

SIGN 159

Epilepsies in children and young people: investigative procedures and management

A national clinical guideline

May 2021

Key to evidence statements and recommendations

Levels of evidence

- 1⁺⁺ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
- 1⁺ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
- 1⁻ | Meta-analyses, systematic reviews, or RCTs with a high risk of bias
- 2⁺⁺ | High-quality systematic reviews of case-control or cohort studies
High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ | Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ | Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 | Non-analytic studies, eg case reports, case series
- 4 | Expert opinion

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

- R** | For 'strong' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good.
- R** | For 'conditional' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

- ✓ | Recommended best practice based on the clinical experience of the guideline development group.



NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2025 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2019 edition (https://www.sign.ac.uk/assets/sign50_2019.pdf). More information on accreditation can be viewed at www.nice.org.uk/accreditation

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SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/sign-50.html. The EQIA assessment of the manual can be seen at www.sign.ac.uk/assets/sign50eqia.pdf. The full report in paper form and/or alternative format is available on request from the Healthcare Improvement Scotland Equality and Diversity Officer.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on our website www.sign.ac.uk

Scottish Intercollegiate Guidelines Network

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1 Introduction

1.1 The need for a guideline

Epilepsy is the most common serious neurological disorder in children.¹

The epilepsies are a heterogeneous group of conditions that have differing diagnostic criteria, management and widely differing outcomes, not only of seizure control but also in terms of implications for learning and behaviour. It is therefore important to identify the specific epilepsy syndrome and aetiology wherever possible to refine the choice of treatment in order to maximise benefit and minimise adverse effects. Children and their parents will also benefit from information appropriate to their particular type of epilepsy.

The number of antiepileptic drugs (AEDs) has rapidly increased in recent years. Owing to a lack of pharmaceutical research in paediatric epilepsy, some of these medications are unlicensed, holding no current marketing authorisation, or are used outside the indication or age range for which they are licensed (off-label use). This makes selecting an appropriate AED even more complex (*see section 1.3.2 and Annex 2*).

Teenagers with epilepsy often have specific needs that are not well addressed by paediatric and adult services. Some of these are covered in SIGN 143: Diagnosis and management of epilepsy in adults.²

Epilepsy is associated with significant comorbidities and increased incidence of neurodevelopmental disorders (*see section 7.1*). Recognition and management of coexisting psychiatric comorbidities can be challenging.

Within NHSScotland, referral, diagnosis and management of childhood epilepsy occur in primary, secondary and tertiary care settings. A guideline specifically addressing the key areas of care in the management of epilepsy in children helps enable a standardised service to be provided across all of these settings.

Taking all of the above into consideration, there is a clear need for evidence-based guidance to enable healthcare professionals to:

- appropriately investigate children presenting with seizures
- consider correct management
- provide appropriate information about epilepsy, morbidity, risks of mortality and comorbidities
- recognise those who do not respond to initial treatment and consider prompt further treatment
- identify neurodevelopmental and psychiatric comorbidities early, for further management, and
- create a clear transition plan for those children who continue to have epilepsy into their adult life.

1.1.1 Gathering views


The guideline on diagnosis and management of epilepsies in children and young people (SIGN 81, published in 2005) was withdrawn in 2015. This new guideline reflects the most recent evidence around current issues. Key issues were agreed after consultation with a wide range of stakeholders, including the Scottish Paediatric Epilepsy Network (SPEN), professional leads, patient representatives, young people and third-sector organisations.


1.1.2 Patient perspective

Patients, carers and service users may have different perspectives on healthcare processes and outcomes from those of healthcare professionals. The involvement of patients, carers and service users in guideline development is therefore important to ensure that their needs, concerns and the issues that matter to them are included.

As part of the guideline development process, third-sector organisations were invited to submit feedback on the views of patients, carers and service users on the guideline topic, for consideration by the guideline development group. Two organisations, Epilepsy Scotland and SUDEP Action, provided feedback for this guideline.

Young people identified by Epilepsy Scotland were invited to attend an interactive group session to discuss their priorities. Their views and preferences were then considered by the guideline group.

The views and preferences from patients, carers and service users are presented throughout the guideline where this symbol  is shown.

 “Having SIGN consult and engage through an interactive session with our Epilepsy Scotland youth group brought up thought-provoking issues. This was a chance for the young people to share what they had been through and would like to change, for their future support or for that of others. Listening to the people that are directly affected empowers young people to raise issues that are important to them... in the guideline, for practitioners and support networks”. Youth worker, Epilepsy Scotland

Common concerns identified included:

- The need for greater emphasis on the role of interdisciplinary teams, which include an epilepsy nurse specialist.
- Comorbidities, including autism spectrum disorder (ASD, a condition that affects social interaction, communication, interests and behaviour) and attention-deficit-hyperactivity disorder (ADHD).
- Access to mental health services.
- Social and behavioural difficulties.
- Neurodevelopmental and psychosocial difficulties, including depression/anxiety, peer relationships, stigma and support, particularly for teenagers.
- Non-pharmacological management options, including vagus nerve stimulation (VNS), ketogenic diet, cognitive behavioural therapy, complementary medicines and exercise.
- Quality of life (QoL), including side effects, effect on sleep, issues related to school and impact on parents, carers and families.
- Knowledge, information and education about self management, for parents and teachers, particularly about sudden unexpected death in epilepsy (SUDEP), preconception counselling for young women and the role of pharmacists in providing information, as well as information on adherence to medication and advice and patient/family involvement in decision making.
- Transition, particularly around planning, support for education and employment opportunities, psychosocial outcomes and multidisciplinary team (MDT) epilepsy transition clinics.
- The role of third-sector organisations in supporting people and their families.

A patient-focused literature search was carried out to identify the issues that are important to patients, carers and service users (see section 12.1.2). Several of the themes identified were also reflected in a survey of patient and carer experience of children and young people with epilepsy across the United Kingdom (n=2,335).³ This showed the strongest factor influencing satisfaction with epilepsy services was 'ease of access' to the service. Other factors that improved satisfaction were a dedicated clinic setting and perceived adequate information and guidance on restrictions (if any) on their child.

In addition, throughout the guideline development process, Epilepsy Scotland, SUDEP Action and Matthew's Friends invited young people, parents and carers to join the guideline development group.

1.2 Remit of the guideline

1.2.1 Overall objectives

This evidence-based guideline covers specific aspects of investigation and management of epilepsies in children and young people aged from 1 month to 19 years if they remain in secondary education. The terms 'child' and 'children' are used throughout the guideline to cover this age, except where there are issues specific to young people. Although the majority of this guideline focuses on children managed in paediatric settings, transition and ongoing management for previously diagnosed teenagers with epilepsy until they leave secondary education are considered.

The guideline does not cover seizures in newborn babies, infants under 1 month of age, referral for diagnosis of epilepsy or the management of non-epileptic seizures. Emergency management of seizures, including status epilepticus, is also excluded as it is covered by the UK Resuscitation Council, Royal College of Emergency Medicine/NHS Institute and Advanced Life Support Group guidelines.⁴⁻⁶ Although surgery for epilepsy is addressed, this guideline does not cover specific surgical treatment, as this is managed on a case-by-case basis. Contraceptive advice and reproductive health are covered in SIGN 143: Diagnosis and management of epilepsy in adults, and advice from the Medicines and Healthcare products Regulatory Agency (MHRA).^{2,7}

Psychiatric and neurodevelopmental comorbidities, QoL and mortality in epilepsy are discussed. Other issues associated with epilepsy, such as learning, education and future employment, are beyond the scope of this guideline.

1.2.2 Definitions

Throughout this guideline reference is made to seizures (synonymous with fit, turn and attack). A seizure may be epileptic or non-epileptic. A convulsion or convulsive seizure refers to a particular type of seizure involving motor movements, which may be epileptic or non-epileptic (*see section 3*).⁸

1.2.3 Target users of the guideline

This guideline will be of interest to all health professionals in primary and secondary care involved in the management of children with epilepsy, including allied health professionals, clinical neuropsychologists, community paediatricians, emergency department specialists, epilepsy specialist nurses, general paediatricians, general physicians, general practitioners, neurologists, obstetricians, pharmacists, practice nurses and psychiatrists. It will also be of interest to those commissioning epilepsy services, public health physicians and social-work staff. It is hoped it will be used, along with the patient booklets, by children/young people and their families and carers.

1.2.4 Patient version

A patient version of this guideline will be available from the SIGN website, www.sign.ac.uk, after the publication of this guideline.

1.3 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.3.1 Influence of financial and other interests

It has been recognised that financial interests in, or close working relationships with, pharmaceutical companies may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from this source, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by the SIGN Executive and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk.

1.3.2 Prescribing of licensed medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have marketing authorisation for medicinal use in humans.

Generally off-label prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.⁹

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."⁹

The General Medical Council (GMC)¹⁰ recommends that when prescribing a medicine off label, doctors should:

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SmPC, www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.¹¹

The use of unlicensed medicines, or licensed medicines for unlicensed applications in paediatric practice, can be found in Annex 2.

1.3.3 Health technology assessment advice for NHSScotland

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHSScotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines, all new formulations of existing medicines and new indications for established products. NHSScotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in section 11.4

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 Investigative procedures

- R** | If a clinical diagnosis of epilepsy has been made, EEG is recommended for further classification of epilepsy. If standard EEG is normal, a second-line EEG that captures sleep should be carried out. This could be an ambulatory, sleep-deprived or melatonin-induced sleep EEG.

2.2 Non-pharmacological management

- R** | A ketogenic diet should be offered as a treatment option in children with drug-resistant epilepsy.
- R** | Children with drug-resistant epilepsy who fulfil referral criteria for assessment for surgery should be identified early.

2.3 Cognitive, developmental and psychiatric comorbidities

- R** | Healthcare professionals should routinely enquire about depression and anxiety symptoms in all children and young people with epilepsy.

2.4 Transition

- R** | Paediatric services providing care to children and young people should consider the use of a planned, structured, educational approach directed at both patients and carers, to help prepare young people with epilepsy for the move to adult healthcare services.

2.5 Mortality

- R** | At or around the time of diagnosis healthcare professionals caring for children and young people with epilepsy should:
- have a face-to-face discussion about SUDEP with families/carers and young people
 - provide written information to reinforce information provided face to face.

3 Definition, classification and diagnosis of epilepsy

3.1 Definition of epilepsy

In 2014 the International League Against Epilepsy (ILAE) task force for the definition of epilepsy proposed that epilepsy be considered a disease of the brain defined by any of the following conditions:⁸

- at least two unprovoked (or reflex) seizures occurring more than 24 hours apart
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or
- diagnosis of an epilepsy syndrome.

3.2 Classification of epilepsy seizures and syndromes

Classification of seizure types and epilepsy syndromes should always be attempted, as both may have implications for management and prognosis.

The ILAE classification systems for seizures and epilepsy syndromes remain the most widely used and recognised systems in clinical practice (www.ilae.org).⁸

The ILAE 2017 operational classification of seizure types provides a revised basic and expanded seizure type classification, with initial division into focal versus generalised onset or unknown onset seizures.⁸ Finding an aetiology and classifying into the appropriate epilepsy syndrome where possible is important for treatment choice, predicting outcome and monitoring. This should be revisited if it is not possible at the time of diagnosis.¹²

For the purposes of this guideline, the 2017 ILAE classification system has been used.

3.3 History and clinical features

Obtaining an accurate description of an event from a witness is crucial and may be difficult. It may be helpful to obtain multiple witness accounts.

Important features to consider when taking a history are:

- What was the child doing and what happened just before and at the time the seizure started?
- Were there any symptoms suggestive of an aura and what were they?
- What was the sequence and timing of events and seizure components?
- What happened as the seizure ended?
- What was the child like after the seizure and for how long?
- Was there:
 - awareness or talking during the event
 - unresponsiveness
 - staring
 - open or closed eyes
 - eyelid flutter
 - eyeball jerking or deviation (note direction)
 - facial twitching
 - body stiffness
 - chaotic jerking of limbs

- rhythmic jerking of limbs
 - pallor or cyanosis
 - any other autonomic features?
- If more than one seizure was witnessed how similar were they?

Staring or blank spells, particularly in children with learning difficulties, often cause diagnostic difficulty. Key features in their history will help select those seizures likely to be non-epileptic.

During the COVID-19 pandemic healthcare sectors across the world have adapted to remote assessment where appropriate.^{13,14} Parent/carer-recorded seizure videos can be extremely helpful in making an accurate and fast clinical diagnosis of seizures. A secure video transfer service can help parents send videos to clinicians for review and to decide on further investigations and management. This may reduce frequent hospital visits and unnecessary investigations. There are circumstances (remote locations, transport issues, epidemics, pandemics and crisis) where children and families may not be able to travel easily to hospitals. This may have a significant impact on diagnosis and management of epilepsy. Every effort should be made with synchronous and asynchronous video communication for the diagnosis and management of epilepsy.

3

There can be appropriate diagnostic uncertainty, particularly after a first seizure. It is appropriate to share the uncertainty surrounding diagnosis and the importance of making a correct diagnosis with the child and family until a definite diagnosis is made.

- ✓ | An accurate history of the event should be taken from first-hand witnesses and the child.
- ✓ | In any child being evaluated for paroxysmal events of uncertain nature, every effort should be made to ensure that a typical event is captured on video and reviewed by a clinician with expertise in epilepsy (see section 4.1.1).
- ✓ | A secure video transfer service and remote monitoring of epilepsy should be considered to ensure fast, accurate diagnosis and management.

Information point – Provide children, young people, families and carers with an explanation and information about epilepsy (see section 10.3 – general epilepsy information)

3.4 Who should make a diagnosis of epilepsy?

The diagnosis of epilepsy should be made by an epilepsy specialist (see Annex 3).¹⁵ An epilepsy specialist has been defined as a trained paediatrician with expertise in epilepsy as demonstrated by training and continuing education in epilepsy, peer review of practice and regular audit of diagnosis. Epilepsy must be a significant part of their clinical workload (equivalent to at least one session a week).¹⁶

The diagnosis of epilepsy is most appropriately delivered in the setting of a dedicated neurology or neurodisability clinic or epilepsy clinic. Appropriate patient information should be given.¹⁷

The diagnosis of epilepsy has important physical, psychosocial and economic implications for the patient. It is therefore important that the diagnosis is correct. It has been shown that a significant proportion of epilepsy diagnoses made by non-specialists are incorrect.^{18,19} Epilepsy may be difficult to diagnose in the early stages, especially in the absence of a witness account.²⁰ Differentiation between epileptic seizures and stereotyped behavioural phenomena can be difficult in people with a learning difficulty or learning disability.

- ✓ | The diagnosis of epilepsy should be made by an epilepsy specialist.

 *What matters to young people*

Young people felt talking to their epilepsy nurses helped, but they felt more information was needed to help them understand their diagnosis.

“My epilepsy nurse came to explain what happened [seizures] and that helped a lot.”

Information point – *The diagnosis of epilepsy should be communicated to children, young people, families and carers with appropriate information about epilepsy and contact details to discuss this further (see section 10.3 – general epilepsy information).*

4 Investigative procedures

4.1 Electroencephalogram

The diagnosis of epilepsy should be primarily clinical. The SPEN pathway on the diagnosis and initial management of epilepsy emphasises the importance of expert clinical opinion prior to the application of any neurophysiological testing (*see Annex 3*). The primary use of the electroencephalogram (EEG) is to help further characterise seizure types and epilepsy syndrome, and can help inform aetiology once a clinical diagnosis of epilepsy has been made. In some cases, the ictal and interictal EEG abnormality is characteristic of a specific epilepsy syndrome or points towards an underlying aetiological diagnosis and can therefore guide further management.²¹ Compared with an awake EEG, an EEG that captures sleep has increased sensitivity for detecting epileptiform discharges.^{22,23} Video recordings of typical events are also a very useful tool to guide the classification of epilepsy (*see section 4.1.1*).

The standard interictal EEG recording is not a diagnostic test for epilepsy. In unselected patients it has very poor positive and negative predictive value for epilepsy.²⁴⁻²⁶ Epileptiform abnormalities are common in the asymptomatic population, and around 40% of children with epilepsy will have a normal EEG between seizures.²⁷⁻³⁵

Where there remains diagnostic uncertainty about whether or not paroxysmal events are epileptic, it may occasionally be helpful to acquire an EEG recording that captures a typical event, though such an approach should rarely be considered prior to clinical review by a paediatrician with expertise in the diagnosis and management of epilepsy. Prolonged recordings of concurrent video and EEG requires a dedicated video-telemetry service, which will require either hospital admission to a specialist facility or the application of a home-video telemetry device. All children should have access to such a facility.

4.1.1 Evaluation of paroxysmal events of uncertain nature

One diagnostic study in adults (n=43) evaluated the utility of video alone versus EEG alone in making or refuting a diagnosis of epileptic seizures.³⁶ It found that the information available from video alone is superior (in terms of sensitivity and specificity) to the information available from EEG alone when both video and EEG are interpreted by a clinician with the relevant expertise. } 2+

Although the evidence is limited to one adult study, filming is easy for families and carers to perform on their own devices, unlikely to be harmful and aids diagnosis. It does not require additional resources or training.

- ✓ | In any child being evaluated for paroxysmal events of uncertain nature, a typical event should be captured on video, when safe to do so, and reviewed by a clinician with expertise in epilepsy.

4.1.2 EEG to assist epilepsy classification where a clinical diagnosis of epilepsy has been made

A first-line EEG test should be a standard 20- to 30-minute awake recording. If this is normal, subsequent options include EEG after sleep deprivation, melatonin-induced sleep EEG, or a 24-hour ambulatory recording which captures sleep.^{22,37,38}

Sleep-deprived EEG

A study of children aged 1 month to 16 years (n=522) assessed the diagnostic utility of EEG after partial sleep deprivation where epileptic seizures had been clinically diagnosed and where standard EEG had been normal. Of this group, 34.5% had epileptiform abnormalities on EEG after partial sleep deprivation.²³ } 2++

Sleep-deprived EEG has a higher yield than a second standard EEG in adults and children.^{39,40} } 2+

Sleep deprivation in young children can be challenging for parents. There are unquantified risks associated with sleep deprivation in relation to increased seizure risk and the parent or carer driving to the appointment.⁴¹ The safety of sleep deprivation is not clear. Given the associated risks, it is good practice for departments to have an established sleep deprivation protocol, with the age of the child taken into consideration.

Melatonin-induced sleep

An alternative way to obtain a sleep recording in children and young people is a melatonin-induced sleep recording, as recommended by the National Institute for Health and Care Excellence (NICE).⁴² When compared with sleep deprivation, melatonin-induced sleep reduces the burden on carers to ensure effective sleep deprivation, so may be more acceptable to families without affecting the quality or yield from the sleep EEG.^{43,44} } 3
4

Melatonin administration is effective at inducing sleep in 70–87% of patients.^{43–48} } 2+
2-
3

When melatonin administration is combined with sleep deprivation, sleep (stage 2, light sleep) can be attained in a higher proportion of patients, and thereby increase the diagnostic yield from EEG. Melatonin-induced sleep may be preferable in younger children (<4 years) where sleep deprivation can be particularly challenging.⁴⁷ A single study showed combined sleep deprivation and melatonin is more effective in achieving sleep than either method alone (n=563, age range 1–17).⁴⁵ This study did not stratify children by age. Given that sleep deprivation can be problematic in young children, this may only be appropriate for older children and adolescents. } 2+

The use of melatonin for sleep induction at EEG was safe, with no significant adverse effects reported in any study.^{43–48} } 2+
2-
3

Ambulatory EEG

A systematic review of ambulatory EEG for the diagnosis of adults with epilepsy or non-epileptic attack disorder (n=1,036) concluded that ambulatory EEG was more sensitive than sleep-deprived EEG.³⁸ The studies included were rated as low quality. } 2-

Another study on the diagnostic accuracy of prolonged ambulatory versus standard 30-minute EEG in a consecutive sample of 72 adult patients found that interictal epileptiform discharges were 2.23 times more likely to occur during ambulatory recording than standard EEG. The sensitivity of ambulatory recording was 58% (95% confidence interval (CI) 44.2% to 70.6%), versus standard (26%, 95% CI 15.9% to 39.6%) and specificity was 95.5% (95% CI 78.2% to 99.2%) compared with standard (100%, 95% CI 85.1% to 100.0%).³⁷ } 2++

In adults who had a normal EEG, sensitivity of sleep-deprived EEG was 45% (95% CI 27% to 64%), with a specificity of 91% (95% CI 70% to 99%), positive predictive value (PPV) 88% and negative predictive value (NPV) 53%, compared with ambulatory EEG, sensitivity 63% (95% CI 44% to 79%) and specificity 95% (95% CI 75% to 100%).²² } 2+

Sleep-deprived EEG and ambulatory EEG are both more sensitive than standard EEG at capturing epileptiform activity. At all ages, sleep is likely to be captured using a 24-hour ambulatory EEG recording; however, this is more resource intensive than a shorter recording performed in a sleep-deprived state. Ambulatory EEG would be preferable if the patient is having daily episodes, as this provides an opportunity to capture the events. No economic evaluations comparing any of the EEG strategies described were identified.

- R** | **If a clinical diagnosis of epilepsy has been made, EEG is recommended for further classification of epilepsy. If standard EEG is normal, a second-line EEG that captures sleep should be carried out. This could be an ambulatory, sleep-deprived or melatonin-induced sleep EEG.**
- ✓ | When deciding on the type of EEG investigation to use as second line the nature and timing of the events and the suspected aetiology/epilepsy syndrome should be taken into consideration.
- ✓ | Where sleep deprivation is used, departments should have an established sleep deprivation protocol, with the age of the child taken into consideration.

Information point – Provide children, young people, families and carers with an explanation of investigative procedures (see section 10.3).

4.2 Brain imaging

Over half of all children with epilepsy have focal epilepsy and around a third have epilepsy that is refractory to medical therapy.⁴⁹⁻⁵¹ Identification of a structural lesion that accounts for focal epilepsy informs decision making about prescribing AEDs and potential surgical treatment. Lesion identification also helps clinical teams counsel patients and parents about prognosis and treatment.⁵²

4.2.1 Computed tomography

Computed tomography (CT) has a limited role in the investigation of a patient with epilepsy. It is of use in urgent assessment when neurosurgical intervention may be required, or when magnetic resonance imaging (MRI) is contraindicated (for example, when patients have pacemakers or other implants that may pose a hazard in the MRI environment). A non-contrast CT scan may fail to identify small tumours, some disorders of cortical development and some vascular lesions. Computed tomography has a limited role in the assessment of intractable epilepsy.⁵³⁻⁵⁵

No studies were identified on the role of CT to determine the aetiology/syndrome of epilepsy in children. Healthcare professionals should refer to existing guidelines for its role in emergency settings.⁵⁶

4.2.2 Magnetic resonance imaging

Magnetic resonance imaging is the imaging modality of choice and should be performed in all patients with epilepsy except children with genetic generalised epilepsy and childhood epilepsy with centrottemporal spikes (CECTS) who respond to drug treatment (see Table 1).^{42,56} Routine MRI using simple standard sequences will detect some of these lesions (for example, brain tumours, disorders of cortical formation and vascular malformations).^{52,56}

Guidelines from ILAE recommend that children younger than 2 years of age require different MRI sequences because of the effect of developmental myelination on the ability to detect certain lesions such as cortical dysplasia.⁵⁶ MRI carried out for the assessment of drug-resistant epilepsy requires specialised protocols and ideally should be carried out by a radiologist with experience in paediatric neuroradiology.^{2,56}

Table 1: Indications for magnetic resonance imaging^{42,56}

Imaging indicated	Imaging not indicated
Localisation related seizures*	Childhood absence epilepsy
Focal history, abnormal examination, focal EEG abnormalities	Juvenile myoclonic epilepsy
Developmental regression <2 years old	CECTS
Symptomatic generalised epilepsy syndrome	Genetic generalised epilepsy
Increased intracranial pressure	
History of status epilepticus	
Atypical course for CECTS/idiopathic generalised epilepsy	

*Except for CECTS

4.2.3 Magnetic resonance imaging (1.5 and 3 tesla)

Twenty to thirty per cent of patients who have refractory focal epilepsy will have normal 1.5-tesla (1.5-T) MRI scans.⁵² Imaging at higher field strength, 3-tesla (3-T), improves lesion detection.^{57,58} } 2+
3

In one study of 3-T MRI, a structural lesion was identified in 20.2% of adults with localisation-related epilepsy (n=2,000).⁵⁸ In another study, (n=40, age range 9-57 years) 3-T MRI yielded additional diagnostic information in 48%. In 37.5% of patients, this additional information led to a change in clinical management. In patients with a prior 1.5-T MRI, interpreted as normal, 3-T MRI resulted in the detection of a new lesion in 65% and 3-T MRI better defined the lesion in 33% of the patients with known lesions.⁵⁷ } 2+
3

In a study of patients with refractory epilepsy (n=804, 87% focal), 12% of new diagnoses were identified with 3-T MRI with a specialist epilepsy protocol that had not been found in previous 1.5-T MRI.⁵⁹ Whilst some of these were incidental findings, subsequent management was affected in 5% of patients. The most common new abnormalities found were hippocampal sclerosis (13%) and malformations of cortical development (8%). This is an important finding as there is potential benefit from surgical treatment in these patients.⁵⁹ } 3

In patients with focal epilepsy and previous negative 1.5-T MRI, 3-T MRI rescanning improved the diagnostic yield in a non-comparative study (n=30, mean age 30 years).⁶⁰ Three lesions in total were identified by general radiologists in non-specialised centres using a 1.5-T standard protocol. In a specialist centre a consensus between two neuroradiologists using an epilepsy protocol identified seven lesions (23%) using 1.5-T and 10 lesions (33%) using 3-T (p<0.01). In 28% of patients this additional information resulted in a change in clinical management. } 3

A further study (n=36, age 13-56 years) highlighted a low frequency of new lesion detection by reimaging patients with refractory focal epilepsy with 3-T MRI. These patients were candidates for surgery and, although new lesions were detected in only two patients, the abnormalities identified had an impact on clinical management, avoiding the need for invasive EEG monitoring and identification of a false positive.⁶¹ } 3

A retrospective study, evaluating 3-T versus 1.5-T MRI (n=25, age range 10 months to 70 years), reported that 3-T MRI was statistically superior to 1.5-T MRI ($p < 0.05$).⁶² With 3-T MRI, lesions were detected in 65/74 individual interpretations compared with 55/74 interpretations from 1.5-T MRI ($p = 0.0364$), and lesions were accurately characterised in 63/74 compared with 51/74 interpretations from 1.5-T MRI ($p = 0.019$). Identification of a focal epileptogenic lesion with 3-T MRI was found to be 2.57 times as likely as identification with 1.5-T MRI and accurate characterisation of lesions to be 2.66 times as likely as characterisation with 1.5-T MRI. The results were not stratified by age. The authors concluded that 3-T MRI should be strongly considered for the evaluation of drug-resistant focal epilepsy when 1.5-T MRI is ambiguous or has normal findings.

