2mg/kg/day across various outcomes measures. It should be noted that fenfluramine 0.2mg/kg/day is an initiation dose, and not the intended maintenance dose, as demonstrated by the primary endpoint of the Lagae 2019 trial being based on the 0.7mg/kg/day dose regimen. The comparison of fenfluramine 0.7mg/kg/day versus fenfluramine 0.2mg/kg/day is therefore not appropriate.	Thank you for your comment. This comparison and its relevant GRADE table has been removed.
Zogenix International Ltd	Evidence review K	030	004	Only 1 study for stiripentol is listed (Chiron 2000); the second RCT of stiripentol (Guerrini 2002 - abstract) is excluded. Although the protocol for this evidence review appears to exclude studies published as abstracts, it states it includes systematic reviews of RCTs. The Cochrane review of anti-seizure medication in Dravet syndrome (see https://www.cochrane.org/CD010483/EPILEPSYantiepileptic-drugs-treatment-infants-severe-myoclonic-epilepsy) includes Guerrini 2002 study with supplementary information to the abstract. It is therefore not clear why the Guerrini 2002 study is excluded from the evidence table.	Thank you for your comment. Chiron 2000 was preferred for inclusion in this review because the only other study included in the Cochrane review was Guerrini 2002, which is a study abstract. We do not consider the inclusion of study abstracts because these do not usually provide sufficient information to assess risk of bias. This is demonstrated in the Cochrane review, where most of the risk of bias parameters for Guerrini 2002 have been rated as "unclear risk, insufficient information to permit judgement". We therefore prioritised inclusion of Chiron 2000 instead of the Cochrane review so the results could be analysed independently from Guerrini 2002.

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The evidence tables exclude all cannabidiol studies. Whilst we note that cannabidiol has been appraised by NICE for Dravet syndrome, we are unclear why the cannabidiol studies would not be included alongside the RCTs for stiripentol and fenfluramine. Interpretation of the quality assessment of the stiripentol and fenfluramine RCTs in this rare disease would be incomplete without consideration of the quality assessment of the cannabidiol RCTs that have been accepted to support the recommendation of cannabidiol in NICE TA614.	The protocol shows that cannabidiol studies were searched for, with cannabidiol considered a relevant intervention. Therefore, studies assessing the effectiveness for cannabidiol would have been included if they had met all of the inclusion criteria as set out in the protocol. The evidence table shows that all excluded cannabidiol studies were excluded on the basis of the article type (narrative review; trial registry) rather than the intervention.
Zogenix International Ltd	Evidence review K	041 – 042 – 045 – 051	004 – 003 – 006 - 006	<p>The outcomes against which stiripentol (Table 7) and fenfluramine (Tables 8, 9, 11) are assessed in the GRADE tables differ.</p> <p>Tables 8, 9 and 11 for fenfluramine include mortality as a critical endpoint. It should be noted that over the 14/15 week treatment periods of the fenfluramine trials, in which sample sizes are small by necessity due to the rarity of the syndrome, it is not possible to power analyses for mortality. The most robust mortality data in Dravet syndrome is from a study by Cooper et al, 2016, which observed a mortality rate of around 15% over 10 years. To power a trial (with 80% power) to show a difference of 5%</p>	<p>Thank you for your comment. As you have noted, Lagae 2019 was not powered to detect differences in mortality due to the rarity of the syndrome. The quality of the evidence in GRADE reflects the extent to which the confidence in an estimate of the effect is adequate to support a particular recommendation, not the quality of a given trial. Additionally, the Cooper 2016 study would not have been included in this review because it is a prospective cohort study and not an RCT or systematic review of an RCT.</p> <p>When extracting data from included studies, all data were extracted for the relevant outcomes specified in the protocol (appendix A) where provided in the studies. Chiron 2000 reported 'Clonic or tonic-clonic</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				<p>in mortality would require 1372 patients to be followed over 10 years (or alternatively 13,720 patients to be followed for 1 year), which is clearly not feasible. Yet the fenfluramine trials are judged to be of low quality for this endpoint, while mortality is not considered for the stiripentol trial.</p> <p>We also note that the endpoint of 100% reduction in convulsive seizure frequency is assessed as a critical endpoint in the fenfluramine trials (and was judged to be of High quality using GRADE), but is not referenced in the stiripentol trial as being absent. The fact that these are considered critical endpoints but were not considered in the stiripentol trial should be reflected.</p> <p>The fenfluramine trials also prospectively collected EQ-5D data from caregivers. The broader quality of life of caregivers is an important consideration in a condition such as Dravet syndrome, as demonstrated by the inclusion of caregiver quality of life in to the base case cost effectiveness analyses supporting cannabidiol in NICE TA614. Yet this is not reflected in the evidence tables for fenfluramine</p>	<p>seizure freedom' as an outcome but did not report '100% reduction in convulsive seizure frequency' as an outcome. We do not indicate in the GRADE tables which outcomes were not reported, however the summary of the evidence section has been amended to clarify that not all outcomes were reported by all the trials. The committee's discussion of the evidence section has also been amended to acknowledge the impact on quality of life for caregivers. Please also note that overall quality of life (reported by caregiver/ the individual with epilepsy and as measured with a validated scale) has been included in the research recommendations as an outcome.</p> <p>EQ-5D is referenced once in the Lagae 2019 study as follows: 'Primary caregivers have reported general health scores on the EQ-5D health questionnaire that are equivalent to someone in the general population living with a major illness (i.e., heart disease, diabetes, cancer). These reports illustrate the high unmet need for new and better therapies in Dravet syndrome.' EQ-5D assessments are not reported as an outcome and the data are not provided. As a result we were unable to extract this data or analyse it as an outcome.</p>

