

Suspected neurological conditions

Suspected neurological conditions: recognition and referral

NICE guideline NG127

Methods, evidence and recommendations

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Final version

*Developed by the National Guideline Centre,
hosted by the Royal College of Physicians*

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Guideline committee members

Name	Role
Richard Grünewald	Chair, Clinical Director of Neurosciences, Central Sheffield University Hospital Trust
Anna Botsie	Locum Children's Physiotherapist, Coventry and Warwickshire Partnership Trust
Katherine Carpenter	Consultant Clinical Neuropsychologist, British Psychological Society
Paul Eunson	Consultant Paediatric Neurologist, Royal Hospital for Sick Children
Susanne Friess	Consultant in Paediatric Neurodisability, Coventry and Warwickshire Partnership Trust
Carole Gavin	Consultant Emergency Physician, Salford Royal NHS Foundation Trust
Paul Hepple	General Practitioner, Muirhouse Medical Group
Nassif Mansour	General Practitioner with Special Interest in Neurology, Surbiton Health Centre
Wojtek Rakowicz	Consultant Neurologist, Royal Hampshire County Hospital
Guy Parckar	Lay Member
Sandra Scrivens	Lay Member
Tony Wootton	Lay Member

NGC technical team members

Name	Role
Mikaela Bartlett	Document Editor/Process Assistant (until July 2016)
Jill Cobb	Information Specialist (from January 2017)
Francesca Fasesin	Research Fellow (from July 2016 until September 2016)
Meredith Faust	Document Editor/Process Assistant (from August 2016)
Elisabetta Fenu	Health Economics Lead (until March 2016)
Andreas Freitag	Senior Research Fellow (from November 2016 until December 2016)
Saoussen Ftouh	Senior Research Fellow
Yee Yen Goh	Clinical Trainee (from May 2016)
Alexander Haines	Senior Health Economist (until May 2017)
Martin Harker	Health Economics Lead (from May 2017)
Bernard Higgins	Clinical Director and Guideline Lead
Natalie Pink	Project Manager (until December 2016)
Joseph Runicles	Information Specialist Assistant
Eleanor Samarasekera	Research Fellow (from December 2016)
Carlos Sharpin	Associate Director/Joint head of Information Science (from April 2016 until May 2016)
Thomas Strong	Research Fellow (until July 2016)
Claire Wallnutt	Information Specialist (until January 2017)
Giulia Zuodar	Project Manager (from January 2017)

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Norma O'Flynn, Chief Operating Officer at the National Guideline Centre, and the experts from the targeted engagement exercise listed in full in appendix P.

1 Guideline summary

1.1 Full list of recommendations

Recommendations for adults aged over 16

Blackouts in adults

1. Refer urgently adults with new-onset blackouts (transient loss of consciousness), accompanied by features that are strongly suggestive of epileptic seizures, for neurological assessment in line with the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.
2. Do not routinely refer adults with blackouts if there are clear features of vasovagal syncope, even if associated with brief jerking of the limbs. See recommendation 1.1.4.3 on uncomplicated faint in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.
3. For adults with sudden-onset dizziness and a focal neurological deficit such as vertical or rotatory nystagmus, new-onset unsteadiness or new-onset deafness:
 - if the person has diabetes, check for and treat hypoglycaemia
 - if the person does not have diabetes, or treating hypoglycaemia does not resolve the symptoms, and benign paroxysmal positional vertigo or postural hypotension do not account for the presentation, refer immediately to exclude posterior circulation stroke, in line with the NICE guideline on stroke and transient ischaemic attack in over 16s.
4. Be aware that dizziness in adults with no imbalance or other focal neurological deficit is unlikely to indicate a serious neurological condition.
5. For adults with transient rotational vertigo on head movement:
 - offer the Hallpike manoeuvre to check for benign paroxysmal positional vertigo (BPPV) if a healthcare professional trained in its use is available. If there is no healthcare professional trained in the Hallpike manoeuvre available, refer in accordance with local pathways.
 - if BPPV is diagnosed, offer the canalith repositioning manoeuvre (such as the Epley manoeuvre) if a healthcare professional trained in its use is available and if the person does not have unstable cervical spine disease. If there is no healthcare professional trained in a canalith repositioning manoeuvre, or the person has unstable cervical spine disease, refer in accordance with local pathways.
 - be aware that BPPV is common after a head injury or labyrinthitis.
6. Be alert to the possibility of vestibular migraine (migraine-associated vertigo) in adults who have episodes of dizziness that last between 5 minutes and 72 hours and a history of recurrent headache.
7. Be aware that, for adults who have been diagnosed with a functional neurological disorder by a specialist, recurrent dizziness might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a

- functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.
8. Advise adults with recurrent dizziness and a diagnosed functional neurological disorder that their dizziness will fluctuate and might increase during times of stress.
 9. Refer adults with recurrent fixed-pattern dizziness associated with alteration of consciousness to have an assessment for epilepsy in line with the NICE guideline on epilepsies.
 10. For adults with sudden-onset acute vestibular syndrome (vertigo, nausea or vomiting and gait unsteadiness) a HINTS (head impulse–nystagmus–test-of-skew) test should be performed if a healthcare professional with training and experience in the use of this test is available.
 11. For adults with sudden-onset acute vestibular syndrome who have had a HINTS test:
 - be aware that a negative HINTS test makes a diagnosis of stroke very unlikely
 - refer immediately for neuroimaging if the HINTS test shows indications of stroke (a normal head impulse test, direction-changing nystagmus or skew deviation).
 12. Refer immediately adults with sudden-onset acute vestibular syndrome in whom benign paroxysmal positional vertigo or postural hypotension do not account for the presentation, in line with local stroke pathways, if a healthcare professional with training and experience in the use of the HINTS test is not available.
 13. Refer urgently adults with facial pain associated with persistent facial numbness or abnormal neurological signs for neuroimaging.
 14. Refer adults with unilateral facial pain that is triggered by touching the affected part of the face (trigeminal neuralgia) and is refractory to treatment, in line with the NICE guideline on neuropathic pain in adults.
 15. For adults with scalp tenderness or jaw claudication suggestive of temporal arteritis, consider blood tests and follow local pathways for suspected giant cell (temporal) arteritis. Be aware that a normal ESR (erythrocyte sedimentation rate) does not exclude a diagnosis of giant cell arteritis.
 16. For recommendations on assessing sudden-onset unsteady gait in adults, see the NICE guideline on stroke and transient ischaemic attack in over 16s.
 17. Refer urgently adults with rapidly (within days to weeks) progressive unsteady gait (gait ataxia) for neurological assessment.
 18. Refer adults with gradually progressive unsteady gait (gait ataxia) for neurological assessment and:
 - take an alcohol history and follow the recommendations in the NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence
 - check thyroid function
 - check for vitamin B12 and folate deficiency
 - consider serological testing for gluten sensitivity as recommended in the NICE guideline on coeliac disease.