2+

No direct harm was reported from MRI, but studies reported that 16–20% of the reported abnormalities were thought to be unrelated to epilepsy or seizure activity.^{58,59} Incidental findings were more common at higher field strength, which may result in patient/parental anxiety and potentially the need for further tests. Many paediatric patients require general anaesthetic for MRI and the potential risk of multiple anaesthetics should also be considered.^{58,62}

2+
3

There are other safety issues that need to be considered when scanning children, such as tissue heating at 3-T MRI, so ideally MRI should be carried out by a radiologist with experience in this area (this may be a neuroradiologist with paediatric interest, or a paediatric radiologist with paediatric neuroradiology interest).

No cost-effectiveness evidence comparing 1.5-T and 3-T MRI in children with epilepsy was identified (see section 11.3).

R | **In children with drug-resistant focal epilepsy, 3-T MRI should be considered if 1.5-T MRI does not detect and define a lesion.**

✓ | MRI carried out for the assessment of epilepsy in children requires specialised protocols, and should ideally be carried out, and the MRI interpreted, by a radiologist with experience in paediatric neuroradiology (this may be a neuroradiologist with paediatric interest, or a paediatric radiologist with paediatric neuroradiology interest).

✓ | When neuroimaging non-urgent cases of children and young people diagnosed to have epilepsy consider:

- appropriate clinical information including EEG findings, where possible
- having standardised epilepsy neuroimaging protocols and sequences.

4.3 Genetic testing

The genetic element of epilepsy is considered a combination of multiple genetic influences, perhaps acting in combination with environmental factors.⁶³ However, in some cases, a single genetic variant may explain an epilepsy phenotype. Such cases are often referred to as monogenic epilepsies. There are various causes of monogenic epilepsy that range from single nucleotide variants (SNVs, single letter changes in the deoxyribonucleic acid (DNA) code) to duplications (copy number variants, CNVs) or deletions of large regions of chromosomes. More than 500 epilepsy-associated genes have now been described. In some cases, phenotypic features of a patient's epilepsy or additional clinical features such as developmental comorbidity, dysmorphism or neuroimaging findings may point towards a specific genetic diagnosis. However, in many cases no specific pointers to the likely cause can be taken from the phenotype, an argument which supports the use of high-throughput gene panel testing for patients with epilepsy.⁶⁴

Over time, the cost of genetic testing has reduced, while both the scope and the sensitivity of genetic testing have increased. As a result, it is now reasonable to consider whether all patients with epilepsy should be offered genetic testing. Modern genetic tests for epilepsy often involve screening for changes in a large number of different genes. There is a high likelihood of finding a variant of uncertain significance from such tests. Clinicians must interpret laboratory reports with this knowledge, and counselling of patients and families before and after genetic testing must take this into account.^{65,66}

4.3.1 Benefits of genetic testing

Identification of a genetic cause of epilepsy has a number of potential benefits for the patient and the family, as well as some potential drawbacks. Before genetic testing is requested families should be fully informed of the implications, ideally through a discussion with an experienced clinician or genetic counsellor.

A genetic diagnosis provides families with an answer as to why the epilepsy has developed. It may reduce the requirement for further diagnostic procedures.⁶⁷⁻⁷⁰

The majority of people affected by familial epilepsy respond positively when offered genetic testing, regardless of whether knowledge of a genetic cause confers any specific clinical use.⁷¹ Qualitative research has identified that having knowledge of an underlying cause helps patients face their epilepsy and gives them the confidence to attend support groups and advocate for others, and it can reduce feelings of self blame.⁷²⁻⁷⁴ It can give families the opportunity to contact others affected by the same genetic condition.⁷⁵

The results of genetic testing, whether positive or negative, may also provide families with information about prognosis and risk of recurrence, which are prominent concerns for families.⁷³ For severe monogenic epilepsies carrier testing, prenatal genetic testing and pre-implantation genetic diagnosis may be offered. Some patients with epilepsy have expressed concern that genetic information could increase stigmatisation of, and discrimination against, people with epilepsy and their family members, for example if genetic information were to become available to private insurers or employers.⁷³

For some monogenic epilepsies there is evidence that specific therapeutic approaches may be more effective than others. Identifying a genetic cause may therefore guide treatment decisions.⁶⁴

4.3.2 Who should receive genetic testing and what test(s) should be offered?

Gene panel testing

When large cohorts of patients with epilepsy are tested for a genetic cause using gene panel testing or whole exome sequencing, between 18% and 38% will have a causative genetic change identified.⁷⁶⁻⁸⁴ In general, studies which have involved testing of a larger number of genes have higher diagnostic yields. Children with early onset of epilepsy (in the first 2 months of life), with drug-resistant seizures or comorbid developmental delay, are more likely to have a genetic cause identified.^{76,82,83} A large number of genes are implicated, although the majority of diagnoses are concentrated in a small number, including *SCN1A*, *KCNQ2*, *CDKL5*, *SCN2A*, *STXBP1*, *PCDH19*, *SCN8A*, *PRRT2*, *MECP2* and *SLC2A1*. A Scottish study of gene panel testing in children (n=333) presenting with seizures before the age of 3 years found that 24% had a genetic diagnosis from gene panel testing and that 80% of these diagnoses had treatment implications.⁸⁵

3

Chromosomal microarray

The current test of choice for detecting CNVs is chromosomal microarray. CNVs are thought to be less common as a cause of epilepsy than single gene variants. The diagnostic yield of chromosomal microarray in patients with epilepsy ranges from 3.6% to 22%.⁸⁶⁻⁹⁰ The majority of children with a positive microarray result will have a recognisable syndrome such as 22q11 duplication, 1p36 deletion, 22q22.3 deletion or 4p16.3 deletion, all of which are typically characterised by developmental delay and dysmorphic features as well as epilepsy. Occasionally patients with no additional feature will have a genetic cause identified on chromosomal microarray testing, so chromosomal microarray should be considered if gene panel testing does not reveal a cause.^{86,91}

One study carried out chromosomal microarray in patients with generalised epilepsy and intellectual disability and reported that 22% had a significant CNV, suggesting that this may be a patient population that would benefit specifically from microarray testing.⁸⁸ However, many of the positive results reported in this study related to CNVs with incomplete penetrance which may have been carried by other asymptomatic family members.⁹⁰ Because of this complexity it is important to involve an experienced clinician in the counselling of families with CNV findings.

3

No studies identified determined the use of genetic testing to examine the aetiology of epilepsy to allow for individualised treatment pathways.

- ✓ Genetic testing should be considered, discussed and offered to the families of all children and young people presenting with epilepsy for whom aetiology cannot be fully explained through history taking, examination, targeted metabolic tests or neuroimaging.
- ✓ Families should be counselled by an experienced professional before genetic testing is undertaken.
- ✓ Discussion or consultation with a clinical geneticist or paediatric neurologist should be considered prior to requesting genetic testing if any of the following additional features are present: onset in first 2 months of life, learning disability, dysmorphic features, motor disorder or movement disorder, biochemical or metabolic test abnormalities, brain imaging abnormalities, neurocutaneous signs or drug-resistant seizures.

5 Pharmacological management

5.1 Antiepileptic drugs

What matters to young people

Young people spoke about side effects from medication. They mentioned feeling sick, feeling tired and experiencing headaches. They didn't know that they might feel that way and would have liked to have been made aware of this before trying a new medication.

Information point – Discuss treatment options with young people and their families/carers and offer written and verbal information on:

- choice of drug
- efficacy
- adverse effects/side effects
- adherence, including how it should be taken
- dosage
- drug interactions.

Antiepileptic drugs (AEDs) are the first-line and mainstay treatment for children with epilepsy. The aim of treating seizures with AEDs is to achieve seizure freedom or reduction; this in turn should decrease rates of hospital admissions, reduce morbidity and mortality, improve learning and lead to significant improvement in QoL. The timing of starting treatment once the diagnosis is confirmed is variable depending on a number of factors, including severity of epilepsy, epilepsy syndrome, seizure burden, age, and the child and their family's preference.^{92,93} It is important to discuss the options available, considering potential side effects, likely treatment response, the need for concordance and potential length of treatment. With children, concordance to AEDs can be a significant problem and it is important to recognise this to overcome potential barriers.^{94,95}

All AEDs have adverse effects, most commonly behavioural problems and drowsiness. Occurrence of adverse effects is reported in 31% of children taking AEDs.⁹⁶ The risk was lower in patients receiving monotherapy than those receiving polytherapy.⁹⁶

SPEN care pathways 2 and 3 highlight the use of drugs within an overall approach to care of children with epilepsy (see Annexes 3 and 4).

The initial choice of AEDs for differing epilepsy syndromes is challenging because of a lack of head-to-head trials. This may be because of the difficulty in running randomised controlled trials (RCTs) in these children. The advice in this section is informed by the NICE guideline on Epilepsies: diagnosis and management (NICE 137, first published in 2012 and updated in 2020) and evidence published after the NICE guideline.⁴² A summary of the recommended pharmacological therapies can be found in Annex 5.

Diagnosis and management, including use of AEDs, should be made under the guidance of a consultant paediatric neurologist or a paediatrician with an interest in epilepsy. For further advice on prescribing in paediatric practice see section 1.3.2 and Annex 2. Advice from SMC can be found in section 11.4.

- ✓ | All children with complex epilepsies should be managed in tertiary epilepsy clinics or have ongoing management with a tertiary epilepsy specialist.

5.2 Focal epilepsy

5.2.1 First-line treatment

NICE identified low-quality evidence that carbamazepine and lamotrigine were both effective in the reduction of seizures in children and recommends either as first-line treatment for children and young people with newly diagnosed focal seizures.⁴² When combined with adult data, NICE concluded that carbamazepine and lamotrigine were superior to other AEDs in terms of adverse events. Gabapentin was less clinically effective than other AEDs. Based on low-quality evidence from child and adult studies, levetiracetam, oxcarbazepine and sodium valproate were found to have similar efficacy for seizure freedom; however, NICE recommended them for second-line treatment, based on cost and adverse events. Levetiracetam is not licensed for use in children under 16 years of age, but may be useful in girls as it does not have the teratogenic risks in pregnancy associated with sodium valproate. Use of sodium valproate, however, must take into account MHRA safety advice on the use of valproate medicines in women and girls of childbearing potential and the conditions of the pregnancy prevention programme.^{2,7}

4

Levetiracetam, oxcarbazepine or sodium valproate can be offered if carbamazepine and lamotrigine are not suitable or tolerated.⁴²

4

A meta-analysis of 11 RCTs (n=1,241, age range 3-17 years) found that oxcarbazepine had a comparable seizure-free rate (39%) to other AEDs (37.7%, relative risk (RR) 1.06, 95% CI 0.94 to 1.20).⁹⁷ Oxcarbazepine had a similar effect to phenytoin (RR 1.01, 95% CI 0.79 to 1.31), levetiracetam (RR 0.98, 95% CI 0.84 to 1.14), sodium valproate (RR 1.27, 95% CI 0.92 to 1.77) and placebo (RR 4.67, 95% CI 0.55 to 39.47). Oxcarbazepine was also comparable to other AEDs for reduction in seizures. The incidence of adverse events was similar to the other AEDs (RR 1.01, 95% CI 0.92 to 1.11).⁹⁷

1++

An RCT (n=90, age <16 years) compared low- and high-dose zonisamide as monotherapy in children with epilepsy over a 28-week period.⁹⁸ Six months of freedom from seizures was achieved in 63.1% of those in the low-dose group and 57.6% in the high-dose group (p=0.66). This represented freedom from seizures in 60.5% overall. Seizure types included localisation related (idiopathic, cryptogenic and symptomatic), idiopathic generalised and undetermined. There were no significant response differences between the doses in any of the epilepsy type subgroups. However, when comparing different seizure types, zonisamide, across the doses, was found to be more effective in patients with localisation-related epilepsies (66%) than in those with idiopathic generalised epilepsies (38.1%) (p=0.017). Low-dose zonisamide produced a less detrimental effect on cognition, particularly the development of language.⁹⁸ Although well recognised as adjunctive therapy, results of this study illustrated its use as monotherapy in previously untreated children with epilepsy.⁹⁸

1+

Lacosamide was effective in reducing seizure frequency compared with placebo (n=340, age 4-17 years). Focal seizure frequency after 16 weeks reduced by 51.7% for lacosamide and 21.7% for placebo. Adverse effects were mostly mild or moderate, with dizziness and somnolence the most common.⁹⁹

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- R** | **Carbamazepine or lamotrigine could be considered for children and young people with focal epilepsy.**
- R** | **Levetiracetam, oxcarbazepine or sodium valproate could be considered for children and young people with focal epilepsy if carbamazepine and lamotrigine are not suitable or tolerated.**
- ✓ | Sodium valproate should not be used in girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.

5.2.2 Adjunctive treatment

Adjunctive therapy should be considered if two first-line therapies have been tried and seizures are still poorly controlled or the therapy is not well tolerated.⁴² 4

NICE recommends that carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate can be offered as adjunctive treatment if first-line treatments are ineffective or not tolerated, based on effectiveness of achieving a 50% reduction in seizures compared with placebo in trials in children, young people and adults.⁴² The overall quality of the trials was rated as low. 4

An RCT (n=200) of children (age 6–17) with focal epilepsy taking one or two AEDs showed adjunctive zonisamide treatment to be effective and well tolerated. Rates of response were 50% for zonisamide versus 31% for placebo (p=0.0044).¹⁰⁰ The overall incidence of adverse events was similar for zonisamide (55.1%) and placebo (50.0%), with low rates of serious adverse effects. Adverse effects reported more frequently with zonisamide than placebo were decreased appetite, decreased weight, somnolence, vomiting and diarrhoea. 1++

A non-comparative extension study (n=144) investigated the safety, tolerability and efficacy of long-term adjunctive zonisamide and its impact on growth and development in children aged 6–18 years with focal epilepsy.¹⁰¹ Adjunctive zonisamide therapy was well tolerated and efficacious over a treatment period of at least 1 year; 56.3% of patients responded to treatment and 11.1% achieved seizure freedom.¹⁰¹ 3

Another RCT (n=85 treatment, 48 placebo) looked at adjunctive perampanel in adolescents (age 12–17) with inadequately controlled focal seizures.¹⁰² Median reduction in seizure frequency over the 19-week trial was 58% for perampanel and 24% for placebo (p=0.079). More patients had a 50% reduction in seizure frequency after perampanel (59%) than placebo (37%, p=0.0144). Eighty per cent of participants in the treatment group experienced an adverse effect, compared with 64% on placebo. Dizziness was the most commonly reported. Aggression as an adverse effect resolved in several patients when the dose of perampanel was adjusted.¹⁰² 1++

SMC has advised that zonisamide is accepted for use in Scotland for adjunctive therapy in young people and children over 6 years of age, following specialist advice of paediatric neurologists or paediatricians with expertise in epilepsy. Perampanel is accepted for use as second-line adjunctive therapy in young people over 12 years who have seizures with or without secondary generalised seizures (*see section 11.4*).

R | **Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate or zonisamide (over 6 years of age) can be considered as adjunctive therapies in children and young people with focal epilepsy if first-line therapies are ineffective or not tolerated.**

✓ | Sodium valproate should not be used in girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.

R | **Perampanel could be considered as adjunctive therapy in adolescents from 12 years of age with focal epilepsy.**

5.3 Generalised epilepsy

In the majority of generalised epilepsies the evidence to support recommendations for first-line AEDs has not changed significantly since the publication of NICE 137: Epilepsies: diagnosis and management (2012).^{42,103} Other treatment options include ketogenic diet (*see section 6.1*) and vagus nerve stimulation (*see section 6.3*). In this guideline evidence for specific epilepsy syndromes was reviewed, including absence epilepsy.

5.3.1 Absence seizures

NICE recommends ethosuximide or sodium valproate as first-line treatment for children and young people with absence seizures.⁴² This advice is based on a high-quality RCT and two low-quality studies in adults. Lamotrigine was found to be less effective, but had fewer adverse effects, so could be considered if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated.⁴² A combination of two or three AEDs is recommended if two first-line AEDs are ineffective. If treatment is still ineffective, advice should be sought from, or the patient should be referred to, a tertiary epilepsy specialist to consider the use of clobazam, clonazepam, levetiracetam, topiramate or zonisamide. There is no evidence that carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin is effective in children and young people with absence seizures, and these drugs should not be offered because of the risk of exacerbating seizures.⁴²

4

Levetiracetam monotherapy was shown to have a modest, but not statistically significant, effect over placebo in the number of patients free from seizures after 14 days in a small RCT (n=59, age range 4–16 years).¹⁰⁴

1+

An open-label continuation study in childhood absence epilepsy (n=208, mean age 7 years) looked at second-line monotherapy after failure on ethosuximide, valproic acid or lamotrigine.¹⁰⁵ Freedom from treatment failure rates at weeks 16–20 were similar for children on ethosuximide (63%) and valproate (65%) and higher than for those on lamotrigine (45%, overall p=0.051). Pair-wise comparisons showed higher freedom from treatment failure rates for the ethosuximide versus lamotrigine (odds ratio (OR) 2.0, 95% CI 0.99 to 4.09) and valproate versus lamotrigine (OR 2.27, 95% CI 1.12 to 4.59) groups than for those on valproate versus ethosuximide (OR 1.13, 95% CI 0.58 to 2.18).¹⁰⁵ At month 12, 49% of the children were still free from treatment failure, with rates similar for children on ethosuximide (57%), lamotrigine (36%) and valproate (49%; overall p=0.062). Pair-wise comparative results showed higher rates for ethosuximide versus lamotrigine (OR 2.35, 95% CI 1.15 to 4.81) than for valproate compared with ethosuximide (OR 0.71, 95% CI 0.37 to 1.34) or lamotrigine (OR 1.66, 95% CI 0.82 to 3.37).¹⁰⁵ At both timepoints, for each treatment, the response rates for second monotherapy were similar to those for first-line treatment and were not dependent on which treatment was used first line.¹⁰⁵

2-

A Cochrane review identified one RCT (n=446, age range 7 months to 12 years 11 months) that compared ethosuximide, lamotrigine and valproic acid in treatment-naïve children with newly diagnosed childhood absence epilepsy. After 12 months, freedom from seizure was 45% for ethosuximide, 44% for valproic acid and 21% for lamotrigine.¹⁰⁶

1++

Sodium valproate was reported to have a higher rate of adverse events than ethosuximide or lamotrigine.^{105–107} Levetiracetam was well tolerated, with no serious adverse events reported.¹⁰⁴

1++

1+

- R | **Ethosuximide should be considered as first-line monotherapy for the treatment of patients with childhood absence epilepsy. Sodium valproate should also be considered, but has a higher risk of adverse events.**
- R | **Lamotrigine could be considered for patients with childhood absence epilepsy if ethosuximide and sodium valproate are ineffective, not suitable or not tolerated.**
- R | **A combination of two or three AEDs could be considered if two first-line AEDs are ineffective. If treatment is still ineffective, advice should be sought from, or the patient should be referred to, a tertiary epilepsy specialist to consider the use of clobazam, clonazepam, levetiracetam, topiramate or zonisamide.**
- ✓ | Sodium valproate should not be used in women and girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.

5.4 Lennox–Gastaut syndrome

The most effective treatment for children and young people with Lennox–Gastaut syndrome (LGS) has not been determined through clinical trials. It remains a difficult-to-treat epileptic encephalopathy, with lifelong comorbidity including variable seizure control, cognitive impairment and behavioural impairment. NICE recommends that children with suspected LGS are referred to a paediatric epilepsy specialist. They should be offered sodium valproate as first-line treatment.⁴² No RCTs were identified, so the recommendation is based on evidence that sodium valproate is effective in reducing seizures in children with idiopathic generalised epilepsy. For adjunctive therapy, two moderate-quality trials found that lamotrigine was effective in >50% reduction in seizure compared with placebo.⁴² Further options are rufinamide and topiramate. NICE advises that felbamate should only be offered where specialist care is available and the other recommended AEDs have failed.⁴² There is no evidence for efficacy of carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin, but there may be a risk that they exacerbate seizures.⁴²

4

Analyses of nine RCTs (n=979, age range 2–60 years) concluded that no one drug was shown to be highly efficacious in patients with LGS. Lamotrigine, rufinamide, felbamate and topiramate were beneficial as add-on treatments. Clobazam may be beneficial for drop seizures.¹⁰⁸

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There is some evidence for improved seizure control with clobazam adjunctive therapy, from post-hoc analysis of previous trials (n=267).¹⁰⁹ Rufinamide showed benefit as adjunctive treatment in a low-quality RCT (n=59, age range 4–30 years).^{110,111} A non-comparative follow-up study of the trial (n=54, mean age 15 years) supported this across paediatric, adolescent and adult age groups, with the risk of side effects.¹¹⁷

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Clobazam was associated with dose-related aggression-related side effects, which may resolve with continued use.¹¹² Rufinamide was frequently associated with somnolence, decreased appetite, transient seizure aggravation, vomiting and constipation, but most adverse effects were mild to moderate.¹¹¹ In an RCT the rate of reported adverse effects from rufinamide was similar to those for other AEDs.¹¹³ Felbamate, although helpful for seizure control, has the potential significant risk of treatment-related aplastic anaemia and hepatic failure and should be avoided.¹¹⁴ Felbamate does not have UK marketing authorisation.

1-

1+

2+

An RCT of the efficacy and safety of cannabidiol added to a regimen of conventional antiepileptic medication for drop seizures in patients with LGS (n=76 on 20 mg/kg cannabidiol, 73 on 10 mg/kg cannabidiol, 76 placebo, age range 2–55 years, mean age 15 years) found a reduction in drop seizure frequency of 41.9% in the 20 mg/kg cannabidiol group, 37.2% in the 10 mg/kg cannabidiol group and 17.2% in the placebo group.¹¹⁵ Another RCT of 20 mg/kg cannabidiol as an adjunctive therapy in children with LGS (n=86 cannabidiol, 85 placebo, age 2–55 years) found a median reduction in total seizures of 41.2% compared with 13.7% in the placebo group over the 14-week treatment period.¹¹⁶ Adverse events reported among the patients in the cannabidiol groups were somnolence, decreased appetite and diarrhoea. These events occurred more frequently in the 20 mg/kg dose group. The most common serious adverse event associated with cannabidiol was elevated liver aminotransferase concentrations.^{115,116}

1++

Rufinamide is accepted for use by SMC for adjunctive therapy in children with LGS over the age of 4 years. Cannabidiol is accepted for use as adjunctive therapy of seizures associated with LGS, in conjunction with clobazam, for patients aged 2 years and older (*see section 11.4*).

Therapy should be tailored, taking into account individual preferences and risk of adverse effects. Earlier and improved seizure control may reduce associated comorbidity of LGS including significant long-term permanent cognitive impairment and behavioural side effects, all of which significantly reduce QoL for patients and their carers.