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				(and was not collected in the stiripentol or cannabidiol trials).	
Zogenix International Ltd	Evidence review K and Guideline	064 101	019 026 – 027	Table 15 states: <i>"The current evidence supports the use of first-line antiseizure medications, but current evidence base does not enable to support evidence-based treatment decisions when first-line therapy is not successful or not tolerated"</i> . This seems to be inconsistent with the Guideline page 101, lines 26 to 27, which states <i>"There was no evidence for first-line treatments, so the committee based their recommendations on clinical experience and expert opinion"</i> , and also with the fact that the only therapies specifically licensed for the management of seizures in Dravet syndrome (stiripentol, cannabidiol and fenfluramine) are add-on therapies that have been assessed in multiple RCTs in patients who have failed to achieve adequate seizure control on first line therapies.	Thank you for your comment. Please note that this research recommendation is relevant for complex epilepsy syndromes, including Dravet syndrome, Lennox-Gastaut syndrome, infantile spasms syndrome and epilepsy with myoclonic-atonic seizures (Doose syndrome) and not only Dravet syndrome. The sentence you made reference to has been amended so it is relevant for all these syndrome types.
Zogenix International Ltd	Guideline	042	008 - 012	We agree with this simplification of first line treatment options in Dravet syndrome. Although stiripentol is licensed as an add-on therapy, it is well established as a part of standard of care AED regimens in Dravet syndrome. However, there are inconsistencies in the descriptions of first-line therapies vs first-line add on therapies	Thank you for your comment. The use of first- and first-line add on therapy in the Dravet syndrome recommendations is consistent with other sections in which the committee recommended 2 or 3 different lines of therapy.