19. Refer adults who have difficulty initiating and coordinating walking (gait apraxia) to neurology or an elderly care clinic to exclude normal pressure hydrocephalus.
20. For adults with unsteadiness of gait who are at risk of falling, follow the recommendations on multifactorial falls risk assessment in the NICE guideline on falls in older people and consider referring to a falls prevention team.
21. Refer adults who have sudden-onset difficulty with handwriting that has no obvious musculoskeletal cause for a neurological assessment according to local stroke pathways.
22. Ask adults who have difficulty with handwriting that has no obvious musculoskeletal cause to demonstrate their handwriting and:
 - if they have a problem with generating language rather than hand function, refer for neurological assessment
 - if their handwriting is small and slow, consider referring for possible Parkinson's disease
 - if their difficulty is specific to the task of handwriting and examination shows no other abnormalities, consider referring for possible focal dystonia.
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23. Be aware that sudden-onset weakness, even in restricted distribution (for example, sudden hand weakness), may be caused by a stroke or transient ischaemic attack. See the NICE guideline on stroke and transient ischaemic attack in over 16s for recommendations on assessing sudden-onset limb or facial weakness in adults.
24. Refer immediately adults with rapidly (within 4 weeks) progressive symmetrical limb weakness for neurological assessment and assessment of bulbar and respiratory function.
25. Refer immediately, in line with local pathways, adults who have severe low back pain radiating into the leg and new-onset disturbance of bladder, bowel or sexual function, or new-onset perineal numbness, to have an assessment for cauda equina syndrome.
26. Refer urgently adults with rapidly (within hours to days) progressive weakness of a single limb or hemiparesis for investigation, including neuroimaging, in line with the recommendation on brain and central nervous system cancers in adults in the NICE guideline on suspected cancer.
27. For adults with slowly (within weeks to months) progressive limb or neck weakness:
 - refer for assessment of neuromuscular disorders in line with the recommendations on recognition and referral in the NICE guideline on motor neurone disease
 - refer urgently if there is any evidence of swallowing impairment
 - refer immediately if there is breathlessness at rest or when lying flat
28. Be aware that lower limb claudication symptoms in adults with adequate peripheral circulation might be caused by lumbar canal stenosis and need specialist assessment and imaging.

29. Be aware that, for adults who have been diagnosed with a functional neurological disorder by a specialist, recurrent limb weakness might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.
30. Advise adults with limb or facial weakness ascribed to a functional neurological disorder that their limb or facial weakness might fluctuate and evolve over time and might increase during times of stress.
31. For adults with clear features of compression neuropathy and no features of a nerve root lesion (radiculopathy) of the radial nerve, common peroneal nerve or ulnar nerve:
- refer to orthotic services for a splint
 - review the symptoms after 6 weeks, and refer for neurological assessment if there is no evidence of improvement.
- For adults with features of radiculopathy see the section on cervical or lumbar radiculopathy.
32. Advise adults with compression neuropathy to avoid any activity that might lead to further pressure on the affected nerve.
33. Do not routinely refer adults with an uncomplicated episode of Bell's palsy (unilateral lower motor neurone pattern facial weakness affecting all parts of the face and including weakness of eye closure) and no evidence of another medical condition such as middle ear disease.
34. Advise adults with Bell's palsy about eye care, and that the rate of improvement is variable and maximum recovery can take several months.
35. Consider referring adults with Bell's palsy who have developed symptoms of aberrant reinnervation (including gustatory sweating or jaw-winking) 5 months or more after the onset of Bell's palsy for neurological assessment and possible treatment.
36. For adults aged under 50 with memory problems and no other neurological signs:
- do not routinely refer if brief testing shows memory function to be normal and symptoms are consistent with concentration difficulties
 - be aware that memory problems or concentration difficulties can be caused by:
 - recreational, and some prescription, drugs
 - alcohol
 - affective disorders
 - stress.
- For more information see initial assessment in non-specialist settings in the NICE guideline on dementia.
37. Be aware that, for adults who have an anxiety disorder or have been diagnosed with a functional neurological disorder by a specialist, memory problems and concentration difficulties might be part of the disorder and the

person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.

38. Do not routinely refer adults for neurological assessment if they have concentration difficulties associated with myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome or fibromyalgia.
39. For guidance on referring adults with progressive memory problems see initial assessment in non-specialist settings in the NICE guideline on dementia.
40. Do not routinely refer adults with a single episode of dense amnesia (inability to recall the recent past or form new memories) if:
 - the episode lasts less than 8 hours and
 - there is complete recovery and
 - there are no features suggestive of an epileptic seizure (see seizure markers for suspected epilepsy in the NICE guideline on transient loss of consciousness ['blackouts'] in over 16s).