- R** | **Sodium valproate could be considered as first-line treatment for seizure reduction in children with Lennox–Gastaut syndrome.**
- R** | **Rufinamide (4 years and older), clobazam (2 years and older), lamotrigine (2 years and older) or topiramate (2 years and older) could be considered as adjunctive therapy in children with Lennox–Gastaut syndrome.**
- R** | **Cannabidiol could be considered as an adjunctive therapy in conjunction with clobazam for children (2 years and older) with Lennox–Gastaut syndrome.**

5.5 Infantile spasms/West syndrome

- Infants with infantile spasms should be referred to a paediatric epilepsy specialist.⁴² NICE recommends that they should be offered a steroid or vigabatrin as first-line treatment unless the spasms are due to tuberous sclerosis (*see section 5.6.1*). The risk-benefit ratio should be carefully considered. This advice is based on small, heterogeneous studies. 4
- Two systematic reviews of infantile spasms (or West syndrome) were identified.^{117,118} A Cochrane review compared single therapies and included 12 small RCTs and two larger RCTs (total n=681).¹¹⁷ Overall the methodology of the studies within this review was considered poor, as some studies were limited by ethical considerations. The evidence supported hormonal treatment (prednisolone or adrenocorticotrophic hormone (ACTH, or tetracosactide)) leading to resolution of spasms faster and in more infants than vigabatrin. 1++
- Another systematic review included 55 studies, one of which was a meta-analysis and nine were RCTs, comparing 12 different pharmaceutical agents, a ketogenic diet and surgical treatment.¹¹⁸ The quality of studies within this review was not assessed. 2-
- Hormonal treatment (ACTH/tetracosactide or prednisolone) was found to be superior to vigabatrin in reducing spasms, except in tuberous sclerosis (*see section 5.6*).^{117,118} Other treatment options for patients with infantile spasms, including zonisamide, topiramate, levetiracetam, sodium valproate, benzodiazepines (clonazepam or nitrazepam), a ketogenic diet and surgery, were not superior to hormonal or vigabatrin treatment.^{117,118} One review also reported that high dosage is recommended if prednisolone or vigabatrin is used.¹¹⁷ 1++
1-
- A multicentre RCT (n=107) compared hormonal treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months and reported spasm cessation of 73% with hormonal treatment alone.¹¹⁹ ACTH was reported to be superior to prednisolone (76% v 70%, OR 1.36, 95% CI 0.41 to 4.53).¹¹⁹ A retrospective study (n=57, age 2–24 months) found once-daily ACTH to be effective in spasm cessation for 70% of study participants (age 2–24 months) at 14 days and 54% at 3 months, and concluded that these results were comparable to twice-daily dosing.¹²⁰ There was no difference in relapse rate with higher versus lower-dose ACTH treatment.¹²¹ 1+
3
- An RCT (n=92, age range 2 months to 2 years) comparing prednisolone with ACTH treatment in patients with West syndrome with the outcome of reducing hypsarrhythmia severity score found that both treatments were effective.¹²² The mean improvement score was significantly higher in the prednisolone arm than the ACTH arm (7.95±2.76 v 6.00±2.61, p<0.01). There was no statistically significant difference in freedom from spasms at 6 or 12 months following treatment with either prednisolone or ACTH.¹²² 1+
- In an RCT of 63 children (age range 3 months to 2 years) high-dose prednisolone achieved higher spasm cessation rates than low-dose prednisolone (51.6% v 25%, p=0.03). The absolute risk reduction was 26.6% (95% CI 11.5 to 41.7). Adverse effects were comparable in both groups.¹²³ 1+

An RCT (n=377, age range 60–240 days) reported that a combination of hormonal (ACTH or prednisolone) and vigabatrin therapy is more effective than hormonal therapy alone at achieving spasm cessation (72% v 57%, 95% CI 5.1 to 24.9, p=0.002).¹²⁴ At 18 months' follow-up there was no difference in developmental outcomes between the two therapies.¹²⁵ } 1+

The use of steroids requires close monitoring, as the side-effect profile is high.¹²⁶ Significant side effects were reported, including immunosuppression, severe infection, hospital admission, visual field defects and even mortality in some studies.¹¹⁷ However, owing to the devastating effects of infantile spasms, the risks of developing side effects may outweigh the risk of not using the treatments.¹¹⁷ } 1++

R | **Hormonal treatment** (adrenocorticotrophic hormone, tetracosactide or prednisolone) **or vigabatrin could be considered as the first-line treatment for infantile spasms. Children should be closely monitored for adverse events.**

5.6 Tuberos sclerosis

One RCT was identified examining the efficacy of adjuvant everolimus therapy (low or high exposure) in 366 patients, age range 2–65 years, with tuberous sclerosis complex (TSC) and treatment-resistant focal-onset seizures.¹²⁷ The median age was 10.1 years and 82% of participants were under 18 years of age. Adjunctive everolimus treatment significantly reduced seizure frequency in patients with TSC and intractable epilepsy. The median percentage reduction in seizure frequency was 14.9% (95% CI 0.1% to 21.7%) with placebo versus 29.3% with low-exposure everolimus (95% CI 18.8% to 41.9%) and 39.6% with high-exposure everolimus (95% CI 35.0% to 48.7%). } 1++

A post-hoc analysis of this trial separately considered the results for the 299 paediatric participants, splitting the results into two age groups (under 6 years and 6 to under 18 years).¹²⁸ Adjunctive everolimus therapy resulted in sustained reductions in seizure frequency after 1 year and was well tolerated in paediatric patients with treatment-refractory seizures associated with TSC. The younger participants appeared to receive greater benefit than older participants. } 3

Everolimus was not found to improve cognitive functioning, autism or neuropsychological functioning.¹²⁹ } 1++

Everolimus showed immunosuppressive properties in the full study cohort. The most common adverse events were stomatitis, diarrhoea, nasopharyngitis, pyrexia and upper respiratory tract infection.¹²⁷ In the post-hoc analysis of patients under 18, grade 3 or 4 adverse events were reported in 45% of participants under 6 years of age (commonly pneumonia) and 38% in older participants (commonly pneumonia and stomatitis). Two deaths were reported during the extension phase, one due to pneumonia which was suspected to be treatment related.¹²⁸ } 1++
3

Everolimus requires dose titration according to blood levels and close monitoring for potential adverse effects, and therefore may necessitate frequent hospital visits.

Everolimus is accepted for use in Scotland by SMC for children aged 2 years and over with refractory seizures associated with TSC (*see section 11.4*).

Whilst there is no QoL data from studies concerning everolimus, its beneficial effect on seizure frequency may allow patients to manage their condition more effectively and in so doing potentially increase independence and participation in school and family life, and reduce carer responsibilities.

The side-effect profile for everolimus, while not insignificant, appears tolerable in the light of the severity of the condition and its associated risk of mortality.

One underpowered RCT reported that sirolimus did not significantly reduce seizure frequency in children with TSC and intractable epilepsy.¹²⁹ } 1-

There is insufficient evidence to indicate using sirolimus to treat refractory seizures in children with TSC.

R | **Everolimus could be considered as an adjunctive treatment for children** (age 2 years and older) **with refractory seizures associated with tuberous sclerosis complex, when other treatments have failed. Children prescribed everolimus should be closely monitored for adverse events.**

5.6.1 Infantile spasms with tuberous sclerosis

NICE recommends offering vigabatrin as first-line treatment to infants with infantile spasms due to tuberous sclerosis.⁴² If vigabatrin is ineffective, a steroid (prednisolone or ACTH) should be offered, with careful consideration of the risk-benefit ratio. This was based on low-quality evidence, which found that vigabatrin was more effective at stopping infantile spasms than steroids. There was also resolution of hypsarrhythmia in the patients taking vigabatrin. 4

A Cochrane review of the treatment of infantile spasms identified two small, underpowered studies which found vigabatrin to be more effective than hydrocortisone at stopping spasms.¹¹⁷ 1++

Vigabatrin is associated with significant adverse events and needs careful counselling and monitoring.⁴² 4

R | **Vigabatrin should be considered as first-line treatment in infantile spasms for children with tuberous sclerosis. Children prescribed vigabatrin should be closely monitored for adverse events.**

5.7 Dravet syndrome

NICE recommends sodium valproate or topiramate as first-line therapy for patients with Dravet syndrome.¹³⁰ NICE found no evidence specifically for children with Dravet syndrome, so the recommendation is based on evidence of efficacy in children with other generalised seizures. One small study found stiripentol as an adjunctive treatment.¹³¹ This study was also cited in a Cochrane review, along with another small RCT (n=64 in total, age range 3 – 20 years).¹⁰⁷ Both studies addressed stiripentol as an add-on therapy with sodium valproate and clobazam. A higher proportion of participants had 50% or more reduction in seizure frequency in the stiripentol group compared with placebo (22/33 v 2/31 participants; RR 10.40, 95% CI 2.64 to 40.87). Seizure freedom was achieved in 12/33 of the stiripentol group compared with 1/31 of the placebo group (RR 7.93, 95% CI 1.52 to 41.21). The quality of the evidence was rated as low to moderate. Only one of the studies reported on adverse effects, with all 21 patients given stiripentol experiencing an adverse effect versus 5 out of 20 given placebo.¹⁰⁷ These were regarded as severe in 24% of participants given stiripentol. The most common adverse effects were drowsiness, loss of appetite and weight loss. 4 1++

An RCT of adjunctive cannabidiol versus placebo in children aged 2–18 years (n=120) with Dravet syndrome found that the median frequency of convulsive seizures decreased from 12.4 to 5.9 with cannabidiol, as compared with 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency –22.8 percentage points, 95% CI –41.1 to –5.4). The number of participants who had at least a 50% reduction in convulsive seizure frequency was 43% with cannabidiol and 27% with placebo (OR 2.00, 95% CI 0.93 to 4.30).¹³² 1++
In an RCT (n=199; age 2–18 years) of different dosages of cannabidiol, both doses were superior to placebo in achieving at least 50% reduction in seizure frequency over 14 weeks of treatment.¹³³ While both the 20 mg/kg/day and 10 mg/kg/day cannabidiol had similar efficacy, the 10 mg/kg/day resulted in slightly fewer adverse effects (87.5% for 10 mg v 89.9% for 20 mg and 89.2% for placebo). Cannabidiol was associated with somnolence, fatigue, pyrexia, gastrointestinal symptoms,

upper respiratory tract infections and convulsions and elevated liver enzymes.¹³²⁻¹³⁴ There was a higher rate of adverse effects when cannabidiol was used with clobazam.¹³³ } 1++

Cannabidiol is accepted by SMC for use as adjunctive therapy of seizures associated with Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older (*see section 11.4*).

Two RCTs of fenfluramine, in addition to standard AEDs, demonstrated benefit in seizure reduction with treatment versus placebo in children with Dravet syndrome (n=173, 115; ages 2–18 years).^{135,136} A dose of 0.7 mg/kg/day resulted in a mean monthly seizure frequency reduction of 74.9% versus 42.3% for 0.2 mg/kg and 19.2% for placebo, over 14 weeks.¹³⁵ In the other trial there was a 54% monthly seizure reduction with 0.4 mg/kg/day fenfluramine, compared with 5% with placebo.¹³⁶ The most commonly reported side effects were decreased appetite, diarrhoea and fatigue. Cardiac monitoring found no signs of valvular heart disease or pulmonary arterial hypertension.^{135,136} } 1++

- R | **Sodium valproate or topiramate could be considered as first-line therapy for children with Dravet syndrome.**
- R | **Stiripentol or clobazam could be considered as an adjunctive therapy for children (3 years and older) with Dravet syndrome whose seizures are poorly controlled with sodium valproate.**
- R | **Cannabidiol could be considered as an adjunctive therapy in conjunction with clobazam for children (2 years and older) with Dravet syndrome.**

5.8 Steroids and immune therapy for drug-resistant epilepsy

A small (n=21) observational study reported the effectiveness of a hybrid corticosteroid regimen for the treatment of refractory childhood seizures.¹³⁷ Participants received high-dose intravenous methylprednisolone for 3 days and then low-dose alternate-day prednisolone for 12 weeks, before tapering, and this improved seizures (>50% reduction) in 43% of the study population, with 29% becoming seizure free. However, this cessation was short term and the seizures relapsed in all but one patient over the longer term.¹³⁷ } 2-

No other robust evidence on the role of immunoglobulins or corticosteroids in the treatment of children with drug-resistant epilepsies were identified.¹³⁸ } 1++

6 Non-pharmacological management

6.1 Ketogenic diet

6 What matters to young people

Young people highlighted the issue of compliance with a ketogenic diet and how it may cause difficulties in social situations with friends.

"I like the idea of it but I'm just not sure how it would work, especially when I go out with friends."

Information point:

- Discuss options with young people and their families/carers and offer written and verbal information on how to make a ketogenic diet work, for example choices of meals when eating out.
- Signpost to appropriate charities/organisations/peer support/online resources (see section 10.4).

A ketogenic diet is a non-pharmacological treatment for people with drug-resistant epilepsy. A ketogenic diet is high in fat and low in carbohydrate, and aims to induce ketosis. There are various forms of ketogenic diet, and factors related to the individual child and family lifestyle are used to decide which is the most appropriate.

6.1.1 Ketogenic diet in drug-resistant epilepsy

A Cochrane review of 11 RCTs, with 10 studies in children and one in adults with drug-resistant epilepsy (n=778, 712 children and adolescents and 66 adults), reported rates of seizure freedom at 55% in the ketogenic diet group after 3 months and 85% for rates of seizure reduction.¹³⁹ The authors concluded that the results were promising for the use of ketogenic diets in children with epilepsy, but the limited number of studies, small sample sizes and short-term follow up meant the quality of the evidence was low.¹³⁹

1++

Another Cochrane review identified only one study with follow-up over 3–6 years, which reported only 10% of participants remaining on the diet because of restrictiveness or ineffectiveness.¹³⁹ A systematic review of 45 RCTs and observational studies (three in the UK population) of paediatric patients with epilepsy reported the total retention rates of the diet for 1 and 2 years were 45.7% and 29.2%, respectively.¹⁴⁰ Nearly half of the participants discontinued the diet because of lack of efficacy.¹⁴⁰

2++

Cognitive improvements are often seen in addition to seizure reduction.¹⁴¹ Alertness, attention, concentration and global cognition were frequently reported subjectively. In studies where cognition was objectively assessed improvements in alertness, but not global cognition, were confirmed.

3

A follow-on study (n=50, age range 1–18 years) from an RCT evaluating the cognitive and behavioural impact of a ketogenic diet in patients with refractory epilepsy concluded that the ketogenic diet group had lower anxiety and fewer mood disturbances, as well as being more productive and active, than the control group who received standard care.¹⁴² Cognitive tests also showed improvement for the ketogenic diet group.

3

All studies reported adverse effects with a ketogenic diet, with the most frequent being gastrointestinal, such as vomiting, diarrhoea and constipation.^{139,140,143,144} Constipation is recorded as the most common side effect. Severe adverse effects, such as respiratory failure and pancreatitis, were rarely reported (in 0.5% of children).¹⁴⁰ Studies of at least 12 months' duration into the tolerability and adverse effects of a ketogenic diet are required.¹⁴⁴

1++

2++

The International Ketogenic Diet Study Group recommends that a ketogenic diet should be considered after a child has failed two AEDs.¹⁴⁵ It also recommends that a ketogenic diet should be tried for at least 3 months to assess efficacy. Risks and benefits should be considered at each clinic visit and after 2 years of continuous use.¹⁴⁵ 4

SPEN pathway 3 (*see Annex 4*) shows a ketogenic diet as a non-pharmacological option for patients with drug-resistant epilepsy after failure to respond to two AEDs over 6 months or longer.

Ketogenic diet treatment should be available at tertiary centres, ideally as part of an MDT approach, and an experienced dietitian is an integral part of the team. Children should be seen regularly by the ketogenic team, and have nutritional bloods and side-effect monitoring at each visit.¹⁴⁵ 4

No cost-effectiveness studies relevant to NHSScotland were identified.

R | A ketogenic diet should be offered as a treatment option in children with drug-resistant epilepsy.

R | A ketogenic diet should be considered after a child has failed to respond to two antiepileptic drugs.

R | A ketogenic diet should be tried for at least 3 months in children with drug-resistant epilepsy to assess efficacy, with consideration of continuation of the ketogenic diet based on risk and benefits at each visit and after 2 years of continuous use.

6.1.2 Glucose transporter 1 deficiency

Glucose transporter protein type 1 deficiency (glut1D) syndrome is a metabolic disorder that impairs brain metabolism and manifests as early-onset epilepsy, developmental delay, movement disorders and microcephaly. It has been suggested that there is phenotype diversity within this condition, which results in variations in presentation and symptoms.¹⁴⁶ The ketogenic diet is a first-line treatment for patients with glut1D syndrome as it provides ketones as an alternative fuel for cerebral metabolism.¹⁴⁷⁻¹⁴⁹ Conducting RCTs of AEDs in this group of patients would be unethical.¹⁴⁸

A small study of seizure control and acceptance of a ketogenic diet over 2-5.5 years showed 12/15 of the paediatric and adolescent patients with glut1D syndrome became seizure free after ketosis was achieved. Seventy-five per cent of parents and caregivers ranked the ketogenic diet as highly effective in improving their child's symptoms and reported improvements in the child's alertness, demeanour and physical and mental endurance.¹⁴⁷ No serious adverse effects were reported.¹⁴⁷ 3

The largest study of epilepsy in patients with glut1D syndrome (n=87, mean age of 6.5 years) showed that where a ketogenic diet was used 67% of participants were seizure free. Sixty-eight per cent of the seizure-free patients achieved seizure remission within 1 week and 76% within 1 month.¹⁴⁸ No adverse effects were identified. Problems with concordance were reported by 13/78 families, but despite this 5/13 still achieved seizure freedom, suggesting that suboptimal maintenance of a ketogenic diet may still be of benefit with regard to seizure control.¹⁴⁸ 3

Families of patients with glut1D syndrome have reported that, of those with seizures, 95% of the children had >50% seizure reduction and 80% had >90% seizure reduction when treated with a ketogenic diet. Children who were seizure free were currently younger on average (8.2 v 11.6 years, p=0.01) and slightly younger at diagnosis (3.8 v 5.3 years, p=0.05). Early diagnosis and treatment was associated with success.¹⁴⁹ 3

A small study (n=6, 4 children) with a 6- to 17-month follow-up looked at cognitive function. All children on a ketogenic diet had improvements in motor deficits, dysarthria, co-ordination, ataxia and exercise-induced dyskinesia, evaluated using various neuropsychological assessments.¹⁵⁰ The 3

youngest patients saw the most significant improvements, which highlights the importance of early diagnosis and commencement of a ketogenic diet.¹⁵⁰ A retrospective study (n=10) highlighted improved outcomes with earlier diagnosis but also identified positive effects from a ketogenic diet in newly diagnosed adolescents.¹⁴⁶ 3

The International Ketogenic Diet Study Group recommends that in individuals with glut1D syndrome a ketogenic diet should be considered earlier in the child’s epilepsy management and continued into adulthood.¹⁴⁵ 4

R | **A ketogenic diet is recommended in children with glucose transporter 1 deficiency syndrome and should be started as soon as possible after diagnosis.**

✓ | A ketogenic diet should be continued into adulthood (lifelong treatment) in children with glucose transporter 1 deficiency syndrome.

6.1.3 Pyruvate dehydrogenase complex deficiency

Pyruvate dehydrogenase complex deficiency (PDCD) is a rare disorder of carbohydrate metabolism caused by a deficiency in one of the enzymes in the pyruvate dehydrogenase complex. Only one small study was identified; research in this group of patients is difficult and it would be unethical to perform an RCT.

In a longitudinal cohort study (n=19, children, median age 2.5 years) on the short- and long-term outcomes of the effects of a ketogenic diet in patients with PDCD, improvements were observed in epilepsy, ataxia, sleep disturbances and development of motor and neurocognitive function.¹⁵¹ Families reported increased alertness and improved behaviour. When concordance was poor, some symptoms relapsed and further development was stalled. Side effects were observed in 13/19 individuals, the majority of which were mild, such as constipation, vomiting and increased production of saliva, although one patient had to stop the ketogenic diet because of pancreatitis.¹⁵¹ It is thought early introduction may prevent further metabolic damage to the brain, so starting a ketogenic diet as early as possible after diagnosis is suggested.¹⁵¹ 3

The International Ketogenic Diet Study Group recommends that PDCD is a condition for which a ketogenic diet should be considered early in a child’s epilepsy management.¹⁴⁵ 4

R | **A ketogenic diet could be considered as a treatment option, as early as possible, for children with pyruvate dehydrogenase complex deficiency, ideally as part of a clinical trial with monitoring.**

✓ | If successful, a ketogenic diet should be continued into adulthood for children with pyruvate dehydrogenase complex deficiency.

6.1.4 Myoclonic-atonic epilepsy

A ketogenic diet has been shown to be an effective treatment option for patients with myoclonic-atonic epilepsy (MAE).^{152,153} In one study over half the children (n=11) had a >50% reduction in seizures and 18% were seizure free.¹⁵² The authors concluded that a ketogenic diet should be considered earlier in treatment in children with drug-resistant epilepsy with myoclonic-atonic seizures. A retrospective study (n=23) considering different antiepileptic treatments, including AEDs and ketogenic diet, concluded that a ketogenic diet was the most effective treatment for achieving seizure freedom for children with MAE and suggested it should be considered as an early treatment option.¹⁵³ 3

A retrospective study of 50 children with drug-resistant MAE showed that a ketogenic diet is effective in the short term with >86% of patients having >70% seizure reduction (mean time on 3

ketogenic diet of 10.2 months).¹⁵⁴ In the longer term, 54% of the children achieved seizure freedom after 6 months on a ketogenic diet. A good developmental outcome was reported for 50% of patients.¹⁵⁴ Adverse effects were observed in 22% (11/50) and these included anorexia, hunger, severe constipation, weight gain and hyperlipidaemia. A good cognitive outcome was observed with earlier introduction of the ketogenic diet (after failure to respond to three AEDs, $p < 0.01$), a shorter duration of epilepsy before the introduction of the ketogenic diet ($p < 0.011$) and seizures stopping ($p < 0.01$).¹⁵⁴

Another retrospective study of 30 children with MAE on a ketogenic diet found that 25/30 of patients had a >50% seizure reduction after 18 months of observation, with 14/30 patients becoming seizure free up to 11 months after starting the ketogenic diet.¹⁵⁵

The International Ketogenic Diet Study Group recommends that MAE is a condition for which a ketogenic diet should be considered early in a child's epilepsy management.¹⁴⁵

R | A ketogenic diet could be considered as a treatment option for children with drug-resistant myoclonic-atonic epilepsy.

✓ | A ketogenic diet should be started early for children diagnosed with drug-resistant myoclonic-atonic epilepsy and tried for at least 3 months to assess efficacy, with consideration of stopping the ketogenic diet after 2 years.

6.1.5 Infantile spasms

For many years, a ketogenic diet was not recommended in children under 2 years of age, but the use of a ketogenic diet as an effective and safe treatment in infants has been increasingly reported. For first-line treatment, see section 5.5.

A review of observational studies of the ketogenic diet for patients with drug-resistant infantile spasms found a median rate of 64.7% of patients who experienced a reduction in spasms of more than 50%. Patients with infantile spasms of unknown aetiology had an increased probability of achieving freedom from seizures (RR 1.72, 95% CI 1.18 to 2.53). Long-term follow-up data reported a median seizure-free rate of 9.54%. A median rate of 64.7% of patients with >50% reduction in seizures was reported.¹⁵⁶

A systematic review identified nine studies, including one RCT, but did not assess the quality of the studies. The RCT showed similar response rates between participants receiving the ketogenic diet for short and long durations. The observational studies showed complete cessation of spasms in 15–53.5% of patients on a ketogenic diet. A study of a modified Atkins diet, one of the ketogenic diets available, reported complete cessation of spasms in 40% of patients.¹¹⁸

A ketogenic diet was effective at reducing seizures at 3 months in 63% of 104 children with infantile spasms. This increased to 77% at 12 months. There was a >90% reduction in spasms for 31% of patients at 3 months and up to 43% at 12 months.¹⁵⁷

A retrospective study ($n=115$) compared the efficacy of a ketogenic diet on seizure frequency in infants less than 18 months of age ($n=58$) with those >18 months ($n=57$).¹⁵⁸ Significantly more infants were seizure free with the ketogenic diet (34.5% ν 19.2%, $p=0.069$). This trend continued at 6 and 12 months. Just over half the participants had a diagnosis of infantile spasms and the outcomes for the ketogenic diet were higher in this group.

Adverse effects associated with the ketogenic diet included constipation, gastro-oesophageal reflux, behavioural problems, haematuria, diarrhoea, kidney stones, acidosis and dyslipidaemia.¹⁵⁷

R | A ketogenic diet could be considered as a treatment option for infants and children with infantile spasms who have not responded to standard treatment.

- ✓ A ketogenic diet should be tried for at least 3 months to assess efficacy for children with infantile spasms, with consideration of stopping the ketogenic diet after 2 years.

6.1.6 Dravet syndrome

A before-and-after study on the outcome of 24 paediatric patients with Dravet syndrome who were followed up for a minimum of 2 years found that 66.5% (16/24) remained on the ketogenic diet for the full duration of the study.¹⁵⁹ Of these 16 patients two were seizure free, 10 had a 75–99% reduction in seizure frequency and the remaining four patients had a 50–74% reduction in seizure frequency.¹⁵⁹ No complications were reported in the 16 children who stayed on the ketogenic diet for longer than 2 years. Reasons for discontinuation were lack of effect and severe vomiting.

3

In a study of various treatments, in which 10 children with Dravet syndrome were on a ketogenic diet, there was a 70% seizure reduction at 3 months and a 60% seizure reduction at 12 months with the ketogenic diet.¹⁶⁰ At 3 months the efficacy of the ketogenic diet was similar to a triple combination of AEDs. There were no significant adverse events reported, and no severe side effects caused withdrawal from the ketogenic diet. There was no occurrence of status epilepticus while the patients were on the ketogenic diet compared with 8/10 patients before the ketogenic diet was initiated.

3

R A ketogenic diet could be considered as a treatment option in children with drug-resistant Dravet syndrome.

- ✓ A ketogenic diet should be tried in children with Dravet syndrome for at least 3 months to assess efficacy, with consideration of stopping the ketogenic diet after 2 years.

6.2 Surgery for drug-resistant epilepsy

Surgical treatment for drug-resistant epilepsy involves removal or disconnection of part of the brain with the purpose of alleviating seizures. It is estimated that 5% of children with drug-resistant epilepsy may be suitable candidates for surgery.¹⁶¹

The primary aim of surgery for patients with epilepsy is seizure freedom or a significant reduction in seizure frequency. Secondary gains include improved neurodevelopmental progression and improved QoL.