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				throughout the guideline and evidence review appendix.	
Zogenix International Ltd	Guideline	042	006 - 007	Stiripentol is only licensed for use in combination with both valproate and clobazam. We understand that stiripentol may be used in clinical practice before clobazam, but strictly speaking it should be noted that use of stiripentol before/without clobazam would be off-label.	Thank you for your comment. The recommendation has been amended so that it no longer states that stiripentol should be added first.
Zogenix International Ltd	Guideline	043	014 - 018	Under the heading of Second-line treatment it is stated: <i>"If triple therapy is unsuccessful for Dravet syndrome, consider cannabidiol in combination with clobazam as a second-line add-on treatment option in line with NICE's technology appraisal on cannabidiol with clobazam for treating seizures associated with Dravet syndrome."</i> However, on page 102, lines 019 to 021 it is stated: <i>"The committee agreed that the NICE technology appraisal guidance on cannabidiol with clobazam for treating seizures associated with Dravet syndrome supports the use of this combination as a third-line treatment option."</i> Need consistency in the line of treatment cannabidiol is considered to fall into, and care not to confuse line of treatment vs line of add-on treatment.	Thank you for your comment. The relevant discussion sections for Dravet syndrome have now been amended to specify that the recommendation on cannabidiol with clobazam for treating seizures associated with Dravet syndrome is a second-line treatment option.
Zogenix International Ltd	Guideline	043	015 - 018	It should be clarified that add on therapy would typically involve adding in cannabidiol with the	Thank you for your comment. Section 4.1 'Treatment with antiseizure medications' of this guideline outlines that any add-on therapies should be carefully titrated

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				aim of trying to reduce dose and ultimately remove other agents from the patient's regimen.	and monitored and the importance of ensuring that the patient is taking as few medications as possible to maintain seizure freedom or control. The committee also agreed that the tailoring of these medications for people with Dravet Syndrome would be done by specialists and therefore did not think it necessary to include this level of detail.
Zogenix International Ltd	Guideline	043	023	Further treatment options: As is noted for LGS, it should also be note that seizures in Dravet syndrome can be exacerbated by sodium channel modulator AEDs that are used in general epilepsies, such as carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin. This significantly limits the available treatment options for Dravet syndrome compared with other epilepsies, and contributes to the considerable unmet medical need for these patients to have access to new, effective and well-tolerated therapies that reduce the frequency of seizures.	Thank you for your comment, this was an omission and a recommendation has been added to the Dravet Syndrome section 6.1.
Zogenix International Ltd	Guideline	101	026	It is stated that: " <i>There was no evidence for first-line treatments, so the committee based their recommendations on clinical experience and expert opinion.</i> " We note that stiripentol is listed under the heading of First-line treatment on page 043, lines 005 to 009. A Cochrane review identified 2 RCTs of Stiripentol used specifically	Thank you for your comment. The Cochrane review linked states: "stiripentol (STP) has been recently licensed for treatment when given in combination with other antiepileptic drugs. In this review, we evaluated the efficacy and tolerability of STP and other antiepileptic drugs for the treatment of SMEI." Therefore the statement 'There was no evidence for

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Consultation on draft guideline - Stakeholder comments table
11/11/2021 – 22/12/2021

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				for the management of seizures in Dravet syndrome (see https://www.cochrane.org/CD010483/EPILEPSYantiepileptic-drugs-treatment-infants-severe-myoclonic-epilepsy).	first-line treatments' is correct. The 2 studies included in the Cochrane review are Chiron 2000 and Guerrini 2002. Chiron 2000 was included in this review for its analysis of stiripentol as an add-on therapy, while Guerrini 2002 was excluded because it is a study abstract. We do not consider the inclusion of study abstracts because these do not usually provide sufficient information to assess risk of bias, and proof of this is in the Cochrane review where most of the risk of bias parameters have been rated as "unclear risk, insufficient information to permit judgement".
Zogenix International Ltd	Guideline	102	012 - 016	This section states: "...the committee agreed that it supported triple therapy as second-line treatment option ...". However, page 043, lines 005 to 009 includes triple therapy under the heading of First-line treatment . Need consistency in the line of treatment and line of treatment vs line of add-on treatment.	Thank you for your comment. The relevant discussion sections have now been updated to say that if sodium valproate alone is unsuccessful as first-line monotherapy for Dravet syndrome, triple therapy with stiripentol and clobazam should be considered as first-line add-on therapy.

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