No systematic reviews addressing surgery outcomes specifically in children with epilepsy were identified. A Cochrane review of surgery for both children and adults with epilepsy reviewed nine RCTs, cohort studies and case series with a total of 16,855 participants.¹⁶² Outcome data was obtained for 16,501 patients from 182 studies of which 65% (range 13.5–92.5%) achieved a good result from surgery (defined as at least 1 year seizure free or free of disabling seizures).

2++

A high-quality RCT in adults with epilepsy included in the Cochrane review randomised patients either to surgery (temporal lobe surgery) or to remain on antiepileptic medication. Each arm had 40 patients.¹⁶² After 1 year 58% of the surgical group were free of seizures impairing awareness compared with 8% in the medical group ($p < 0.001$).

1++

The only RCT of children with drug-resistant epilepsy ($n = 116$, 18 years of age or younger) compared brain surgery appropriate to the underlying cause of epilepsy along with medical therapy, versus medical therapy alone. At 12 months, freedom from seizures occurred in 44 participants (77%) in the surgery group and in four (7%) in the medical-therapy group ($p < 0.001$) along with improved scores with respect to behaviour and QoL. Surgery resulted in anticipated neurological deficits related to the region of brain resection.¹⁶³

1+

One longitudinal cohort study in children reported that 80% of the surgical group (n=31) were seizure free 2 years after surgery: 9.6% had a significant reduction in seizures and 9.6% had worthwhile improvement at 2 years after surgery.¹⁶⁴ No patients in the control group (medical treatment, n=14) were seizure free after 2 years although 26% had a worthwhile decrease in seizures. Another non-comparative study (32 children; age at surgery 2 months to 4 years) reported seizure-free rates of 70% at 1–11.6 years' follow-up (mean 4.1 years). In children who underwent surgery before the age of 3 years 20% had a worthwhile improvement whilst 10% gained no benefit from surgery.¹⁶⁴ Comparable results are reported in another study (n=120) where 77.5% of patients achieved seizure freedom, 6.7% had occasional disabling seizures, 7.5% had a worthwhile improvement and 8.3% had no worthwhile improvement.¹⁶⁶ A cohort study (n=42) reported that 86% of patients undergoing surgery were seizure free compared with 36% of controls (11 patients) at 5–15 years' follow-up (mean 9 years, p=0.002).¹⁶⁷

2+
3

Of children with 'catastrophic epilepsy', 73.7% were reported to be seizure free 5 years or more after having a hemispherectomy (19 children; age at surgery 5 months to 5 years), 10.5% (2/19) had rare disabling seizures and 15.8% had a worthwhile improvement.¹⁶⁸ Despite higher surgical risk and more severe epilepsy this is comparable to a 70% seizure freedom rate in adults undergoing anterior and medial temporal lobe resection.² Children with refractory epilepsy who had hemispheric surgery had a seizure-free rate of 79% at 7-year follow-up (n=24, mean age 3 years).¹⁶⁹

3
4

A Swedish study (n=46) reported lower rates of seizure freedom following surgery for epilepsy compared with other studies (53% at 2 years, 44% long term); however, the results were still significant in terms of outcome compared with the group that did not undergo surgery (0 of 39 patients, p<0.0005).¹⁷⁰

2+

A higher seizure-free rate after surgery was found in infants (89.5%) than in children/adolescents (72.9%, p=0.33).¹⁷¹ Younger children (<3 years) were 2.76 times as likely to achieve a seizure-free outcome as children in the older groups (4–17 years, OR 2.76, 95% CI 0.56 to 13.39, p=0.21). No studies were identified that reported a detrimental effect of early surgery compared with late surgery.

3

A prospective study (n=49) reported that 45% and 50% of children who underwent surgery for epilepsy between 2 months and 4 years of age were seizure free at 5 and 10 years respectively. A greater than 75% reduction in seizure frequency was found in 31% of children. An increased seizure frequency was reported in 13%.¹⁷²

3

In children with newly diagnosed epilepsy, a strong predictor of medical intractability is abnormal neuroimaging (RR 7.0, p=0.0006).¹⁷³ For those with medically intractable epilepsy and abnormal imaging there is a role for early surgery to limit comorbidities of ongoing, intractable seizures.¹⁷³ Response to medical treatment can identify patients whose epilepsy will be drug resistant and could be considered for surgery. Medically intractable epilepsy can be identified early, as patients who do not respond to the first or second AED are likely to continue to have seizures.¹⁷⁴

3

Consideration of surgery in children must take into account that drug-resistant epilepsy is likely to have consequences on neurodevelopment and cognitive function. However, studies show that most children continue to progress, and some children had improved outcomes (for example, intelligence quotient, cognitive processing and memory quotient) compared with those on medical treatment, particularly if they are seizure free.^{163–165,167,175–177}

1+
2+
3

One RCT in children evaluated QoL as a secondary outcome. Higher QoL scores were reported at 12 months after surgery using the Paediatric Quality of Life Inventory (difference 21.9, 95% CI 16.4 to 27.6) versus those who continued medical therapy alone.¹⁶³

1+

Similar findings have been reported in an RCT in adults and observational studies in children. Improved QoL was correlated to better seizure outcome and control.^{167,177–180}

1+
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The Cochrane review of surgery for epilepsy for both adults and children did not identify high-quality data on adverse events because of unreliable reporting in the included studies.¹⁶² The results describe a rate of transient adverse effects of 6% (within 12 months) and a 7.4% risk of permanent adverse effects.

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Another systematic review, which analysed studies mainly in adults but included some paediatric and adolescent data, found a 0.1% mortality rate following surgery for epilepsy (n=2,725).¹⁸¹

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In the paediatric studies there was 0% mortality.^{163,168,172} In the RCT serious adverse events, including monoparesis, hemiparesis, generalised hypotonia (one patient) and language deficit (one patient), were reported in 19 patients in the surgery group, but not in the medical therapy group.¹⁶³ Improvements in functional ability were noted at 12 months in 15 (88%) of the patients with monoparesis or hemiparesis. A study set up to compare seizure outcomes after surgery in infants (n=19) versus children (n=59) reported a temporary complication rate of 15.3% across both groups with no major complications or mortality.¹⁷¹ The study was not powered to report the difference between the two groups.

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The Paediatric Epilepsy Surgery Subcommittee of the ILAE has recommended that children with drug-resistant epilepsy should be referred to dedicated paediatric epilepsy surgery centres.¹⁸² The Scottish Paediatric Epilepsy Surgery Service (SPESS) is a nationally funded service that accepts referrals from specialists throughout Scotland. Children enter the SPESS assessment process following identification through the SPEN Continuing epileptic seizures pathway (see Annex 4) and follow the SPESS referral to MDT pathway (see Annex 6), then the SPESS MDT pathway (see Annex 7). Children are referred to the SPESS assessment process if they fulfil one or more of the referral criteria (see Annex 4).

R | **Children with drug-resistant epilepsy who fulfil referral criteria for assessment for surgery should be identified early.**

✓ | Children who are candidates for surgery should be referred to a comprehensive epilepsy surgery programme.

6.3 Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a neuromodulatory treatment which involves electrical stimulation to the vagus nerve from a pacemaker-type device in the chest wall. This is inserted surgically and the device can be programmed in the outpatient setting.

NICE recommends VNS as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for specialised surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalisation) or generalised seizures.^{42,183}

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Studies assessing VNS solely in the paediatric population are of poor quality.¹⁸⁴⁻¹⁸⁶

A Cochrane review of the efficacy of VNS in reducing focal seizures identified five RCTs (439 patients).¹⁸⁴ Four of the studies included children over the age of 12 and one of the studies was exclusively in a paediatric population (age range 3-17 years). High-frequency VNS was found to be superior to low-frequency stimulation in achieving >50% reduction in seizure frequency (RR 1.73, 95% CI 1.13 to 2.64). Slight improvements in QoL were also reported. There was no statistical difference between high- and low-frequency VNS for QoL, cognition or mood. A follow-up to the paediatric RCT included in the review also reported improvements in mood and depression scores in all participants, unrelated to seizure frequency.¹⁸⁷

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Adverse effects associated with implantation and stimulation were hoarseness, cough, dyspnoea, pain, paraesthesia, nausea and headache. Hoarseness and dyspnoea were more likely to occur with high stimulation than low stimulation.¹⁸⁴ This was based on studies in the review rated as moderate to low quality. The risk ratio for treatment withdrawal was 2.56, (95% CI 0.51 to 12.71); however, evidence for this outcome was rated within the review as low quality. Adverse effects noted in the solely paediatric study were voice alteration and coughing, tingling sensation in the throat, pain, behavioural change, infection, headache, spontaneous swelling around the stimulator and pain around the stimulator during exercise, and itch.

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VNS implantation requires a general anaesthetic and therefore standard risks of general anaesthetic apply. The procedure has low morbidity (no reports of intra-operative haemorrhage, although postoperative infection occurred in 0.6%).¹⁸⁴ The need to change the battery in the device after 4–8 years is another consideration in terms of further intervention for patients and cost implications, in addition to restrictions around MRI.

One NHS-based pre- and post-design study reported that VNS is associated with increased outpatient resource use and decreased inpatient admissions, with a reduction in long-term epilepsy-related medical costs after implantation.¹⁸⁸ Similarly, a case-control study in Denmark, with an economic evaluation, found VNS to be potentially cost saving.¹⁸⁹ VNS was found to be comparatively less efficient than ketogenic diet and other treatments (including surgery and usual care), although these analyses were not conducted within the NHS and therefore cost utility will vary.^{189–191}

SPEN has included VNS in the care pathway for children with continuing epileptic seizures (*see Annex 4*) as a treatment option for drug-resistant epilepsy.

R | **Vagus nerve stimulation could be considered as an adjunctive treatment for children with drug-resistant epilepsy who are not candidates for surgery, under the specialist guidance of a consultant paediatric neurologist.**

6.4 Deep-brain stimulation

Deep-brain stimulation (DBS) has been used for a number of neurological conditions, including epilepsy, and involves stimulation to specific targets within the brain. Neurosurgically placed electrodes are connected to an implanted pulse generator (pacemaker-like device) which is usually sited within the chest wall. The generator is programmed in the outpatient setting.

A Cochrane review of DBS in patients with epilepsy included 12 RCTs with a number of different intracranial targets for stimulation, and concluded that a significant reduction in seizure frequency was found for anterior-thalamic DBS (109 patients with -17.4% reduction compared with sham treatment; 95% CI -32.1 to -1.0), hippocampal DBS (15 patients with -28.1% reduction compared with sham; 95% CI -34.1 to -22.2) and ictal-onset cortical stimulation (191 patients with -24.9% reduction in seizures compared with sham; 95% CI -40.1 to 6) in short-term RCTs (1–3 months).¹⁹² No statistically significant effects were demonstrated for centromedian-thalamic stimulation (20 patients) and cerebellar stimulation (22 patients), although the evidence was of low to very low quality.

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Only one study included children (5 out of 13 patients were between 4 and 15 years old). This study was not included in the meta-analysis because of its design. Patients received DBS for 6 months, following which a double-blind protocol was performed with a 3-month 'on' versus 3-month 'off' period.^{192,193} One of the two outcome measures was seizure frequency with reported seizure freedom in one patient (7.7%) and a mean seizure frequency reduction of 72% at maximum follow-up (12–94 months).

There were significantly fewer epilepsy-related injuries following anterior-thalamic DBS compared with sham treatment (7.4% v 25.5%; p=0.01).¹⁹² Surgical adverse effects included asymptomatic intracranial haemorrhage in 3-4% of patients and soft tissue infections in 5-13% of patients in the two largest trials. There were no permanent perioperative complications from DBS, although in the small numbers of children with implants there were cases of skin erosion requiring removal of the implant.

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Despite a reduction in seizure frequency in both anterior-thalamic and ictal zone onset cortical stimulation there was no meaningful effect on QoL in one study. Anterior-thalamic DBS was associated with higher rates of self-reported depression (14.8% v 1.8%; p=0.02, Fisher's exact test) and subjective memory impairment (13.8 v 1.8%; p=0.03).¹⁹² Adverse effects on subjective mood was also reported in an RCT of bilateral anterior DBS (depression was reported in 14.8% of the study group and 1.8% from the controls, p=0.016, age range 18-65 years).¹⁹⁴

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Further research into DBS in a paediatric population is required before recommendations for its use can be made.

7 Cognitive, developmental and psychiatric comorbidities

What matters to young people

Young people discussed feeling low in mood at times because of their epilepsy. In addition to their epilepsy nurse specialist, they wondered who else they could talk to about this and how they could get appropriate support.

“I feel down, sad, worried for the future and what will happen. Annoyed.”

Information point – allow sufficient time to discuss the following issues:

- *perceived stigma and how patients view their epilepsy*
- *memory issues*
- *mood/anxiety disorders*
- *maintaining mental well-being*
- *self esteem*
- *the availability of counselling/support from both healthcare professionals and support groups for young people with epilepsy.*

Signpost young people and their families to appropriate charities, peer support opportunities and online resources (see section 10.4).

7.1 Cognitive, developmental and psychiatric comorbidities

7.1.1 Neurodevelopmental disorders

The prevalence of neurodevelopmental disorders is higher in children and adolescents with epilepsy.¹⁹⁵⁻¹⁹⁷ The relationship between epilepsy and neurodevelopmental disorders is complex. There are various mechanisms which may explain the high rates of comorbidity between epilepsy and neurodevelopmental disorders (ASD, ADHD and intellectual disability). It is possible that epileptic seizures early in development have a direct impact on the development of the immature brain. Alternatively, a common underlying pathology or genetic condition may contribute to the aetiology of both seizures and atypical development.¹⁹⁸

Information about the risk of certain neurodevelopmental disorders in children and young people with epilepsy can be used to form a clinical profile of those who may be at greater risk of comorbidities, and this may allow for earlier identification and diagnosis. Early and appropriate identification of comorbidities can help tailor appropriate interventions and modifications to lessen their impact on the child or young person’s development and wider functioning.

7.1.2 Autistic Spectrum Disorder

In some epilepsy syndromes ASD symptoms may overlap with the phenotype of the epilepsy condition, for example the linguistic and social regression observed in Landau-Kleffner and West syndromes.¹⁹⁹ Seizure presentations may also mimic sensory or stereotyped behaviours observed in some children and young people with ASD and a detailed account of presentation is required to differentiate seizure variables from features of potential ASD.²⁰⁰

One meta-analysis found a 6.3% prevalence rate for ASD in children with epilepsy compared with the general population prevalence of 0.75% to 1.1%.²⁰¹ A higher prevalence was associated with younger age and the presence of a comorbid intellectual disability. Specific epilepsy syndromes were also associated with increased risk (those with infantile spasms, focal seizures and Dravet syndrome having a reported risk of 19.9%, 41.9% and 47.4%, respectively).

7.1.3 Screening methods for autistic spectrum disorder in epilepsy

The guideline on Assessment, diagnosis and interventions for autism spectrum disorders (SIGN 145) does not recommended screening for ASD at a population level.²⁰² Instead, the emphasis is on the need for careful screening of ASD features in at-risk children and adolescents (that is, populations where prevalence is higher). No single screening instrument is recommended as each one is designed for use with a particular age group and often focuses on one particular ASD condition.²⁰² Across Scotland a range of screening tools is used to identify those children and young people who should be referred for a specialist diagnostic assessment and tend to be selected based on the child's age and cognitive and linguistic abilities.

A non-comparative observational study (n=236, mean age 6 years 7 months) examined the degree to which two ASD screening tools predicted subsequent diagnosis in children and adolescents with epilepsy; the Social Communication Questionnaire (SCQ) was administered in children aged 4 years and over and the modified Checklist for Autism in Toddlers (mCHAT) in those under 3 years. Of the 139 children screened using the SCQ, 21 were identified as at risk and of these 12 were subsequently clinically diagnosed with ASD (57%). The mCHAT was less likely to identify those who would receive a clinical diagnosis; out of the 37 younger age group identified at risk, only three were subsequently diagnosed (8%).²⁰³

There are limitations of using screening measures with a younger age group when core ASD symptoms may not be present or reliably identified using screening tools.^{201,203} Screening tools alone may not be specific in the identification of ASD as they are sensitive to risk of wider neurodevelopmental disorders and may result in false positives.²²⁴ In the study of the 15 children diagnosed with ASD, 12 were also identified as having developmental delay or an intellectual disability, highlighting the prevalence of comorbidities in this population and the likelihood of this confounding any screening measure.²⁰³

No screening tools specific for children with epilepsy that were specifically designed and validated for use with this at-risk group were identified. Therefore the same screening tools described in SIGN 145²⁰² can be used in children and adolescents with epilepsy, as in a non-epilepsy population, to identify those presenting with ASD features.²⁰² However, caution should be exercised in interpreting these tools and they should only be used in conjunction with a detailed developmental history and referral for specialist assessment if impairments in social communication skills are identified.

- ✓ Given the higher prevalence of ASD in this population, clinical assessment of children with epilepsy should incorporate a high level of vigilance for features suggestive of ASD, in the domains of social interaction and play, speech, language and communication difficulties, and behaviour.
- ✓ The same screening tools can be used to assess ASD in at-risk children with epilepsy as those who do not have epilepsy. However, caution should be exercised in interpreting these tools and they should only be used in conjunction with a detailed developmental history.

The following recommendation from SIGN 145 should be followed:²⁰²

R | **A diagnostic assessment, alongside a profile of the individual's strengths and weaknesses, carried out by a multidisciplinary team which has the skills and experience to undertake the assessments, should be considered as the optimum approach for individuals suspected of having ASD.**

7.1.4 Attention-deficit-hyperactivity disorder

There is a strong association between epilepsy in children and adolescents and developing ADHD, even when socioeconomic, perinatal and family history factors are taken into consideration. One study reported an adjusted hazard ratio of 2.54 for children with epilepsy versus those without (95% CI 2.02 to 3.18) and another found an adjusted incidence risk of 2.72 (95% CI 2.53 to 2.91).^{204,205} Follow up of a high-quality RCT (n=393 >4 years), looking at neurocognitive deficits associated with newly-diagnosed childhood absence epilepsy, found attention deficits in 36% of newly-diagnosed children of average intellectual functioning before being medicated for their epilepsy.²⁰⁶ These impairments identified on neuropsychological tasks persisted even when children become seizure free with an AED, suggesting that attentional deficits may not be a direct consequence of seizure activity.

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7.1.5 Screening methods for attention-deficit-hyperactivity disorder in epilepsy

An RCT found a parental proxy screening of general behavioural symptoms (Child Behavior Checklist, CBCL) did not identify those children with epilepsy who were impaired on a neuropsychological test of attention.²⁰⁶ General screening measures may identify those children with more severe levels of emotional/behaviour dysregulation associated with hyperactivity but may not be sensitive to more subtle symptoms of inattention.²⁰⁶ Attention has a direct effect on memory which consequently impacts on executive functioning and learning and achievement. These attention deficits were not generally identified using parental screening measures. There is a need for more detailed, sensitive assessment of at-risk children to ensure appropriate treatment and management.

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The NICE guideline on Attention deficit hyperactivity disorder; diagnosis and management (CG 87) does not identify any specific screening tool that can robustly and reliably identify children with possible ADHD.²⁰⁷ It recommends that diagnosis should be made on the basis of a clinical and psychosocial assessment, a detailed developmental and psychiatric history and observation.

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- ✓ | In children and young people with epilepsy, the same screening measures can be used to identify those at risk of ADHD as those used with the general population. However, caution should be given to their interpretation and should be used in association with information from other sources, including a detailed developmental history and parental report of their child's symptoms.
- ✓ | If, on the basis of preliminary assessment, it is suspected that a child or young person has ADHD associated with significant impairment, referral for specialist assessment by a child and adolescent mental health clinician or paediatrician with a specialist interest in this field is recommended.

7.2 Neurocognitive/academic outcomes

Children and young people with more complex epilepsies (epileptic encephalopathies, structural abnormalities or where there is an additional neurological comorbidity or neurodevelopmental disorder) may be appropriately identified as at risk of cognitive impairment.

Neuropsychological assessment involves more detailed assessment of a broad range of cognitive domains including attention, executive functioning, language, memory, psychomotor speed and academic attainments. This type of assessment can help identify specific impairments in those children and adolescents with epilepsy who may be otherwise considered low risk or where difficulties may not be easily identified or understood by general measures of intelligence.²⁰⁸ Neuropsychological assessment can also be used to identify specific cognitive impairments in children and young people with uncomplicated epilepsies typically considered lower risk, that is childhood absence epilepsy, CECTS and those with average intellectual functioning.^{208,209} Neuropsychological screening will also help identify those children with epilepsy functioning significantly below their peers and allow for tailored educational interventions.

7.2.1 Neuropsychological assessment

A meta-analysis of 42 studies (1,237 children with CECTS and 1,137 controls) found that children with CECTS, an average intelligence quotient (IQ) and no comorbid conditions demonstrated significantly lower scores across a range of neuropsychological domains than controls.²¹⁰ Pooled standard deviations (SDs) with the largest effect sizes were observed for long-term memory and the smallest for visual processing. Overall results indicated that children with CECTS display a variable profile of pervasive deficits across cognitive domains, highlighting the need for a detailed neuropsychological assessment to identify the specific pattern of strengths and weaknesses.

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Children with epilepsy have also been found to function below their peers in terms of educational attainment, even in those who function in the average range intellectually, have no comorbid neurodevelopmental disorders and are in mainstream education.²¹¹⁻²¹³ Strong to moderate differences in literacy and language skills between children with CECTS and comparison peers were found, with children with CECTS performing significantly below age expectations.²¹¹

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In a systematic review, 14/20 studies indicated that children and young people with epilepsy obtained significantly lower academic achievement scores than control groups (whilst six found no difference).²¹² Another systematic review found children with temporal lobe epilepsy (TLE) (n=207) were significantly below peers and age expectations in reading accuracy, with 40% of those with TLE more than one academic year behind the school grade in their reading of regular and irregular words (compared with 10% of controls).²¹³ Children with TLE were functioning significantly below age expectations in their understanding of texts.²¹³

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As different measures of educational abilities were used across studies it is not possible to compare the relative reliability and validity of specific measures. However, the three reviews found that standardised measures of educational attainment can be used to identify educational underperformance in children and adolescents with epilepsy who may be otherwise considered at low risk of cognitive impairment (that is, with well-controlled epilepsies of childhood, average IQ and no other developmental comorbidities).

R | Healthcare professionals should be aware that all children and young people with epilepsy are at increased risk of cognitive and academic impairments, even those with epilepsies considered to be more benign or well controlled.

✓ | Healthcare and education professionals should seek information about the child or young person's cognitive function and educational attainment. At regular intervals educational attainment should be obtained (via school reports or curriculum-based assessments where possible).

✓ | Where there is evidence that a child with epilepsy is not making appropriate academic attainments or is presenting with difficulties in cognitive functioning, healthcare professionals should first liaise with education professionals (including educational psychology and learning support staff) to discuss supports in place.

Where there is evidence of more severe and persistent impairments in cognitive functioning or where difficulties are less well understood, healthcare professionals should refer for specialist neuropsychological assessment. Such assessments are completed by specialist neuropsychology services, where available, or via paediatric psychology or clinical psychology within child and adolescent mental health services.

7.3 Psychiatric comorbidity

While children and young people with epilepsy have significantly higher rates of behavioural and mood disturbance, these may go unrecognised and they may not receive the mental health interventions or support they need.^{214,215}

Depression is a common comorbidity in children and young people with epilepsy and can have a detrimental impact on QoL. Suicide rates in adults with epilepsy are three times higher than in the general population, with some reports indicating a higher prevalence (see SIGN guideline 143 on diagnosis and management of epilepsy in adults).² It is also a risk factor for people with refractory epilepsy.²¹⁶ Prevalence rates of depression in children and adolescents with epilepsy range from 5.2% to 39.6%.^{144,199,217} Risk factors for depression in children and young people with epilepsy are likely to be multifactorial involving neurobiological, psychosocial (including familial factors) and iatrogenic risks.²¹⁷ There are no consistent findings across studies relating to seizure-related variables and depression risk.

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Prevalence rates of anxiety symptoms range between 11% and 50% in children and young people with epilepsy.²¹⁷ Additional risk factors for increased anxiety include lower levels of epilepsy knowledge and increased parental anxiety.

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Higher rates of both mood and anxiety disturbance are reported in specialist centres which is likely to reflect the complexity of the child's presentation. The risk of developing depression and/or anxiety was found to increase with age.²¹⁷

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R | Healthcare professionals should routinely enquire about depression and anxiety symptoms in all children and young people with epilepsy.

7.3.1 Screening tools for depression and anxiety

One case-control study compared three commonly used paediatric screening measures for their sensitivity and specificity in predicting mood/anxiety disorders in children and adolescents with epilepsy (n=57).²¹⁵ Two self-report measures were used: the Children's Depression Inventory (CDI) and the Multidimensional Anxiety Scale for Children (MASC). A parental proxy measure was also administered, the CBCL, which includes subfactors assessing anxiety/depression, hyperactivity and social symptoms. The MASC was found to provide the best sensitivity (86.7% of cases) and the CBCL anxiety/depression factor score the best specificity (91.9%) in predicting a mood and anxiety disorder. For maximum sensitivity/specificity a combination of self-report and proxy measures could be used. A pre-post behavioural screening study also highlighted the clinical utility of the CDI as a tool for screening depression in routine clinical care.²¹⁸ This study screened levels of self-reported depression in 159 children and young people with epilepsy attending behavioural consultation appointments at epilepsy clinics at two time points over a 24-month period. The CDI was effective in identifying changes in depressive symptomatology over this time.

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While screening measures can be used in primary care and hospital settings to identify those at risk of a possible affective disorder, diagnostic interviews by experienced clinicians will be more accurate in identifying depression and anxiety in children and young people with epilepsy than behavioural checklists as they allow for discussion and differentiation between seizure-related characteristics and those symptoms specific to a psychiatric condition.^{199,215}

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Screening tools for detecting mood and anxiety disorders in children and young people with epilepsy are generally the same as for those without epilepsy. No tools designed and validated specifically for screening for depression and anxiety in an epilepsy population were identified.

- ✓ Healthcare professionals should consider using brief screening measures of mood and anxiety symptoms when concerns are identified. These should be administered to the child or young person where possible (and not rely solely on parent or carer proxy measures).
- ✓ Although not specifically validated in children with epilepsy, screening tools such as Children's Depression Inventory, Child Behavior Checklist, and Multidimensional Anxiety Scale for Children could be considered.
- ✓ Where screening identifies risk of psychiatric disturbance, referral to the appropriate mental health services for specialist diagnostic assessment and, where recommended, treatment should be considered.

7.4 Management of psychological, psychiatric, social and cognitive comorbidities

7.4.1 Psychological interventions

A systematic review found cognitive behavioural therapy (CBT) targeting depression symptoms was effective in reducing depression symptomatology in children and young people with epilepsy.²¹⁹ Although only two controlled studies within this review reported effect sizes, these were moderate to large. One RCT, reported as high quality in the review, found improvements in depression symptoms, QoL measures and psychosocial well-being, compared with treatment as usual in young people with epilepsy following a CBT intervention.²²⁰ These effects were maintained at 6- and 9-month follow-up. The review also highlights emerging evidence for psychosocial interventions (including educational approaches) improving epilepsy knowledge, QoL and psychological outcomes.²¹⁹ However, given the small sample sizes, different intervention approaches and delivery methods, it is difficult to draw conclusions about what the therapeutically effective components of these interventions are.

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An RCT found a manual-based psychosocial group intervention was significantly more effective than a waiting list control in increasing epilepsy knowledge and confidence in talking about their epilepsy in young people with epilepsy.²²¹ This purpose-designed intervention, however, did not find any significant improvements in health-related QoL or in measures of emotional distress after intervention or longer-term follow-up (3-6 months). This RCT excluded participants who were experiencing suicidal ideation or clinically significant levels of anxiety or depression and those with comorbid learning disability or neurological conditions, and it is not possible to conclude whether psychosocial group interventions are effective in managing psychiatric comorbidities.

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Individual CBT was found to be effective for improving depression in adolescents and adults with epilepsy²²² and CBT could therefore be used for adolescents transitioning to adult care.

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R Cognitive behavioural therapy focusing on depression could be considered in children and adolescents with epilepsy and comorbid depression.

7.4.2 Antidepressant medication

A Cochrane review of eight studies looked at the efficacy and safety of antidepressant medication in people with epilepsy.²¹⁶ Of these eight studies in the review, three included a child and adolescent population or mixed adult and child population. All studies showed some improvement in depression symptoms with a responder rate between 24% and 97% compared with placebo or no treatment.

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In those including children and young people the response rate was between 69% and 97%. Studies using selective serotonin reuptake inhibitors (SSRIs) did not indicate any significant increase in seizure activity.

One moderate-quality RCT within the Cochrane review found child and adult patients with epilepsy who were treated with the SSRI venlafaxine, 25–75 mg/day, showed greater improvements in depression symptoms than in those who did not receive treatment. Sixty-nine per cent (22/32) of those prescribed venlafaxine showed improvements compared with only 6/32 in the no-treatment group. The RR for the proportion with a $\geq 50\%$ improvement in depression scores with venlafaxine versus no treatment was 3.25 (95% CI 1.19 to 8.90, $p < 0.05$). The SmPC for venlafaxine states that it is not recommended for use in children and adolescents; therefore, use in this population would be outside the terms of the product licence for this medicine.²²³

One cohort study found 35/36 patients (97%) showed $\geq 50\%$ improvement in depression scores on the Kiddie Schedule for Affective Disorders and Schizophrenia depression scale following 1 year of treatment with sertraline (mean dose 111 mg/day) or fluoxetine (mean dose 46 mg/day).²¹⁶

While the quality of evidence is limited, there was no, or limited, worsening of seizures across the three studies that include children and young people following treatment with antidepressants.

One cohort study within the review found no statistically significant increase in seizure activity following treatment with sertraline compared with baseline monitoring.²¹⁶ A second study found 2/36 participants experienced an increase in seizure activity following commencement of a low dose of sertraline. In one case, adjustment of their antiepileptic medication led to seizure control without discontinuation. In the second case, the antidepressant was discontinued as the child's parents did not wish to adjust their AED medication. None of the three studies including children and young people reported episodes of status epilepticus when taking antidepressants.

A range of other adverse effects were reported across the three studies, including sedation, hypomanic symptoms, rheumatic pain, myoclonus, facial rash and gastrointestinal symptoms. Consideration should also be given to interactions between AED and antidepressant medication.

There is no evidence specifically evaluating the efficacy or safety of other types of SSRI, including fluoxetine, which is currently recommended as the first-line pharmacological intervention for moderate to severe depression in children and adolescents without epilepsy.²²⁴ Sertraline is recommended only for those unresponsive to previous treatment or with recurrent depression.

R | Treatment with selective serotonin reuptake inhibitors could be considered in children and adolescents with epilepsy and comorbid depression.

7.5 Management of children with epilepsy and ADHD

7.5.1 Methylphenidate

Methylphenidate is a medicine for managing ADHD symptoms in children and young people. Although historically there have been concerns that psychostimulant medication can lower seizure threshold in those with epilepsy, methylphenidate is used in clinical practice to manage ADHD symptoms in children and young people who are also prescribed AEDs.

ADHD symptoms

There is a consistent body of evidence from a systematic review and 10 further studies that methylphenidate improves ADHD symptoms with no significant and lasting impact on frequency of seizures.^{225–235} Response rates ranged from 61% to 83.3%.^{230–234} The lower response rate of 61% was observed in a study which included children with more severe or poorly controlled epilepsy and comorbid intellectual disability.²³² The age range of participants was 4–18 years and all followed similar diagnostic procedures for both epilepsy and ADHD.

Two studies reported improvements in QoL following initiation of methylphenidate in children and young people with ADHD and comorbid epilepsy.^{229,230} } 2+
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One study included a working memory task and indicated improvements on the task following initiation of methylphenidate in children with ADHD (in both the epilepsy and non-epilepsy groups).²²⁶ } 4

Most studies reported no increase, or no significant increase, in seizure frequency with methylphenidate.^{229-231,234} In a small percentage of cases initiation of methylphenidate has been followed by an increase in seizure frequency from baseline or recurrence of seizures following a period of stability; however, this tends to be in the context of those who have a history of poor seizure control, anxiety disorders and poor response to AEDs. In a number of these cases, seizure control was attained with adjustment of AED or adjustment of methylphenidate dose rather than discontinuation of methylphenidate.^{228,232,233} } 2+
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The most commonly reported adverse effects were loss of appetite, headache, insomnia, and emotional or behavioural changes.^{228,232,233,230} These are consistent with those reported in a non-epilepsy population and studies indicate these are generally mild and transient. Consideration also needs to be given to potential adverse interactions between AED and ADHD medication. } 2+
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R | Methylphenidate could be considered as a first-line medication in the management of ADHD in children and adolescents with comorbid epilepsy.

- ✓ | Prior to and following initiation of methylphenidate children and young people with ADHD and comorbid epilepsy should be monitored for any change in seizure frequency and severity, seizure control and anxiety disorders. This should be recorded (for example, through the use of a seizure log).

7.5.2 Amphetamine and atomoxetine

One study found that amphetamine was not as effective as methylphenidate for children and adolescents with epilepsy and comorbid ADHD (response rate 24% v 63%).²³³ More participants discontinued treatment due to adverse effects in the amphetamine group (53% v 37%). Worsening agitation and emotional ability were the most commonly cited reasons.²³³ Methylphenidate was associated with a 5.57-fold greater chance of treatment response than amphetamine preparation (p=0.015), although this should be interpreted with caution as participants were not randomised to these groups. } 3

Another study found only 37% of participants responded to atomoxetine for ADHD symptoms. This study, however, included children with severe epilepsy, taking multiple AEDs, with high levels of comorbidities and previously failed trials of stimulant medication.²³⁵ Nine of the 27 participants discontinued treatment due to increased irritability and behavioural activation, decreased appetite, and emerging psychotic-like symptoms. There was resolution of behavioural activation and irritability once medication was ceased (in five of the seven children a psychotropic medication was commenced or the dosage increased). } 3

7.5.3 Guanfacine

No evidence was identified relating to the use of guanfacine in children with epilepsy and comorbid ADHD.

8 Transition

8.1 What is transition?

Young people with epilepsy will require to transition from paediatric to adult epilepsy services. Transition refers to the process by which these young people and their parents/caregivers are prepared for this transfer of care. It can be defined as “a purposeful, planned process that addresses the medical, psychosocial and educational needs of young adults with chronic physical and medical conditions as they move from child-centred to adult-orientated healthcare systems”.²³⁶

Transition should be a preparatory process that leads to a change from parent- to patient-focused self management, which encourages independence and empowerment on the part of the young person involved. Where full independence is not achievable, such as in those with severe learning disability or exceptional healthcare needs, transition remains an important process. Families are empowered to manage issues such as capacity and consent, where necessary (parental legal guardianship). The process gives them legal rights to make informed decisions about their child/young person legally beyond the age of 16 years in Scotland. Every child and young person should have access to an epilepsy specialist nurse, with this being even more important during transition and handover to adult services.²³⁷

There are many aspects to good transition, including chronic disease knowledge, self management, transition readiness, general healthcare behaviour, well-being, QoL and rates of transfer. There is much discussion about the timing of young people moving to adult service provision but little evidence to support any particular age. Timing is usually set by institutional regulations rather than young person readiness, developmental ability and condition knowledge. However, many advocate transition being person centred, person appropriate and person ready for transfer.^{238–241}

What matters to young people

Young people discussed how they would be worried about moving from paediatric to adult services as it would be new doctors and a bigger hospital. They felt they should have the opportunity to visit the new hospital and meet new doctors several times before moving into adult services. They would like the opportunity to ask questions.

“I would find it hard at the start. It’s important to talk to new doctors before the move.”

Information point – When moving from child to adult services, ensure the young person and their families/carers are aware of the following:

- what will happen
- when will this happen
- who will be involved and support the move, for example an epilepsy nurse specialist.

8.2 Review and grading of the evidence for transition

Owing to the nature of the topic and available evidence, a range of literature sources were retrieved from this search, including one quantitative cross-sectional study, one largely descriptive article with a small section relating to a process evaluation, and systematic, mixed-methods, scoping and narrative reviews.

The single systematic review was graded according to SIGN methodology.^{242,243} The quantitative study was assessed for methodological quality using the Joanna Briggs Institute (JBI) critical appraisal tool for analytical cross-sectional studies.²⁴⁴ It was predetermined that a score of 7 or 8 (out of 8) would be graded as high quality and 5 or 6 (out of 8) as moderate quality (for that study type).

The descriptive article was assessed for methodological quality using the JBI critical appraisal tool for narrative opinion and text, with cut-off scores of 5 or 6 (out of 6) predetermined as high quality and 4 as moderate quality (for that study type). Owing to the lack of critical appraisal tools specifically for mixed-methods, scoping and narrative reviews, these have not been formally graded. However, the guideline development group considered the information contained within this body of literature to be relevant to the key question and therefore worthy of inclusion, particularly given the lack of available primary research studies directly relating to transition in children and young people with epilepsy.

8.3 The process of transition

A Cochrane review on the transition of care for adolescents from paediatric services to adult health services focused on a range of patients aged 16–18 years with chronic conditions including cystic fibrosis, inflammatory bowel disease, type 1 diabetes, heart disease and spina bifida.²⁴² Children and young people with epilepsy were not included in this review and all studies excluded participants with intellectual disability or cognitive impairment. The results may however be transferable to children and young people with epilepsy.

This Cochrane review concluded that when using a one-to-one meeting with an experienced nurse or a technological web-based/short messaging service (SMS) educational intervention some young people were more knowledgeable regarding self care. There was little or no effect on health status, QoL, well-being or rates of transfer. However, the supporting evidence was limited, so no firm conclusions could be made.

A mixed-methods systematic review of five intervention studies, four quantitative studies and 10 qualitative studies on the knowledge and information needs of young people with epilepsy and their parents (13- to 19-year-olds within the UK and other European countries) was identified.²³⁹ It was not possible to grade this review but it was well conducted, using appropriate methodology and detailed reporting. The studies included varied in the quality of reporting but none had a fatal flaw (threshold for exclusion set by the authors). Three propositions were made based on a narrative synthesis:

- age-appropriate psycho-educational programmes may increase medical knowledge and improve QoL
- educating parents about epilepsy enables parents to advocate for their child, and
- education makes parents realise the gaps in their knowledge, motivating them to seek further information.

A further overarching narrative synthesis resulted in a list of critical success factors for information exchange for 13- to 19-year-olds with epilepsy (that is, around the time of transition to adult services):

- accessible age- and gender-appropriate self care and lifestyle management information
- engaging methods of information provision (a variety of types and age-appropriate formats)
- active facilitation by healthcare professionals, including around sensitive topics
- introducing information in the clinic at staged and regular intervals during teenage years
- active ongoing engagement and follow-up
- building rapport by seeing the same healthcare professionals
- awareness that healthcare professionals can be barriers to positive information exchange
- opportunities to talk without parents being present
- addressing ongoing information, advice and support needs of parents
- awareness that some young people require ongoing support and repeated information provision

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- engagement with young people to inform service delivery/organisation of care
- regular and meaningful review of the effectiveness of services
- use of information sources provided by epilepsy charities.

This mixed-methods review also identified that the perceptions of young people and their parents were that the healthcare workers were only primarily interested in the information they required rather than the information the parents/young people needed or wanted and that this stopped young people from being honest about what they were truly doing or wanted to question as it may not be the agenda of the healthcare professional.²³⁹

Both reviews are limited due to the lack of studies meeting the inclusion criteria, but they do suggest that a structured transition may be superior to unstructured transition for young people and parents or caregivers.^{239,242} Sufficient information needs to be provided regarding condition and lifestyle issues both for parents or caregivers and the young people themselves. Practical lifestyle advice should be given regarding adult life, such as how to make an appointment, order a prescription, collect medication, names of doctors involved in their care and how long these processes take, as well as advice regarding sexual health, drugs and driving.

The descriptive article described the development, implementation and evaluation of a nurse-led adolescent epilepsy transition clinic in Alberta, Canada. It included young people with epilepsy, aged 16-18 years, and their parents/caregivers.²³⁸ Transition in Canada was driven by a set discharge time to adult services rather than a 'ready to move' timeline, similar to Scotland. The authors describe developmental, lifestyle and education needs and condition management education needs and also addressed the needs of those with cognitive delay on an individual basis and included the needs of parents/carers. They evaluated the clinic's effectiveness at different timepoints: at the end of the transition clinic appointment and another 2-3 months after the young person had been seen by the adult epilepsy specialist.

High quality

A planned educational intervention covering the differences between adult and paediatric care and providing education regarding lifestyle and self management of health and epilepsy for both young people and their parents or carers can promote a successful handover to adult care, lessen fear and anxiety and empower independence. Such interventions could be nurse led within an adult facility using an adult services nurse and the paediatric nurse to deliver the intervention prior to handover to an adult services consultant.²³⁸ A transition clinic reduces anxiety about transition, and both patients and caregivers are more prepared to move to adult services.

High quality

All of the studies advocate the use of a planned educational intervention over time and information to be repeated over time.^{238,239,242}

One scoping review was identified with separate qualitative and quantitative syntheses on transition of adolescents with juvenile idiopathic arthritis or epilepsy.²⁴⁵ Although it was not possible to formally grade this scoping review, its conduct is in keeping with recognised scoping review methodology. Methodological quality of the included studies was not reported, but this is not unusual for scoping reviews. Eight qualitative studies were included, two of which focused on epilepsy. Twenty-three quantitative studies were included, nine on neurology and six specifically on epilepsy. This included literature relating to young people and their families. From the qualitative studies within this review it was identified that communication, continuity and capability are important aspects of transition. From the quantitative studies the barriers identified for healthcare providers were lack of information and education or training for children, young people and parents, and lack of information about the adult specialist. Facilitators identified were preparation, longer follow-up by the same paediatric neurologist, staff availability, transfer after the age of 18, stable medical condition, individualised approach and a transition appointment.

A narrative review of 49 articles, ranging from primary research studies to reviews and opinion

articles, highlighted the lack of evidence on the effectiveness of transfer processes, although they are accepted as beneficial. The risk of psychosocial problems during transition from paediatric to adult care is also highlighted because intellectual disability, and behavioural and psychiatric disorders are more common in children with epilepsy, so developmental maturity, not age, should determine the process of transition to adulthood.²⁴⁰

R | **Paediatric services providing care to children and young people should consider the use of a planned, structured, educational approach directed at both patients and carers, to help prepare young people with epilepsy for the move to adult healthcare services.**

This could include:

- educating both parents and young people on epilepsy
- education regarding lifestyle management and self management of health, for example how to make an appointment, order a prescription, know the names of the doctors involved in their care, as well as age-appropriate advice regarding sexual health, drugs and driving
- gender-appropriate advice, for example contraception whilst on AEDs
- one-to-one meetings with a healthcare professional/specialist nurse
- direction to web-based resources following a one-to-one conversation, with transition and specific condition advice
- an explanation of the differences between adult and paediatric care.

And ideally would:

- be individualised to the young person's needs and preferences
- be coordinated between paediatric and adult services
- include regular and meaningful review of the effectiveness of services.

✓ | Transition would ideally be followed up jointly by paediatric and adult health services over a longer time period while the young person is within adult healthcare services.

✓ | Transition would ideally be measurable and evaluated before and after handover to adult services.

9 Mortality

Children with epilepsy have a higher mortality rate than the general population, with standardised mortality rates of 2.61 or 3.51 deaths per 1,000 person-years.^{246,247} Those who died young either had neurological impairment or died from epilepsy-related conditions; later deaths often followed non-epilepsy-related conditions. Most deaths in children with epilepsy are not seizure related.²⁴⁸

Causes of death include complications of seizures, for example aspiration during seizures, status epilepticus, accidental deaths (including drowning), secondary to mental health issues, suicide and due to an underlying aetiology (neurodegenerative conditions, brain tumour and shunt malfunction), as well as SUDEP.^{248,249} Every effort should be made to reduce mortality by identifying and managing the risks. It is important to provide families with information on the risks and safety issues associated with seizures in a child or young person diagnosed with epilepsy as close to diagnosis as possible.²⁵⁰ These issues should be revisited periodically and additionally when identified risks of morbidity and mortality are assessed to be higher. Written information should also be provided to reinforce verbal information and signpost to sources of further advice and information. Further information on safety is available from SPEN and in SIGN guideline 143 on Diagnosis and management of epilepsy in adults (*see section 10*).^{2,251}

Several potentially modifiable factors have been associated with reducing the risk of morbidity or mortality associated with epilepsy, including adhering to and optimising seizure control, by exploring all treatment options and following nationally agreed seizure pathways to ensure timely assessment and intervention (for example, seizure pathways from SPEN).²⁵² Examples of modifiable risk factors include giving parents general safety advice and specific safety advice on bathing, water sports and heights.²⁵¹

The use of teenage clinics is essential to share information about the impact of risk behaviours, such as drug and alcohol use, on seizure control.² This medium can also be used to identify young people more vulnerable to mental illness, although this is not exclusive to the teenage population (*see section 7*).

Many parents worry about their child having seizures through the night and not being there for them, but do not articulate this concern. For some children the risk of nocturnal seizures is low and for others much higher. These risks should be discussed with parents routinely so that appropriate information can be given with regard to safety and monitoring (*see section 9.3*).

- ✓ Information should be provided to children/young people and families/carers on the risks and safety issues associated with a diagnosis of epilepsy, as near to diagnosis as possible.
- ✓ Risks (including SUDEP) and safety issues should be discussed periodically with children/young people and families/carers at follow-up visits with healthcare professionals, and additionally when an identified risk of morbidity and/or mortality is assessed to be higher.

6 What matters to young people and their families

“I think it is important to be told the likelihood of SUDEP according to the type of seizures someone has. There should be a chance to be able to ask questions and have enough time to talk about it in a relaxed way without being rushed.”

“At no point from her diagnosis to her death was SUDEP ever mentioned.”

9.1 Sudden unexpected death in epilepsy

The focus on SUDEP within this guideline arose from a person-centered approach and the concern voiced by patient representatives and families.

Of all the causes of premature mortality in children and young people with epilepsy, SUDEP commands the most attention, because of its sudden appearance and devastating aftermath. It can be defined as 'sudden, unexpected, non-traumatic and non-drowning death in an individual with epilepsy, with or without evidence of a seizure, and excluding documented status epilepticus, where post mortem examination does not reveal a toxicological or anatomic cause for death'.²⁵³ Diagnosis of SUDEP is difficult, as a post mortem may not take place after every epilepsy death.²⁵⁴

The incidence of SUDEP varies across populations, and depending on the severity of the epilepsy, with children and young people with more complicated or difficult-to-control epilepsies being at higher risk.²⁴⁸

A population study in children with epilepsy in Canada (mean age 7.3 years (SD 5.0), age range 6 months to 15 years) reported an overall incidence of SUDEP as 1.17 per 1,000 person-years (95% CI 0.68 to 1.88).²⁵⁵ An American practice guideline found SUDEP risk in children with epilepsy (aged 0–17 years) to be 0.22 per 1,000 patient-years (95% CI 0.16 to 0.31) and 1.2 per 1,000 patient years in adults (95% CI 0.64 to 2.32).²⁵⁶ In a Swedish population (median 46 years, age range 0–106 years) the incidence of definite/probable SUDEP was 1.20 per 1,000 person-years and was higher in men (1.41) than in women (0.96). SUDEP incidence at ages <16, 16–50 and >50 years were 1.11, 1.13 and 1.29 per 1,000 person-years, respectively.²⁵⁷ The causes of SUDEP are not well understood.²⁵⁸

9.2 When, where and how discussions about SUDEP should take place

During the consultation process for this guideline, one of the issues raised from the patient group was around timings of discussions around SUDEP.

A gap in the literature was identified after a systematic search, so a mixed-methods systematic review was conducted.²⁵⁹ The Scottish Centre for Evidence-based Multi-professional Practice: A Joanna Briggs Institute Centre of Excellence, in partnership with SIGN and the guideline group, undertook this review on the views and experiences of children and young people with epilepsy, their family members/carers and clinicians, on conversations between healthcare professionals and patients/family members about the possibility of SUDEP in children and young people with epilepsy. This review followed JBI methodology for conducting mixed-methods reviews²⁶⁰ and included five cross-sectional studies, four qualitative studies and one opinion piece. Studies included in the review were moderate to high quality. Thirty-four review findings, organised in five categories, resulted in two overall integrated findings:

- caregivers, and where appropriate children and young people with epilepsy, should be provided with information on SUDEP and how it relates to them, and
- SUDEP information should be delivered face to face with supporting written information, by a suitably qualified healthcare professional with whom the caregiver/child feels comfortable, at an appropriate time at or close to diagnosis.

In addition to the mixed-methods review, one mixed-methods survey and two qualitative studies were identified.^{261–263} The quality of all three studies was assessed using the JBI critical appraisal tool for qualitative studies.²⁴⁴ The ConQual method was applied to establish the dependability and credibility of the studies, each study was rated (possible ratings high, moderate, low, very low).²⁶⁴ These ratings are for qualitative studies only and are not in comparison to other (quantitative) study designs.

All three qualitative studies were rated as moderate (dependability) with indisputable findings. The first surveyed 101 epilepsy-bereaved families and friends,²⁶¹ another explored discussion of SUDEP in focus groups with healthcare professionals,²⁶⁰ and the third interviewed 27 relatives bereaved by SUDEP.^{261–263}

All three studies were conducted in non-UK settings (Australia, USA, Canada). In the qualitative studies it is not clear whether families of children and young people who experienced SUDEP were included in the sample, and in the survey, although there were families of deceased children and young people (the youngest aged 7 years), the mean age was 32 years (range 7–84 years), suggesting that many were adults.

Families and friends in two studies were clear in their recommendation that information on SUDEP should be provided at the time of, or close after, a diagnosis of epilepsy being made.^{261,263} The healthcare professionals in the other study did not reach consensus, providing reasons for and against discussing SUDEP with patients and families.²⁶²

Overall it was agreed that discussion of SUDEP should be face to face and with a clinician, with written materials to support.^{262,263} Families and friends want to know what SUDEP is, the risk factors and preventive measures that can be taken, and where to find sources of support.^{261,263} Healthcare professionals felt that discussions and written materials should be standardised but tailored to each individual's circumstances.²⁶²

R | **At or around the time of diagnosis healthcare professionals caring for children and young people with epilepsy should:**

- **have a face-to-face discussion about SUDEP with families/carers and young people**
- **provide written information to reinforce information provided face to face.**

The information should describe:

- **what SUDEP is**
- **the risk factors associated with SUDEP and measures that can be taken to reduce risk**
- **where to find further information and sources of support.**

✓ | Allow sufficient time to discuss the availability of counselling/specialist support, both from healthcare professionals and support groups for parents, family or carers who have been bereaved.

9.3 Monitoring and SUDEP

Most people achieve seizure freedom with one or two antiepileptic medications, thus, theoretically, negating the need to monitor for seizures. Twenty to thirty per cent of people have uncontrolled seizures and have a higher mortality ratio attributed to them because of the refractory nature of their epilepsy. Seizures are variable and unpredictable in frequency. Eight per cent of people are thought to have daily seizures.²⁶⁵

Approximately 20% of patients experience seizures only during the night, approximately 40% only during the day and 35% during the day and night.²⁶⁶ In certain epilepsy syndromes, the occurrence of seizures is strongly related to sleep or awakening.²⁶⁶

The mechanisms underlying SUDEP are still not well understood.²⁵⁸ Despite multimodal monitoring and the higher level of supervision present in a hospital setting SUDEP can still occur.²⁶⁷

A Cochrane review on the treatments for prevention of SUDEP identified only one observational case-control study (n=154) in an adult population.²⁶⁸ It is therefore difficult to draw conclusions from this for children with epilepsy. } 2+

A survey of patient and caregivers' views on listening devices (n=92, 27 paediatric) assessed their degree of concern for undetected seizures. This showed the impact of this concern on sleep and diurnal functioning was moderate, and that some indicated their preferred time for use of a detection device was when sleeping at night. There was generally significant interest in using seizure detection devices.²⁶⁹] 3

Using a listening device may allow a parent/caregiver some level of comfort having done what they could to keep their child safe, even if death still occurs. Many seizure detection/monitoring devices are available for children and young people with epilepsy, but there is no robust clinical evidence to support their use for preventing SUDEP. Monitoring devices may not totally eradicate the chances of SUDEP as there are many case reports of sudden death following sudden unresponsiveness without motor manifestations.²⁷⁰ More controlled studies are required.] 2+

Issues to consider when discussing monitoring with families include seizure type, seizure control, the pros and cons of monitoring, whether or not the parent or carers wish to monitor, clarification of parents' expectations of monitoring devices and advice about the most suitable options for monitoring tailored to the family's needs. If there is a risk of SUDEP, the use of listening devices, nocturnal supervision or sharing the same bedroom could be discussed with the young person and their family or carers on a case-by-case basis, with the understanding that monitoring may not prevent SUDEP or mortality.²⁵⁶ Healthcare professionals should support the individual family's approach to alleviate their anxiety.] 4

- ✓ | If there is a risk of SUDEP, healthcare professionals should discuss the advantages and disadvantages of the use of listening devices, nocturnal supervision or sharing the same bedroom with young people, their families and carers.

10 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing epilepsy with children and young people, parents and carers and in guiding the production of locally produced information materials.

10.1 Publications from SIGN

SIGN patient versions of guidelines are documents that ‘translate’ guideline recommendations and their rationales, originally developed for healthcare professionals, into a form that is more easily understood and used by patients and the public. They are intended to:

- help patients and carers understand what the latest evidence supports around diagnosis, treatment and self care
- empower patients to participate fully in decisions around management of their condition in discussion with healthcare professionals
- highlight to patients where there are areas of uncertainty.

10.2 Advice and information on epilepsy

People with epilepsy and their carers have a need for clear, accurate and appropriate information and advice. Surveys have reported that up to 90% of patients want more information and felt that they had received little advice about the cause of epilepsy, effects and interactions of drugs and the avoidance of potentially dangerous situations.^{271,272} Conversely, it is known that patients can forget or fail to take in much of what they are told during clinic visits, so written information, helpline telephone numbers and contact details of voluntary organisations should be given to all patients and carers. Children, young people and their families should be empowered to manage their condition as well as possible and information should be tailored to the individual’s needs.

Almost as important as the quality of information is the manner in which it is given. Many patients prefer talking to an epilepsy nurse or someone from a voluntary organisation with whom they feel more at ease.²⁷³ Information should be age appropriate and may have to be repeated on different occasions to ensure understanding. Patients with epilepsy place great importance on having a doctor who is approachable, communicative and knowledgeable, and on receiving adequate information about their condition.²⁷⁴

A general information leaflet should be offered to all patients at the time of diagnosis. Epilepsy checklists are available from support organisations (*see section 10.4*). Information for patients should be suited to their understanding, making adjustments for different developmental ages, gender, culture and the person’s stage of life.²⁷⁵

Guidelines for teachers and information booklets for preschool, primary and secondary school-aged children have been produced by Epilepsy Scotland. Training is offered in schools, colleges and universities; data relating to outcomes from such training is currently lacking.

In Scotland, 4% of the population is from an ethnic minority background. Language, cultural issues, stigma and belief systems of people from black and minority ethnic groups may have an impact on an individual’s access to information about their condition, their treatment and care, adherence to medication, and ability to cope with and manage their condition. Research is needed to identify any real or perceived barriers relating to diagnosis, receipt of information about epilepsy and treatment for epilepsy to allow healthcare professionals to take these into consideration when working with patients from minority ethnic groups.

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- ✓ Information should be given in an appropriate manner with sufficient time to answer questions.
- ✓ How to access an epilepsy specialist nurse, including contact details, should be included with any information given.
- ✓ Information should be age appropriate, repeated over time and reinforced to ensure understanding.
- ✓ Patients should be given information to take home in the most suitable format, for example leaflets, factsheets or specialised material for people with learning disability, making adjustments for age and for patients from black and minority ethnic groups. All information and literature provided should be subject to regular review.
- ✓ Healthcare professionals should be aware that the cultural differences and belief systems of patients from black and minority ethnic groups may have an impact on levels of understanding, management of the condition and adherence to medication and treatment.

10.3 Checklist for provision of information

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

General epilepsy information	Possible psychological consequences
<p>Explain the following to young people and their families/carers:</p> <ul style="list-style-type: none"> • what epilepsy is • probable cause, if known • investigative procedures • classification of seizures • syndrome, if known • prognosis • genetics, if appropriate • sudden unexpected death in epilepsy (SUDEP) • non-drug management as appropriate, eg ketogenic diet, surgery • how to access appropriate services • reviews, with which healthcare professionals and when, eg GP, consultant, nurse specialist. 	<p>Allow sufficient time to discuss the following issues:</p> <ul style="list-style-type: none"> • perceived stigma and how patients view their epilepsy • memory issues • mood/anxiety disorders • maintaining mental well-being • self esteem • availability of counselling and support from healthcare professionals and support groups for young people with epilepsy • availability of counselling/specialist support both from healthcare professionals and support groups for parents/families/carers who have been bereaved by SUDEP.

Antiepileptic drugs	Lifestyle
<p>Discuss treatment options with young people and their families/carers and offer written and verbal information on:</p> <ul style="list-style-type: none"> • choice of drug • efficacy • adverse effects/side effects • adherence, including how it should be taken • dosage • drug interactions • action to take in case of missed or delayed medication • importance of consistency. 	<p>Mention and discuss (if applicable) the following with patients/young people and their families/carers/parents:</p> <ul style="list-style-type: none"> • choices/decisions/possible lifestyle changes • safety in the home • leisure/play/sport, including water safety • education (eg Epilepsy Action Scotland guidelines for teachers and also from Young Epilepsy) • relationships/social life/support from family and friends and support groups • risk management (including risk of SUDEP/death) and risk management tools • alcohol advice • employment • welfare benefits • driving regulations • entitlement to a free bus pass.
First aid	Issues for female adolescents/young people
<p>Ensure the young person's relatives are aware of the following:</p> <ul style="list-style-type: none"> • general first aid • when to take action and when to engage with health services • when to call an ambulance. 	<p>The following issues should be discussed with female adolescents/young people and sufficient time given for them to ask questions:</p> <ul style="list-style-type: none"> • contraception • planning pregnancy • pregnancy and breastfeeding.
Seizure triggers	Transition
<p>Ensure young people and their families/carers are aware that the following may trigger seizures:</p> <ul style="list-style-type: none"> • lack of sleep • alcohol and recreational drugs • stress • photosensitivity. 	<p>When moving from child to adult services, ensure the young people and their families/carers are aware of the following:</p> <ul style="list-style-type: none"> • what will happen • when will this happen • who will be involved and who will provide support, eg epilepsy nurse specialist.

Format

Any information offered should be appropriate to the patient's level of understanding (eg websites, audio, pictorial aids) and language specific.

The following should be considered:

- literacy level
- learning disability
- visual impairment
- hearing difficulties
- the need for interpreter services for those whose first language is not English.

Information should be repeated at each appointment.

Sources of support

Ensure patients and carers (including children) are aware of where they can go to for further information and support (*see section 10.4*).

10.4 Sources of further information

10.4.1 Sources of information specific to epilepsy

The Daisy Garland

Units A1 and A2, Dart Marine Park, Steamer Quay Road, Totnes TQ9 5AL

Tel: 01803 847999

Email: info@thedaisygarland.org.uk

www.thedaisygarland.org.uk

The Daisy Garland is a family-run, national, UK registered charity that aims to offer help and support to those whose lives are touched by drug-resistant epilepsy.

Epilepsy Action

New Anstey House, Gate Way Drive, Yeadon, Leeds LS19 7XY

Helpline: 0808 800 5050

Email: helpline@epilepsy.org.uk

www.epilepsy.org.uk

The aim of Epilepsy Action is to raise awareness about epilepsy and bring about permanent change for the social and medical benefit of people with epilepsy.

Epilepsy Connections

Suites 129-134, Baltic Chambers, 50 Wellington Street, Glasgow G2 6HJ

Tel: 0141 248 4125

Email: info@epilepsyconnections.org.uk

www.epilepsyconnections.org.uk

Epilepsy Connections provides information, advice and support to people with epilepsy and their carers on a one-to-one basis and to families and groups in the NHS Greater Glasgow and Clyde and NHS Forth Valley areas. Services include self-management support; advice about managing epilepsy at home, school, university or work; advice about housing, benefits, travel and balancing risk and safety; formal and informal counselling; befriending for adults; social activities for adults and children; epilepsy and memory workshops, epilepsy awareness and rescue medication training for paid and unpaid carers; epilepsy awareness sessions for students and teachers in schools and colleges. Information and advice is available in English, Urdu, Punjabi, Cantonese and Polish.

Epilepsy Consortium Scotland

Email: enquiries@epilepsyconsortiumscotland.co.uk
www.epilepsyconsortiumscotland.co.uk

The Consortium is a collaboration of organisations and individuals in Scotland coming together to highlight epilepsy issues. This partnership has been developed to inform Scottish Government and other policy makers about areas of concern around health, social care and related public policy matters.

Epilepsy Scotland

48 Govan Road, Glasgow G51 1JL
Helpline: 0808 800 2200
Email: contact@epilepsyscotland.org.uk
www.epilepsyscotland.org.uk

Epilepsy Scotland is the national organisation representing people living with epilepsy in Scotland. Services include the Wellbeing Service, which includes counselling, outreach and group-based support; youth groups, a welfare rights service; campaigning and lobbying; policy; the provision of information and training. The contact team provide guidance, support and information on the telephone, via social media, email or text and in different languages via a telephone interpretation service.

Epilepsy Society

Chesham Lane, Chalfont St Peter, Buckinghamshire SL9 0RJ
Helpline: 01494 601400
Email: enquiries@epilepsysociety.org.uk
www.epilepsysociety.org.uk

The Epilepsy Society provides epilepsy services throughout the UK. Through research, awareness campaigns, information resources and expert care, they work for everyone affected by epilepsy in the UK.

Joint Epilepsy Council of the UK and Ireland

Tel: 01943 871 852
Email: Tommy@jointepilepsycouncil.org.uk
www.jointepilepsycouncil.org.uk

This Council represents the united voice of epilepsy in the UK and Ireland. It presents evidence-based views on the need for improved epilepsy services, and influences decision makers in health, social care and education.

Matthew's Friends

Matthew's Friends Charity and Clinics, St. Piers Lane, Lingfield, Surrey RH7 6PW
Tel: 01342 836571
Email: enq@matthewsfriends.org
www.matthewsfriends.org

Matthew's Friends are specialists in medical ketogenic dietary therapies for drug-resistant epilepsy and other neurological and metabolic conditions. They cover all aspects of ketogenic therapy for both children and adults, providing support services, training and education for both families and professionals. They work with the European Reference network for Rare and Complex Epilepsies and the international consensus group for Ketogenic Therapy.

Quarriers Epilepsy Services (Scottish Epilepsy Centre and Epilepsy Fieldwork Services)

The William Quarrier Scottish Epilepsy Centre, 20 St Kenneth Drive, Glasgow G51 4QD

Tel: 0141 445 7750

Email: Scottishepilepsycentre@quarriers.org.uk

www.scottishepilepsycentre.org.uk

The William Quarrier Scottish Epilepsy Centre is an independent hospital run by Quarriers charity. It offers a multidisciplinary in-patient assessment and treatment to people with complex diagnostic and treatment needs, as well as outpatient and telemedicine clinics.

Scottish Paediatric Epilepsy Network

www.spen.scot.nhs.uk

The Scottish Paediatric Epilepsy Network (SPEN) is a national managed clinical network. SPEN brings together people involved in paediatric epilepsy from all over Scotland to agree the way forward for epilepsy services. The SPEN membership includes patients, parents and carers, paediatric neurologists, epilepsy nurse specialists, paediatricians, voluntary sector organisations, neurophysiologists, GPs, dietitians, NHS managers and social workers.

The aims of SPEN are:

- to promote the delivery of high-quality care to children and adolescents with epilepsy in Scotland
- to be patient centred and deliver seamless care between organisations and professional groups involved in epilepsy care
- to contribute to the setting of standards for epilepsy care and to audit the care provided
- to ensure equity of services for all children and young people with epilepsy wherever they live in Scotland.

SUDEP Action

18 Newbury Street, Wantage, Oxfordshire OX12 8DA

Support line: 01235 772852

Email: info@sudep.org

www.sudep.org

SUDEP Action aims to increase awareness of epilepsy risks and tackle all epilepsy-related deaths, including sudden unexpected death in epilepsy. The charity works alongside, and supports, those whose loved ones have died suddenly from epilepsy. Services include bereavement support, counselling and help with understanding the inquest process. Free tools, information and resources are provided to people with epilepsy, their families and clinicians.

Young Epilepsy

St Piers Lane, Lingfield, Surrey RH7 6PW

Helpline: 01342 831342

Email: helpline@youngepilepsy.org.uk

www.youngepilepsy.org.uk

Young Epilepsy is a UK charity that provides diagnosis, assessment and rehabilitation for children and young people with epilepsy. Its specialist services include a school, college and residential services providing education and healthcare. The charity also provides a range of support and information for parents, children and young people, as well as training for professionals.

10.4.2 Other sources of information

Citizens Advice Scotland

www.cas.org.uk

The Citizens Advice Bureau can give free, confidential, impartial and independent advice and information on a wide range of subjects: benefits, debt and money advice, consumer issues, work-related problems and housing.

NHS 24

Tel: Freephone 111

www.nhs24.scot

NHS 24 is an online and out-of-hours phone service providing the Scottish people with access to health advice and information 24 hours a day, 365 days a year.

NHS Inform

www.nhsinform.scot

Scotland's national health information service provides patient information on medical conditions, self-help advice and a directory of local support groups.

11 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

11.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS board, including health and care partnerships, and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

11.2 Auditing current practice

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and MDT working.

SPEN will work with NHS boards and other stakeholders nationally and locally around data gathering ideally at baseline before and after publication of this guideline. SPEN will look at the feasibility of collection and collation of the data, described in Table 2, at baseline and annually, and use this to inform the need for further resources.

11.3 Resource implications of key recommendations

No recommendations are considered likely to reach the £5 million threshold, which warrants resource impact analysis.

Implementation, audit and potential resource implications identified by the guideline development group are listed in Table 2.

Table 2: Implementation, audit and potential resource implications of the recommendations

Section	Recommendations/ good practice points	Implementation and audit	Resource requirements/other considerations/actions
4	Investigative procedures		
4.1.2	R If a clinical diagnosis of epilepsy has been made, EEG is recommended for further classification of epilepsy. If standard EEG is normal, a second-line EEG that captures sleep should be carried out. This could be an ambulatory, sleep-deprived or melatonin-induced sleep EEG.	<p>Consultants should consider and decide on the use of melatonin, and prescribe melatonin, for the sleep EEG, as appropriate.</p> <p>The clinical physiologist doing the EEG is not qualified to administer medication, but will advise on the timing of when the melatonin should be given to the child.</p> <p>EEG departments to audit diagnostic yield of second-line sleep EEG investigations in confirming or refuting a diagnosis of epilepsy or assisting with syndromic diagnosis, where the standard EEG is normal.</p>	<p>Most EEG departments will already be equipped to provide this service.</p> <p>EEG departments should have a protocol for the administration of melatonin for sleep induction. Melatonin-induced sleep EEGs require more clinical neurophysiology technician time to obtain and interpret.</p> <p>SPEN will consider the resource(s) required to audit/collate this at a national level alongside other priorities for the network.</p>
4.1.2	GPP Where sleep deprivation is used, departments should have an established sleep-deprivation protocol, with the age of the child taken into consideration.	NHS board governance groups and consultants/clinical physiologists should ensure that departments have a sleep deprivation protocol and that this is followed by all staff involved.	<p>The use of sleep-deprivation EEG currently varies across Scotland.</p> <p>SPEN will consider the resource(s) required to audit/collate this at a national level, alongside other priorities for the network.</p>
4.2.3	R In children with drug-resistant focal epilepsy, 3-T MRI should be considered if 1.5-T MRI does not detect and define a lesion.	<p>3-T MRI facilities should be provided in tertiary centres with appropriate expertise from radiology.</p> <p>Audit the clinical practice of carrying out 3-T MRI as per the recommendation to identify any barriers (eg waiting time, access and referral to specialist tertiary centres).</p>	<p>3-T MRI and other appropriate facilities (general anaesthesia and expertise within the radiology department).</p> <p>As 3-T MRI is provided in only four centres across Scotland, some children and families will need to travel to their nearest centre.</p> <p>Increased workload in tertiary centres and the use of day-case admissions, anaesthetics and resources in relation to hospital utilisation.</p>

Section	Recommendations/ good practice points	Implementation and audit	Resource requirements/other considerations/actions
6	Non-pharmacological management		
6.1.1	<p>R A ketogenic diet should be offered as a treatment option in children with drug-resistant epilepsy.</p> <p>R A ketogenic diet should be tried for at least 3 months in children with drug-resistant epilepsy to assess efficacy, with consideration of continuation of the ketogenic diet based on risk and benefits at each visit and after 2 years of continuous use.</p>	<p>SPEN will explore the feasibility of working with healthcare professionals, NHS boards, charities and other stakeholders locally and nationally to evaluate service need, and access and explore potential solutions.</p> <p>Audit would ideally include:</p> <ul style="list-style-type: none"> • number of new referrals for ketogenic diet • number of infants referred for ketogenic diet • number of patients staying on the ketogenic diet. <p>A more intensive audit could include:</p> <ul style="list-style-type: none"> • type of epilepsy • type of diet • the response and any adverse effects • the duration over which the diet was implemented. 	<p>If more children were referred for implementation of the ketogenic diet there is the potential that more dietetic time would be required and further recruitment of dietitians may be necessary.</p> <p>Aside from prescribed blood ketone testing strips for patients on the ketogenic diet, trends in the availability of prescribable food items may have a resource impact that is hard to predict and will partly depend on uptake by the families of children and young people with epilepsy.</p> <p>Ketogenic dietitians are funded or partially funded by charities in some parts of Scotland. Sustained funding is required to maintain ketogenic dietitians to implement the SIGN guidelines.</p> <p>SPEN will consider the resource(s) required to audit/collate referrals for a ketogenic diet at a national level alongside other priorities for the network.</p>
6.1.2	<p>R A ketogenic diet is recommended in children with glucose transporter 1 deficiency syndrome and should be started as soon as possible after diagnosis.</p>	<p>As 6.1.1</p> <p>Audit would ideally include:</p> <ul style="list-style-type: none"> • incidence of new diagnoses of individuals with glut1D syndrome. 	<p>If more children are diagnosed with glut1D syndrome this would require more dietetic time, especially as these patients ideally stay on a ketogenic diet as lifelong treatment.</p> <p>Funding for young people transitioning to adult services, especially patients with glut1D syndrome, as this is potentially a lifelong treatment.</p> <p>SPEN will consider the resource(s) required to audit/collate referrals for a ketogenic diet at a national level alongside other priorities for the network.</p>

6.2	<p>R Children with drug-resistant epilepsy who fulfil referral criteria for assessment for surgery should be identified early.</p>	<p>Audit would ideally include:</p> <ul style="list-style-type: none"> • number of referrals for surgical evaluation • recording of complexity of cases and additional staff resources, eg staff time spent on these cases, invasive monitoring • outcomes from surgery, eg seizure freedom, QoL, educational attainment, reduced costs of AEDs, readmissions • audit of resources, eg staff time • number of children undergoing surgical assessment referred to each centre for neuropsychological assessment. <p>The national paediatric epilepsy surgery service is commissioned through NHS National Services Division, who, as commissioners, would need to consider any resource implications of implementation.</p>	<p>The number of referrals for surgical assessment are less than expected from epidemiology figures. Increased knowledge of surgery, including dissemination of this guideline, is likely to lead to an increase in the number of referrals for surgical assessment and the requirement for resources to respond to this. Currently surgery is practised in tertiary centres and considered on a case-by-case basis, through a nationally-funded service (SPESS).</p> <p>The workload and the complexity of cases will increase as more children are referred for treatment for drug-resistant epilepsy.</p> <p>The resource required to support this includes:</p> <ul style="list-style-type: none"> • MDT specialists: epilepsy nurse specialists, paediatric neuroradiologists, neurophysiologists, clinical psychologists, paediatric neurology consultants • availability of investigative procedures needed before surgery, eg EEG, 3-T MRI with general anaesthetic • availability of theatre time • availability of beds • rehabilitation/community services for support postoperative and postdischarge support. <p>SPEN will explore the feasibility of working with healthcare professionals, NHS boards, charities and other stakeholders locally and nationally to evaluate service need, and access and explore potential solutions.</p>
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Section	Recommendations/ good practice points	Implementation and audit	Resource requirements/other considerations/actions
7	Cognitive, developmental and psychiatric comorbidities		
7.3	<p>R Healthcare professionals should routinely enquire about depression and anxiety symptoms in all children and young people with epilepsy.</p>	<p>Epilepsy health professionals (paediatric neurologist/ paediatrician/epilepsy specialist nurse) should enquire about depression and anxiety symptoms at each clinical contact. Where concerns are identified professionals should consider the use of standardised screening tools, which could indicate raised levels of psychological distress.</p> <p>This should be recorded in the child's notes along with screening questionnaire responses, any recommendations made and actions taken.</p> <p>Where available, epilepsy health professionals can liaise with their local paediatric psychology provision where a child or young person with epilepsy presents with milder mental health concerns. Paediatric psychology services can provide education and information (including self-help resources) as well as direct input where required.</p> <p>Epilepsy health professionals should refer to the local child and adolescent mental health services (CAMHS) when presentations are consistent with more severe or complex mental health disorders (including anxiety and depression), as they may require more specialist risk assessment and multidisciplinary input, including psychiatry.</p>	<p>More time for health professionals to ask about mental health issues and use screening questionnaires.</p> <p>Access to psychologists with knowledge of epilepsy to offer psychological consultation will be required for epilepsy services. There is a need for psychology staff provision to provide consultations in paediatric epilepsy services and psychological input for those presenting with mild to moderate anxiety and depression which may not meet criteria for CAMHS. Currently not all regions have paediatric psychology input dedicated to epilepsy services.</p> <p>In regions without paediatric psychology/neuropsychology input this would present a gap in service delivery and a potential inequity in service provision.</p> <p>SPEN will explore the feasibility of working with healthcare professionals and NHS boards locally and nationally to evaluate service need/access and explore potential solutions to ensure equity of provision.</p> <p>SPEN will consider the resource(s) required to audit/collate referrals as detailed above in all children and young people with epilepsy at a national level alongside other priorities for the network.</p>

		<p>Epilepsy health professionals should refer to the local CAMHS when presentations are consistent with more severe or complex mental health disorders (including anxiety and depression), as they may require more specialist risk assessment and multidisciplinary input, including psychiatry.</p> <p>SPEN and the wider epilepsy community and charities should consider ways of raising awareness of mental health concerns in children and adolescents with epilepsy within education and community settings, so that 'at-risk' children and adolescents can be identified and supported in a timely fashion.</p> <p>Audit would ideally include:</p> <ul style="list-style-type: none">• number of children and young people with epilepsy screened as presenting with clinically significant levels of depression/anxiety symptoms• number of referrals or consultations of children and adolescents with epilepsy and mild/moderate anxiety/depression referred to consultations with paediatric psychology services (where available)• number of referrals of children and adolescents with epilepsy and severe anxiety/depression to local CAMHS• number of referrals of children and young people with epilepsy not accepted for psychology/CAMHS input to identify unmet need in the service.	
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Section	Recommendations/ good practice points	Implementation and audit	Resource requirements/other considerations/actions
7.2.1	<p>R Healthcare professionals should be aware that all children and young people with epilepsy are at increased risk of cognitive and academic impairments, even those with epilepsies considered to be more benign or well controlled.</p> <p>GPP Healthcare and education professionals should seek information about the child or young person's cognitive function and educational attainment. At regular intervals educational attainment should be obtained (via school reports or curriculum-based assessments where possible).</p> <p>GPP Where there is evidence that a child with epilepsy is not making appropriate academic attainments or is presenting with difficulties in cognitive functioning healthcare professionals should first liaise with education professionals (including educational psychology and learning support staff) to discuss supports in place.</p>	<p>Epilepsy health professionals (paediatric neurologist/ paediatrician/epilepsy specialist nurse) should routinely ask parents/children and young people about academic progress and cognitive functioning (including memory, attention and language).</p> <p>Where concerns are raised about academic attainments, more detailed information could be obtained by asking parents to provide copies of school reports, outcomes from examinations or curriculum-based assessments.</p> <p>Details of the nature of academic progress and cognitive functioning across settings can also be obtained by health professionals (including epilepsy specialist nurses) who liaise with schools and attend formal review meetings including child's plan or 'team around the child' meetings. Learning support currently in place (including tailored interventions for learning and input from educational psychology) can also be identified by this route.</p> <p>This information should be recorded in the child or young person's clinic notes.</p>	<p>More time for health professionals to ask about cognitive functioning/ scholastic attainments and to collate and document reports, where available.</p> <p>More time required for health professionals (typically epilepsy specialist nurses) to attend review meetings where needed.</p> <p>Access to specialist neuropsychology services is not available across all regions. Even where services are available, resources are limited and therefore will accept only the more complex/ severe presentations.</p> <p>CAMHS and paediatric psychology services may not accept referrals for specialist assessment of cognitive/ scholastic functioning (in the absence of suspected intellectual disability).</p> <p>In regions without paediatric psychology/neuropsychology input this would present a gap in service delivery and a potential inequity in service provision.</p> <p>SPEN will explore the feasibility of working with healthcare professionals and NHS boards locally and nationally to evaluate service need/access and explore potential solutions to ensure equity of provision.</p> <p>SPEN will consider the resource(s) required to audit/collate referrals as detailed above in all children and young people with epilepsy at a national level alongside other priorities for the network.</p>

8	Transition		
8.3	<p>R Paediatric services providing care to children and young people should consider the use of a planned, structured, educational approach directed at both patients and carers, to help prepare young people with epilepsy for the move to adult healthcare services.</p> <p>This could include:</p> <ul style="list-style-type: none"> educating both parents and young people on epilepsy education regarding lifestyle management and self management of health, eg how to make an appointment, order a prescription, know the names of the doctors involved in their care, as well as age-appropriate advice regarding sexual health, drugs and driving gender-appropriate advice, eg contraception whilst on AEDs one-to-one meetings with healthcare professional/specialist nurse direction to web-based resources following a one-to-one conversation, with transition and specific condition advice an explanation of the differences between adult and paediatric care. <p>And ideally would:</p> <ul style="list-style-type: none"> be individualised to the young person's needs and preferences be coordinated between paediatric and adult services include regular and meaningful review of the effectiveness of services. 	<p>Governance and quality improvement oversight groups within NHS boards, for both adult and paediatric services, would ideally review and report on the service level delivery of transition/handover (as per the recommendation).</p> <p>Healthcare professionals (epilepsy specialist nurse, paediatric neurologist, paediatrician) should discuss and support transition (as per the recommendation) with the child/young person/caregiver to address their needs, provide appropriate information and advice and signpost to additional support networks and resources. This should be recorded in the child or young person's notes. Feedback from the child/young person/caregiver would ideally be recorded and addressed (if appropriate) in relation to their experience through transition, during handover to adult healthcare and post-handover, at follow-up visits.</p> <p>Audit would ideally include:</p> <ul style="list-style-type: none"> numbers within transition numbers of handover clinics rates of handover drop out/deterioration in seizure control after handover to adult healthcare. 	<p>There are currently eight NHS boards that have a transition/handover service (baseline). NHS boards without a service should consider how to provide a service for transition and handover as per the recommendation.</p> <p>SPEN will explore the feasibility of working with healthcare professionals and NHS boards locally and nationally to evaluate service need/access and explore potential solutions to ensure equity of provision.</p> <p>SPEN will consider the resource(s) required to audit/collate referrals as detailed above in all children and young people with epilepsy at a national level alongside other priorities for the network.</p>

Section	Recommendations/good practice points	Implementation and audit	Resource requirements/other considerations/actions
9	Mortality		
9.2	<p>R At or around the time of diagnosis healthcare professionals caring for children and young people with epilepsy should:</p> <ul style="list-style-type: none"> • have a face-to-face discussion about SUDEP with families/carers and young people • provide written information to reinforce information provided face to face. <p>The information should describe:</p> <ul style="list-style-type: none"> • what SUDEP is • the risk factors associated with SUDEP and measures that can be taken to reduce risk • where to find further information and sources of support. 	<p>Healthcare professionals (epilepsy specialist nurse, paediatric neurologist, paediatrician) should discuss SUDEP (as per the recommendation) with families/carers, provide appropriate information and advice and signpost to additional support networks and resources as appropriate.</p> <p>This should be recorded in the child or young person's notes.</p> <p>Audit of patient notes to evidence documentation of discussions.</p>	<p>A national Epilepsy 12 audit with standardised national data capture was explored and was considered not to be a feasible option for Scotland. SPEN may support with an audit system for Scotland.</p>

11.4 Additional advice to NHSScotland from the Scottish Medicines Consortium

Cannabidiol (Epidyolex®) is accepted for use as adjunctive therapy of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome, in conjunction with clobazam, for patients 2 years of age and older. This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower. This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting. (September 2020)

<https://www.scottishmedicines.org.uk/medicines-advice/cannabidiol-epidyolex-full-smc2262/>

<https://www.scottishmedicines.org.uk/medicines-advice/cannabidiol-epidyolex-full-smc2263/>

Eslicarbazepine acetate (Zebinix®) is accepted for restricted use within NHSScotland as adjunctive therapy in adolescents and children aged above 6 years with partial-onset seizures with or without secondary generalisation. Restriction for patients with highly refractory epilepsy who have been heavily pretreated and remain uncontrolled with existing AEDs. (February 2019)

<https://www.scottishmedicines.org.uk/medicines-advice/eslicarbazepine-acetate-zebinix-abbsub-smc2087/>

Everolimus (Votubia®) dispersible tablets are accepted for use within NHSScotland for the adjunctive treatment of patients aged 2 years and older whose refractory partial-onset (focal) seizures, with or without secondary generalisation, are associated with tuberous sclerosis complex (TSC). This SMC advice takes account of the benefits of a PAS that improves the cost effectiveness of everolimus. The advice is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower. (May 2018)

<https://www.scottishmedicines.org.uk/medicines-advice/everolimus-votubia-fullsubmission-133118/>

Lacosamide (Vimpat®) is accepted for restricted use within NHSScotland as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. Lacosamide use is restricted to patients with refractory epilepsy and treatment should be initiated by physicians who have appropriate experience in the treatment of epilepsy.

<https://www.scottishmedicines.org.uk/medicines-advice/lacosamide-vimpat-fullsubmission-53209/>

Levetiracetam (Keppra®) 100mg/ml oral solution is accepted for restricted use within NHSScotland as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in children and infants from 1 month to 4 years of age with epilepsy. (January 2011)

<https://www.scottishmedicines.org.uk/medicines-advice/levetiracetam-keppra-abbreviated-submission-66110/>

Methylphenidate (Medikinet XL®, Concerta®, Equasym XL®) is accepted for restricted use within NHSScotland as part of a comprehensive treatment programme for attention-deficit-hyperactivity disorder (ADHD) in children over 6 years of age when remedial measures alone prove insufficient. It should be considered second line and used for patients requiring methylphenidate in the morning and afternoon when administration of a midday dose is problematic or inappropriate. Treatment should be under the supervision of a specialist in childhood behaviour disorders. (July 2007)

<https://www.scottishmedicines.org.uk/medicines-advice/methylphenidate-oros-concerta-full-submission-0402/>

<https://www.scottishmedicines.org.uk/medicines-advice/methylphenidate-equasym-xl-fullsubmission-9904/>

<https://www.scottishmedicines.org.uk/medicines-advice/methylphenidate-hci-prolonged-release-medikinet-xl-abbreviatedsubmission-38807/>

Perampanel (Fycompa®) is accepted for restricted use within NHSScotland for second-line adjunctive treatment in patients aged 12 years and older with refractory partial-onset epilepsy. Treatment should be initiated only by physicians who have appropriate experience in the treatment of epilepsy. This advice takes account of the benefits of a PAS that improves the cost effectiveness of perampanel. (August 2019)

<https://www.scottishmedicines.org.uk/medicines-advice/perampanel-fycompa-abbreviated-smc2172/>

Pregabalin (Lyrica®) is accepted for restricted use within NHSScotland as adjunctive therapy in adults with partial seizures with or without secondary generalisation. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anticonvulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contraindications, interaction or poor tolerance. (January 2005)

<https://www.scottishmedicines.org.uk/medicines-advice/pregabalin-lyrica-fullsubmission-14504/>

Rufinamide (Inovelon®) is accepted for restricted use within NHSScotland for adjunctive therapy in the treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years of age or older who have failed treatment with, or are intolerant of, other antiepileptic drugs. (November 2008, July 2012) In April 2019 this was extended to incorporate children aged from 1 year, following changes to the licence.

<https://www.scottishmedicines.org.uk/medicines-advice/rufinamide-inovelon-abb-paed-lic-ext-smc2146/>

<https://www.scottishmedicines.org.uk/medicines-advice/rufinamide-100mg-200mg-400mg-tablets-inovelon-resubmission-41607/>

Stiripentol (Diacomit®) is accepted for use within NHSScotland in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate. (August 2017)

<https://www.scottishmedicines.org.uk/medicines-advice/stiripentol-diacomit-resubmission-52408/>

Topiramate is accepted for restricted use within NHSScotland for its extended (monotherapy) indication. It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy. (January 2004)

<https://www.scottishmedicines.org.uk/medicines-advice/topiramate-topamax-full-submission-7503/>

Zonisamide (Zonegran®) is accepted for restricted use within NHSScotland as adjunctive therapy in the treatment of partial seizures (focal seizures), with or without secondary generalisation, in adolescents, and children aged 6 years and above, on advice from specialists (paediatric neurologists or paediatricians with an expertise in epilepsy). (March 2014)

<https://www.scottishmedicines.org.uk/medicines-advice/zonisamide-zonegran-abbreviated-submission-94914/>

12 The evidence base

12.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include MEDLINE, Embase, CINAHL, PsycINFO and the Cochrane Library. The year range covered was 2007–2017, with a search for RCTs updated to 2020. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two Evidence and Information Scientists using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

The search strategies are available on the SIGN website, www.sign.ac.uk

12.1.1 Literature search for qualitative studies

The review of qualitative studies followed JBI methodology for conducting mixed-methods reviews.²⁶⁰ A SIGN Evidence and Information Scientist conducted a literature search of MEDLINE, Embase and PsycINFO, using a standard qualitative search filter, up to 2019. The studies were appraised and summarised by a qualitative researcher from JBI.

12.1.2 Literature search for patient issues

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to epilepsies in children and young people. Databases searched include MEDLINE, Embase, CINAHL and PsycINFO, and the results were summarised by the SIGN Public Involvement Advisor and presented to the guideline development group.

12.1.3 Literature search for cost-effectiveness evidence

The guideline development group identified key questions with potential cost-effectiveness implications, based on the following criteria, where it was judged particularly important to gain an understanding of the additional costs and benefits of different treatment strategies:

- treatments which may have a significant resource impact
- opportunities for significant disinvestment or resource release
- the potential need for significant service redesign
- cost-effectiveness evidence could aid implementation of a recommendation.

A systematic literature search for economic evidence for these questions was carried out by a SIGN Evidence and Information Scientist covering the years 2007–2017. Databases searched include MEDLINE, Embase and NHS Economic Evaluation Database (NHS EED). Each of the selected papers was evaluated by a Health Economist and considered for clinical relevance by guideline group members.

Interventions are considered cost effective if they fall below the commonly-accepted UK threshold of £20,000 per quality-adjusted life year (QALY).

12.2 Recommendations for research

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- Diagnostic utility of second-line EEG investigation (ambulatory or sleep deprivation) in paediatric patients who have a clinical diagnosis of epilepsy.
- Comparison of home video and hospital video with the outcome measure of diagnostic utility in making a diagnosis of epileptic seizures (sensitivity and specificity, gold standard being final clinical diagnosis).
- Long-term studies, of at least 12 months' duration, of the tolerability and adverse effects of a ketogenic diet.
- Role of 1.5- and 3- tesla MRI in different paediatric epilepsy syndromes.
- Approaches to follow-up imaging in focal and drug-resistant epilepsy.
- Drug treatment for infantile spasms/West syndrome, aetiology and treatment response both short and long term.
- Clinical trials of new AEDs, including longer-term studies of QoL outcomes and neuro-psychological effects.
- Research to establish appropriate psychological screening tools to be used in epilepsy services (that is, to evaluate specificity/sensitivity of screening measures currently available for a child and adolescent population). Screening measures should include those aimed at identifying cognitive/scholastic difficulties and neurodevelopmental concerns (attentional control/social communication skills).
- Research to evaluate psychological interventions for anxiety/depression in children and adolescents with comorbid neurodevelopmental disorders/intellectual disability and their families.
- Research to evaluate psychological interventions for diagnosed anxiety disorders in children/adolescents with epilepsy.
- In addition to interventions to treat diagnosed psychiatric conditions there is also a need to evaluate psychosocial interventions aimed at improving epilepsy knowledge/management and health-related QoL for children presenting with subclinical symptoms of psychiatric distress.
- Optimum drug treatment for children/young people with Lennox-Gastaut syndrome.
- Prognostic predictors in patients with Lennox-Gastaut syndrome.
- Recommendation for studies to include improvement in QoL as an outcome.
- RCTs assessing the effects of immunoglobulins in non-refractory epilepsy.
- Qualitative studies on QoL after surgery for epilepsy.
- Research to establish at what age/stage/process children with epilepsy best move from paediatric to adult care.
- A review of bereavement counselling and discussions regarding risks and risk factors associated with epilepsy deaths for families/carers. It would be ideal to consider whether or not counselling is offered to everyone, who takes up counselling, and the issues families who experience bereavement wish they had been given the opportunity to discuss before a death.
- Research on the effectiveness/safety of SSRIs in the management of more severe forms of anxiety disorders in children and young people with epilepsy.
- Adopting a double-blind, placebo design with larger sample sizes and longer baseline and follow-up periods for all types of stimulant and non-stimulant medication.
- Studies to evaluate safety and efficacy of atomoxetine with a child and adolescent epilepsy population.

- Studies to evaluate safety and tolerability of amphetamine in children with epilepsy and ADHD.
- Studies to evaluate use of guanfacine with a child and adolescent epilepsy population.

12.3 Review and updating

This guideline was issued in 2021 and will be considered for review in 3 years. The review history, and any updates to the guideline in the interim period, will be noted in the update report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh EH12 9EB (email: sign@sign.ac.uk).

13 Development of the guideline

13.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk

This guideline was developed according to the 2015 edition of SIGN 50.

The review of qualitative research followed JBI methodology for conducting mixed-methods reviews.²⁶⁰ Qualitative studies were assessed using the JBI critical appraisal tool for qualitative studies (<http://joannabriggs.org/research/critical-appraisal-tools.html>). The ConQual method was applied to establish the dependability and credibility of the studies and each study was rated (possible ratings high, moderate, low, very low).²⁶⁴

13.2 The guideline development group

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

Guideline development and literature review expertise, support and facilitation were provided by SIGN Executive and Healthcare Improvement Scotland staff. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website www.sign.ac.uk

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13.3 Acknowledgements

SIGN is grateful to the following members of the guideline development group and other key leads from SPEN who contributed during the early stages of the guideline development, including proposing and early instigation of the SIGN guideline.

Professor Martin Kirkpatrick	Consultant Paediatrician Neurologist, Tayside Children's Hospital, Dundee
Mr Carsten Mandt	Scottish Paediatric Epilepsy Network Programme Manager, National Services Scotland
Dr Mary O'Regan	Consultant Paediatric Neurologist, Our Lady's Children's Hospital, Dublin
Dr Krishnayara Kamath Tallur	Clinical Lead, Scottish Paediatric Epilepsy Network

13.4 Consultation and peer review

13.4.1 National open meeting

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 8 November 2018 and was attended by representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period to allow those unable to attend the meeting to contribute to the development of the guideline.

13.4.2 Specialist review

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

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Ms Vicki Whiteley	Advanced Practitioner in Ketogenic Therapies, Royal Manchester Children's Hospital

13.4.3 SIGN editorial group

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on request from the SIGN Executive.

Arlene Coulson	Royal Pharmaceutical Society
Dr Roberta James	SIGN Programme Lead; Co-Editor
Dr Donald MacGregor	Academy of Colleges
Dr Safia Qureshi	Director of Evidence, Healthcare Improvement Scotland
Professor Angela Timoney	Chair of SIGN; Co-Editor
Professor David Wilson	Royal College of Paediatrics and Child Health

Abbreviations

ACTH	adrenocorticotrophic hormone
ADHD	attention-deficit-hyperactivity disorder
AED	antiepileptic drug
ASD	autism spectrum disorder
CAMHS	child and adolescent mental health service
CBCL	Child Behavior Checklist
CBT	cognitive behavioural therapy
CDI	Children's Depression Inventory
CDKL5	cyclin dependent kinase like 5
CECTs	childhood epilepsy with centrotemporal spikes
CI	confidence interval
CNV	copy number variant
CT	computed tomography
DBS	deep-brain stimulation
DNA	deoxyribonucleic acid
EEG	electroencephalogram
glut1D	glucose transporter protein deficiency
GMC	General Medical Council
GP	general practitioner
IQ	intelligence quotient
ILAE	International League Against Epilepsy
JBI	Joanna Briggs Institute
KCNQ2	potassium voltage-gated channel subfamily Q member 2
LGS	Lennox-Gastaut syndrome
MAE	myoclonic atonic epilepsy
MASC	Multidimensional Anxiety Scale for Children
mCHAT	Modified Checklist for Autism in Toddlers
MDT	multidisciplinary team
MECP2	methyl-CpG binding protein 2
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value

OR	odds ratio
PACE	Patient and Clinician Engagement
PAS	Patient Access Scheme
<i>PCDH19</i>	protocadherin 19
PDCD	pyruvate dehydrogenase complex deficiency
PPV	positive predictive value
<i>PRRT2</i>	proline-rich transmembrane protein 2
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
<i>SCN1A</i>	sodium voltage-gated channel alpha subunit 1
<i>SCN2A</i>	sodium voltage-gated channel alpha subunit 2
<i>SCN8A</i>	sodium voltage-gated channel alpha subunit 8
SCQ	Social Communication Questionnaire
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
<i>SLC2A1</i>	solute carrier family 2 member 1
SMC	Scottish Medicines Consortium
SmPC	summary of product characteristics
SMS	short messaging service
SNV	single nucleotide variant
SPEN	Scottish Paediatric Epilepsy Network
SPESS	Scottish Paediatric Epilepsy Surgery Services
SSRI	selective serotonin reuptake inhibitor
<i>STXBP1</i>	syntaxin binding protein 1
SUDEP	sudden unexpected death in epilepsy
T	tesla
TLE	temporal lobe epilepsy
TSC	tuberous sclerosis complex
VNS	vagus nerve stimulation

Annex 1

Key questions used to develop the guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness or risk. These questions form the basis of the systematic literature search.

Section(s)	Key questions
4.1	2. What is the role of diagnostic neurophysiology procedures to determine the aetiology/syndrome of epilepsy in children with a view to a tailored and individualised pathway for the management of epilepsy? Who should have what diagnostic procedure and when?
4.2	1. What is the role of diagnostic imaging procedures to determine the aetiology/syndrome of epilepsy in children with a view to a tailored and individualised pathway for the management of epilepsy? Who should have what diagnostic procedure and when?
4.3	3. What is the role of genetic testing to determine the aetiology/syndrome of epilepsy in children with a view to a tailored and individualised pathway for the management of epilepsy? Who should have what diagnostic procedure and when?
5	4. What are the roles and indications of the new AEDs in patients with drug-resistant epilepsy or status epilepticus to reduce seizure frequency and severity, enhance quality of life and improve educational attainment?
6.1	5. What is the role and indications of ketogenic diet in patients with drug-resistant epilepsy or status epilepticus to reduce seizure frequency and severity, enhance quality of life and improve educational attainment?
6.2	6. What is the role and indications for surgery in patients with drug-resistant epilepsy or status epilepticus to reduce seizure frequency and severity, enhance quality of life and improve educational attainment?
6.3, 6.4	7. What are the roles and indications for VNS or DBS in patients with drug-resistant epilepsy or status epilepticus to reduce seizure frequency and severity, enhance quality of life and improve educational attainment?
7.1, 7.2, 7.3	8. Are there any specialist tools or methods for identifying psychological/psychiatric/social/cognitive comorbidities in children and young people with epilepsy?
7.4, 7.5	9. Are there any specialist psychosocial, mental health and/or educational/neuropsychological interventions for treating psychiatric comorbidities in children with epilepsy?
8	10. At what age and by what process do children/adolescents with epilepsy best transition from paediatric to adult care, compared with transition without a structured process? Compare different models of structured transition. <i>Qualitative key question – What are patients', family members' and clinicians' views of transition from paediatric to adult care?</i>

Section(s)	Key questions
9.2	12. When should children and young people, and parents, be told about the possibility of SUDEP/mortality? <i>Qualitative key question – When, where and how should discussions about the potential of SUDEP take place?</i>
9.3	11. What bed alarms or seizure detection monitors can be used to prevent SUDEP/mortality?

Annex 2

Prescribing unlicensed medicines in paediatric practice

The use of unlicensed medicines or licensed medicines for unlicensed applications in paediatric practice

Policy statement produced by the joint RCPCH/NPPG Standing Committee on Medicines

This statement, originally produced in 2000, has been updated by the Joint Standing Committee on Medicines, a committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group. The update reflects changes in European (including UK) law that aim to facilitate the development of more licensed medicines for children. The purpose of the statement is to inform and guide health professionals, health service managers, parents and carers who prescribe, dispense, administer or have responsibility for medicines for children.

Summary

- Those who prescribe for a child should choose the medicine which offers the best prospect for that child, aware that such prescribing may be constrained by the availability of resources. Children should be able to receive medicines that are safe, effective, appropriate for their condition, palatable and available with minimal clinical risk.
- The informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice.
- Health professionals should have ready access to sound information on any medicine they prescribe, dispense or administer, and its availability.
- In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain the consent of parents, carers and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications.
- NHS Trusts and Health Authorities should support therapeutic practices that are advocated by a respectable, responsible body of professional opinion.

Licensing

1. For a medicine to be marketed in the United Kingdom it must have received a Marketing Authorisation and is then said to be licensed. Many medicines that are given to children are not licensed for the particular indication, the age of the child or for the route of administration. Additionally they may not be in a suitable formulation. This position has arisen when a pharmaceutical company has made an application to the Licensing Authority for a Marketing Authorisation for use of the medicine in adults, but had chosen not to make an application for the use of that medicine in particular ways in children. Certain medicines that are given to children have not received a licence for any indication, and are said to be unlicensed.

In 2007, European (including UK) law introduced a requirement for pharmaceutical companies to undertake studies in children as part of the development plan for most new medicines. Over time, it is anticipated that the number of medicines licensed for use in children will increase.

2. The use of unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice when there is no suitable alternative. Such uses are usually informed and guided by a respectable and responsible body of professional opinion.

3. The Medicines Act and Regulations (which incorporate the relevant EC directives) provide exemptions which enable prescribers to:
 - prescribe unlicensed medicines;
 - use clinical trials medicines which are not yet authorised to be marketed.
 - use or advise on the use of licensed medicines for indications, or in doses, or by routes of administration, outside the recommendations of the licence;
 - override the warnings and the precautions given in the licence.
4. In each case, the prescriber has to be able to justify the action taken as being in accordance with a respectable, responsible body of professional opinion.

Sources of information

5. Although the choice of a medicine is not necessarily determined by its licence status, it will take account of information made available as a consequence of licensing and contained in the marketing authorisation. When the Marketing Authorisation does not include indications for use in children, the licence is of limited help. When the medicine is unlicensed, the necessary information must be sought elsewhere. It often is available, though might not be readily accessible.
6. The British National Formulary for Children (BNF-C) provides sound information and guidance on medicines for children.

Information for other health professionals and the public

7. Parents, patients and teachers, and others in loco parentis, require information about medicines. The information must be given in a way they can understand, and be accurate and consistent. This is particularly important when the specialist who has advised the use of unlicensed medicines or licensed medicines for unlicensed applications, hands over the care of the patient and responsibility for the administration of the medicine to someone else. Given the complexity of therapeutic and pharmacological information, and the burdens upon those giving and receiving it, the need is for sound, practical and sensible arrangements for communication, supplemented by readily available sources of reference.

It is essential that health professionals should have ready access to sound information on any medicine they prescribe, dispense or administer, and on its availability. The BNF-C fulfils most of these roles.

Consent of parents, carers and patients

8. Health professionals respect the right of children and their parents to participate in decisions on the health care of the child, and seek to ensure that those decisions are properly informed. In normal paediatric practice no additional steps, beyond those taken when prescribing licensed medicines, are required to obtain the consent of patients and parents/carers for the use of unlicensed medicines.
9. Prescribers are anxious that the licence status of a drug should not be perceived as reflecting what is or is not best for the child. They are mindful of a possible impact upon the confidence of parents and patients who might then be reluctant to accept advice, with consequences for a child who might not receive a medicine that offers benefit.
10. Most licensed medicines are dispensed in standard packages together with a Patient Information Leaflet (PIL) approved by the Licensing Authority. When the licence does not include indications for children, the PIL may caution against such use. Naturally, this may undermine confidence in the advice given by health professionals, besides provoking a call for explanation. The Committee working in partnership with the WellChild charity has produced leaflets on medicines, including one on Unlicensed Medicines which explains why it may be necessary to prescribe unlicensed medicines or to use licensed medicines for unlicensed applications. This leaflet will be made widely available to all,

especially parents/carers, hospitals and pharmacies via the website www.medicinesforchildren.org.uk where Medicines for Children: Information for Parents/Carers leaflets are freely available to download.

11. There are circumstances when a clinician may decide to give fuller information than is usually judged necessary. These may arise when a medicine is new or experimental; or when the balance of risk versus benefit is less clear or when the concerns of some parents, carers or patients suggest a more detailed discussion is needed.

Policies of NHS Provider Organisations

12. Some NHS Provider Organisations have suggested that a clinician should not use an unlicensed medicine, or a licensed medicine for unlicensed application. In 1993 the Department of Health stated that it would not expect that a health authority would seek to fetter a prescriber's freedom to prescribe by expressly directing its medical staff against prescribing unlicensed products or licensed products for unlicensed purposes. The Department of Health also stated that, should a health authority so direct its medical staff, a court would be reluctant to support the authority in those circumstances.
13. However the emphasis on risk management and evidence-based medicine in Clinical Governance framework implies that Trusts may be encouraged to introduce systems and protocols to monitor, and even direct, the use of both licensed and unlicensed medicines. We understand that, because the Medicines Act (1968) exemptions remain current, the courts would not hold the prescription of an unlicensed medicine to be a breach of the duty of care, if that treatment was supported by a respected body of medical opinion. The best evidence available should always inform the prescription of medicines for children. We consider that NHS Provider Organisations should support therapeutic practices that are advocated by a respectable, responsible body of professional opinion.

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29th October 2010

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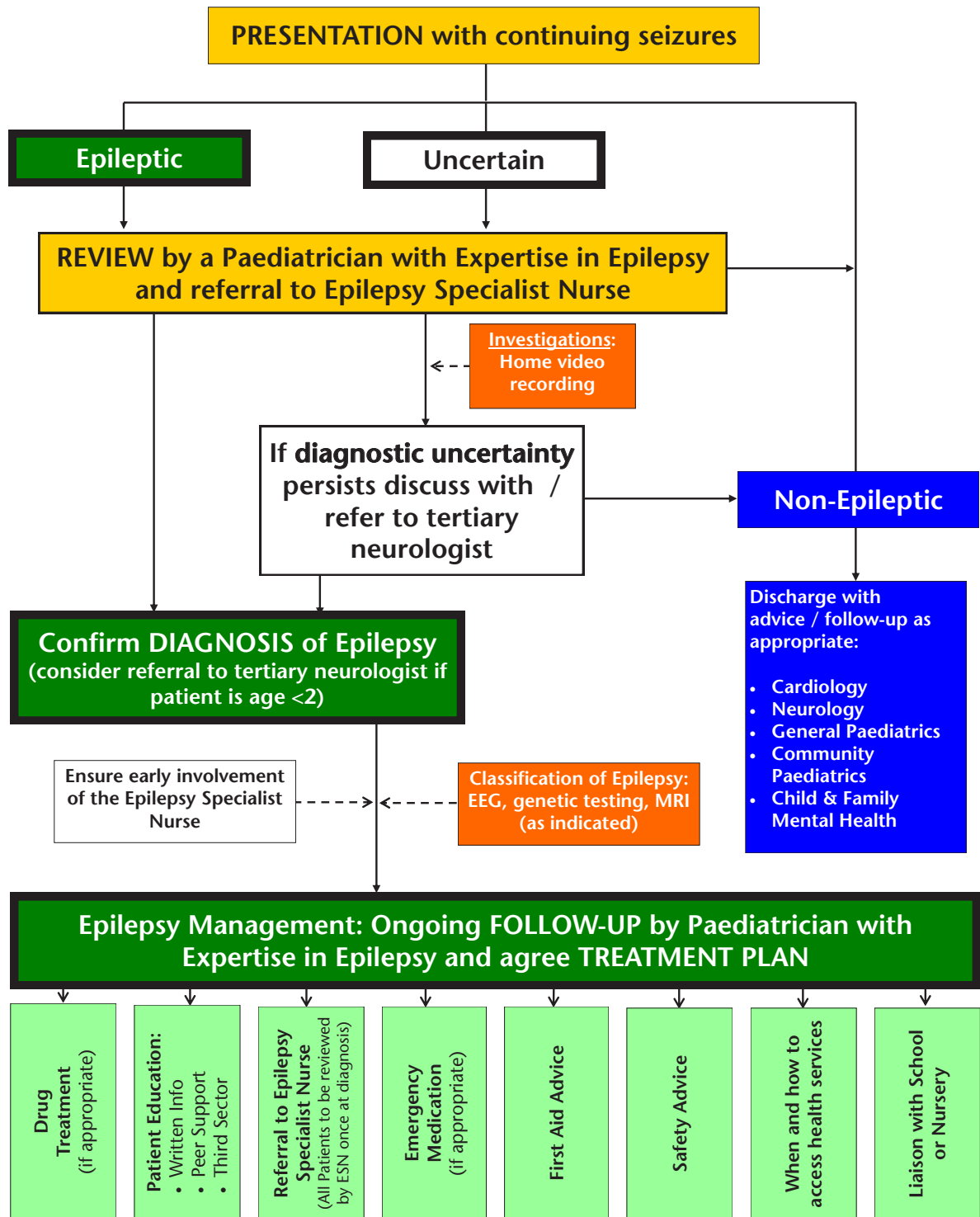
REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, & REGULATION (EC) No 1902/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use.

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Annex 3

Pathway 2: Diagnosis and initial management of epilepsy Scottish Paediatric Epilepsy Network (SPEN)



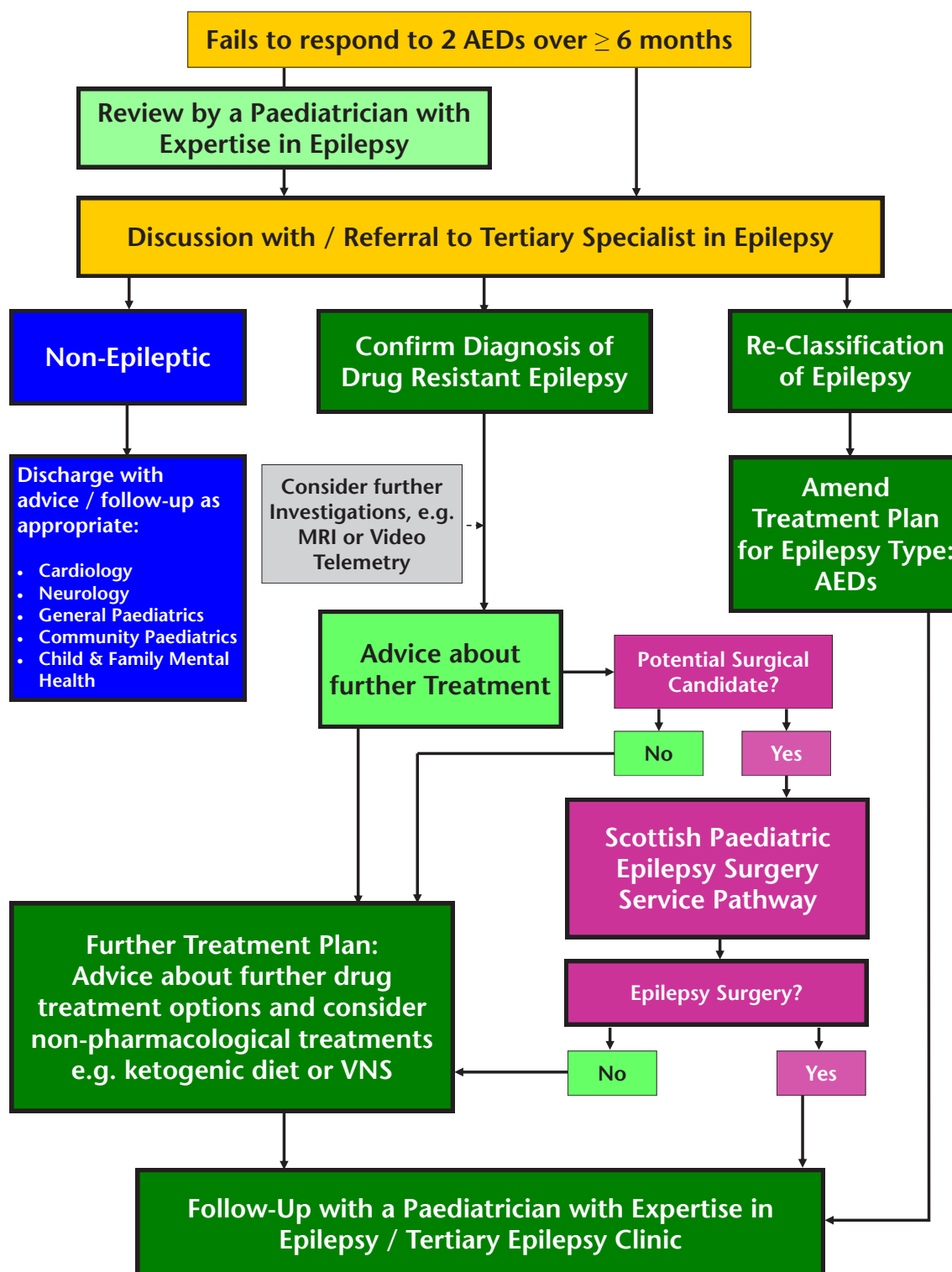
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This pathway is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to the pathway will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national pathway or any local guidance derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Annex 4

Pathway 3: Continuing epileptic seizures

Scottish Paediatric Epilepsy Network (SPEN)



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This pathway is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to the pathway will not ensure a successful outcome in every case, nor should it be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national pathway or any local guidance derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Annex 5

Summary of recommended pharmacological therapies

*Therapies are listed in alphabetical order, not in order of preference for use.

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Generalised tonic-clonic	<ul style="list-style-type: none"> Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate (boys only) 	<ul style="list-style-type: none"> Clobazam Lamotrigine Levetiracetam Sodium valproate (boys only) Topiramate 		<p>If there are absence or myoclonic seizures, or if juvenile myoclonic epilepsy is suspected:</p> <ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Tonic or atonic	<ul style="list-style-type: none"> Sodium valproate (boys only) 	<ul style="list-style-type: none"> Lamotrigine Rufinamide or topiramate may be considered on referral to tertiary care 		<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Absence	<ul style="list-style-type: none"> Ethosuximide Lamotrigine Sodium valproate (boys only) 	<ul style="list-style-type: none"> Ethosuximide Lamotrigine Sodium valproate (boys only) Clobazam, clonazepam, levetiracetam, topiramate or zonisamide may be considered on referral to tertiary care 	<p>Ethosuximide should be considered as first-line monotherapy. Sodium valproate should also be considered, but has a higher risk of adverse events.</p> <p>Lamotrigine could be considered if ethosuximide and sodium valproate are ineffective, not suitable or not tolerated.</p> <p>A combination of two or three AEDs could be considered if two first-line AEDs are ineffective. If treatment is still ineffective, advice should be sought from, or the patient should be referred to, a tertiary epilepsy specialist to consider the use of clobazam, clonazepam, levetiracetam, topiramate or zonisamide.</p> <p>Sodium valproate should not be used in women and girls or childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.</p>	<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Myoclonic	<ul style="list-style-type: none"> Levetiracetam Sodium valproate (boys only) Topiramate 	<ul style="list-style-type: none"> Levetiracetam Sodium valproate (boys only) Topiramate Clobazam, clonazepam, piracetam or zonisamide may be considered on referral to tertiary care 		<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Focal	<ul style="list-style-type: none"> Carbamazepine Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate (boys only) 	<ul style="list-style-type: none"> Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Sodium valproate (boys only) Topiramate Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide may be considered on referral to tertiary care 	<p>Carbamazepine or lamotrigine could be considered.</p> <p>Levetiracetam, oxcarbazepine or sodium valproate could be considered if carbamazepine and lamotrigine are not suitable or tolerated.</p> <p>Carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, topiramate or zonisamide (over 6 years of age) can be considered as adjunctive therapies if first-line therapies are ineffective or not tolerated.</p> <p>Perampanel could be considered as adjunctive therapy in adolescents from 12 years of age.</p> <p>Sodium valproate should not be used in girls of childbearing potential unless there is no suitable alternative and a pregnancy prevention programme is in place.</p>	
Childhood absence epilepsy, juvenile absence epilepsy or other absence syndromes	<ul style="list-style-type: none"> Ethosuximide Lamotrigine Sodium valproate (boys only) 	<ul style="list-style-type: none"> Ethosuximide Lamotrigine Sodium valproate (boys only) Clobazam, clonazepam, levetiracetam, topiramate or zonisamide may be considered on referral to tertiary care 		<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Juvenile myoclonic epilepsy	<ul style="list-style-type: none"> Lamotrigine Levetiracetam Sodium valproate (boys only) Topiramate 	<ul style="list-style-type: none"> Lamotrigine Levetiracetam Sodium valproate (boys only) Topiramate Clobazam, clonazepam or zonisamide may be considered on referral to tertiary care 		<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Epilepsy with generalised tonic-clonic seizures only	<ul style="list-style-type: none"> Carbamazepine Lamotrigine Oxcarbazepine Sodium valproate (boys only) 	<ul style="list-style-type: none"> Clobazam Lamotrigine Levetiracetam Sodium valproate (boys only) Topiramate 		
Idiopathic generalised epilepsy	<ul style="list-style-type: none"> Lamotrigine Sodium valproate (boys only) Topiramate 	<ul style="list-style-type: none"> Lamotrigine Levetiracetam Sodium valproate (boys only) Topiramate Clobazam, clonazepam or zonisamide may be considered on referral to tertiary care 		<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Infantile spasms not due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Steroid (prednisolone or tetracosactide) or vigabatrin		Hormonal treatment (adrenocorticotrophic hormone, tetracosactide or prednisolone) or vigabatrin could be considered as the first-line treatment for infantile spasms. Children should be closely monitored for adverse events.	

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Infantile spasms due to tuberous sclerosis	Discuss with, or refer to, a tertiary paediatric epilepsy specialist Vigabatrin or steroid (prednisolone or tetracosactide)		Vigabatrin should be considered as first-line treatment in infantile spasms for children with tuberous sclerosis. Children prescribed vigabatrin should be closely monitored for adverse events.	
Tuberous sclerosis			Everolimus could be considered as an adjunctive treatment for children (age 2 years and older) with refractory seizures associated with tuberous sclerosis complex, when other treatments have failed. Children prescribed everolimus should be closely monitored for adverse events.	
Benign epilepsy with centro-temporal spikes	<ul style="list-style-type: none"> • Carbamazepine • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) 	<ul style="list-style-type: none"> • Carbamazepine • Clobazam • Gabapentin • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) • Topiramate • Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide may be considered on referral to tertiary care 		

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Panayiotopoulos syndrome	<ul style="list-style-type: none"> • Carbamazepine • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) 	<ul style="list-style-type: none"> • Carbamazepine • Clobazam • Gabapentin • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) • Topiramate • Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide may be considered on referral to tertiary care 		
Late-onset childhood occipital epilepsy (Gastaut type)	<ul style="list-style-type: none"> • Carbamazepine • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) 	<ul style="list-style-type: none"> • Carbamazepine • Clobazam • Gabapentin • Lamotrigine • Levetiracetam • Oxcarbazepine • Sodium valproate (boys only) • Topiramate • Eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin or zonisamide may be considered on referral to tertiary care 		

Seizure type	First line* (as per NICE 2020)	Adjunctive* (as per NICE 2020)	SIGN 2021 recommendation	Do not offer (may worsen seizures)
Dravet syndrome	<ul style="list-style-type: none"> Discuss with, or refer to, a tertiary paediatric epilepsy specialist Sodium valproate (boys only) Topiramate 	Clobazam or stiripentol may be considered on referral to tertiary care	<p>Sodium valproate or topiramate could be considered as first-line therapy.</p> <p>Stiripentol or clobazam could be considered as an adjunctive therapy for children (3 years and older) with Dravet syndrome whose seizures are poorly controlled with sodium valproate.</p> <p>Cannabidiol could be considered as an adjunctive therapy in conjunction with clobazam for children (2 years and older).</p>	<ul style="list-style-type: none"> Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Continuous spike and wave during slow sleep	Refer to a tertiary paediatric epilepsy specialist			
Lennox-Gastaut syndrome	<ul style="list-style-type: none"> Discuss with, or refer to, a tertiary paediatric epilepsy specialist Sodium valproate (boys only) 	<ul style="list-style-type: none"> Lamotrigine Felbamate, rufinamide or topiramate may be considered on referral to tertiary care 	<p>Sodium valproate could be considered as first-line treatment for seizure reduction.</p> <p>Rufinamide (4 years and older), clobazam (2 years and older), lamotrigine (2 years and older) or topiramate (2 years and older) could be considered as adjunctive therapy.</p> <p>Cannabidiol could be considered as an adjunctive therapy in conjunction with clobazam for children (2 years and older).</p>	<ul style="list-style-type: none"> Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Landau-Kleffner syndrome	Refer to a tertiary paediatric epilepsy specialist			
Myoclonic-atic epilepsy	Refer to a tertiary paediatric epilepsy specialist			

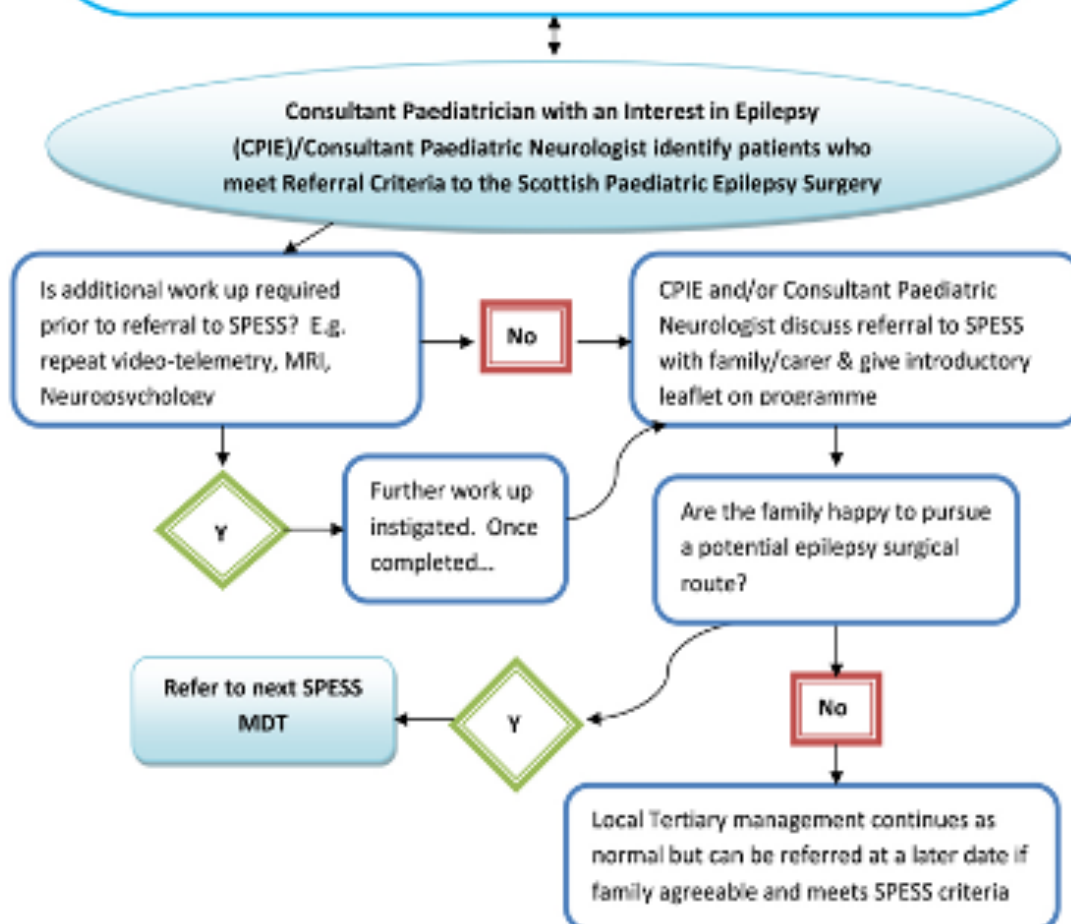
Annex 6

SPESS REFERRAL TO MDT PATHWAY

SPESS Referral criteria (March 2016)

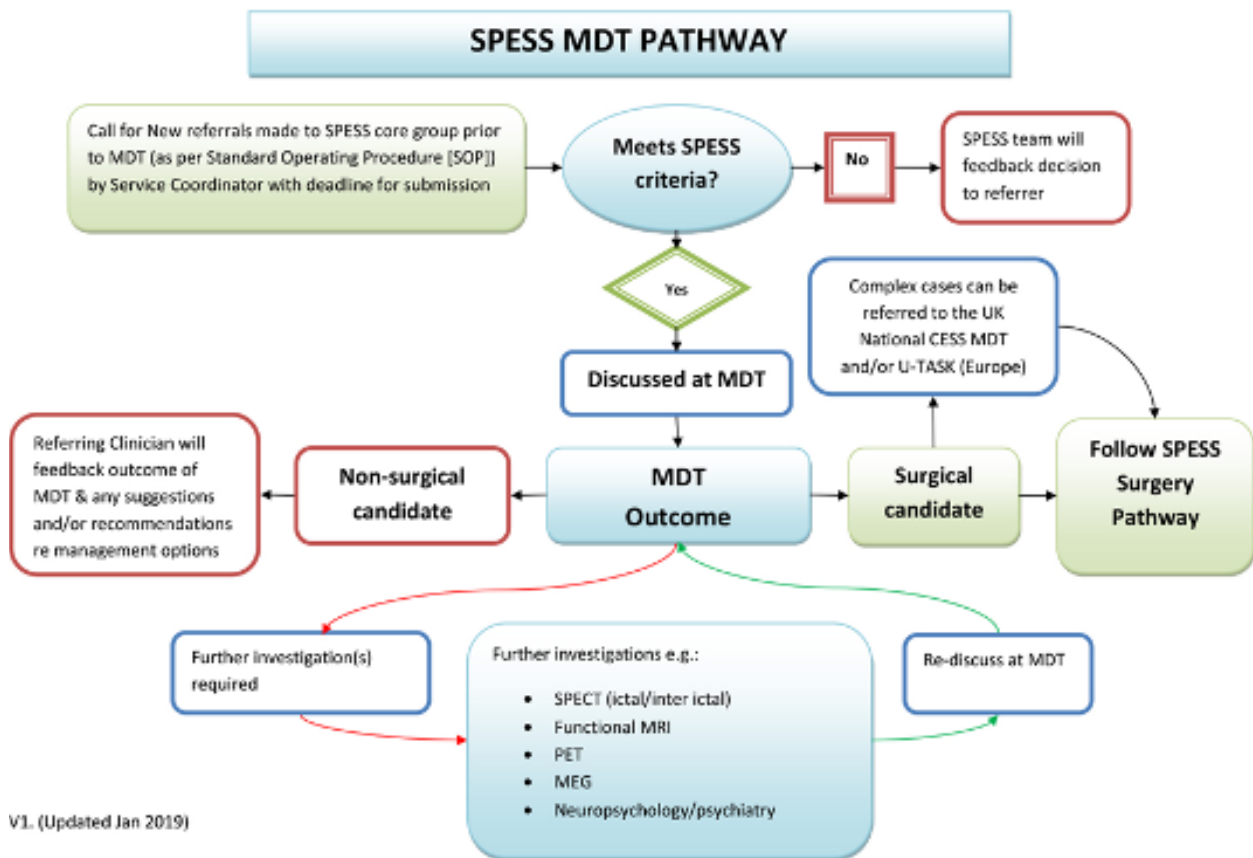
Children should be referred for assessment by the national SPESS centre if they meet one of the following criteria:

- i. Children with catastrophic early onset epilepsy with evidence of lateralisation of the seizure onset
- ii. All children under 24 months old with evidence of focality of seizure onset, with or without an MRI evident lesion
- iii. Children of any age with evident focal epilepsy, or lateralised seizures associated with congenital hemiplegia, resistant to two appropriate antiepileptic drugs (AEDs)
- iv. Children who have epilepsy associated with a lateralised abnormality seen on a brain scan
- v. Children with epilepsy associated with Sturge Weber syndrome, benign tumours with developmental issues and/or ongoing seizures, or Rasmussen's syndrome
- vi. Children of any age with epilepsy associated with tuberous sclerosis resistant to two AEDs where seizures may arise from a single focus (probably from a single tuber)
- vii. Children who have 'drop attacks' as part of a more complex epilepsy
- viii. Children with epilepsy associated with hypothalamic hamartoma



V1. (Updated April 2017)

Annex 7



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