Advise the person that they have probably had an episode of transient global amnesia and that the recurrence rate is low.

41. Refer adults with recurrent episodes of dense amnesia to have an assessment for epileptic amnesia.
42. Suspect cervical dystonia in adults who have persistent abnormalities of head or neck posture, with or without head tremor, especially if the symptom improves when the person touches their chin with their hand.
43. Do not offer cervical imaging to evaluate suspected cervical dystonia in adults.
44. Be aware that dystonia in adults can affect other parts of the body (for example, it can cause writer's cramp or in-turned posture of the foot).
45. Refer adults with suspected dystonia to have an assessment for diagnosis and possible botulinum toxin treatment.
46. Be aware that antipsychotic and antiemetic medicines can trigger or exacerbate dystonia in adults.
47. Assess sudden-onset transient unilateral numbness in adults in line with the NICE guideline on stroke and transient ischaemic attack in over 16s.
48. Refer immediately adults with rapidly progressive (within hours to days) symmetrical numbness and weakness or imbalance to have a neurological assessment.
49. Refer urgently adults with recurrent, brief (less than 2 minutes), fixed-pattern disturbances of sensation to have an assessment for epilepsy.
50. Refer adults with persistent, distally predominant altered sensation in the limbs, and brisk deep tendon reflexes, to have an assessment for possible brain or spine disease.
51. Suspect migraine with aura in adults who have sensory symptoms that occur with or without headache and:
 - are fully reversible and

- develop over at least 5 minutes and
- last between 5 and 60 minutes.

For recommendations on diagnosing and managing migraine with aura, see the NICE guideline on headaches in over 12s.

52. For adults with persistent, distally predominant ('stocking' or 'glove and stocking') altered sensation in the limbs and depressed deep tendon reflexes:
- be alert to the possibility of peripheral neuropathy and consider checking:
 - vitamin B12 deficiency
 - thyroid function
 - for evidence of coeliac disease in line with the NICE guideline on coeliac disease
 - renal function
 - blood glucose
 - ESR (erythrocyte sedimentation rate)
 - alcohol consumption, using a tool such as AUDIT (Alcohol Use Disorders Identification Test), in line with the NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence
 - if no causes of peripheral neuropathy are found, refer for neurological assessment.
53. Be aware that, for adults who have been diagnosed with a functional neurological disorder by a specialist, recurrent numbness and tingling might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.
54. Advise adults with tingling and a diagnosis of functional neurological disorder that the tingling might fluctuate and evolve over time and could increase at times of stress.
55. Refer in line with local pathways if symptoms of carpal tunnel syndrome are severe or persistent after initial management.
56. Reassure adults with unilateral or bilateral numbness, tingling or pain in the distribution of the lateral cutaneous nerve of the thigh (meralgia paraesthetica) that the condition is benign and might improve spontaneously. Consider referring for pain management only if the symptoms are severe.
57. Do not routinely refer adults with symptoms of cervical radiculopathy that have remained stable for 6 weeks or more unless:
- pain is not controlled with analgesics or
 - the symptoms are disabling or
 - one of the following factors is present:
 - age under 20
 - gait disturbance

- clumsy or weak hands or legs
 - brisk deep tendon reflexes (triceps and lower limbs)
 - extensor plantar responses
 - new-onset disturbance of bladder or bowel function.
58. Do not routinely refer adults with symptoms of lumbar radiculopathy that have remained stable for 6 weeks or more unless pain is not controlled with analgesics or symptoms are disabling, in line with the NICE guideline on low back pain and sciatica in over 16s..
59. Do not routinely refer adults with recurrent episodes of tingling or sensory disturbance in the limbs that are present on waking from sleep and last less than 10 minutes.
60. Offer advice on sleep hygiene to adults with insomnia.
61. Do not routinely refer adults with insomnia, jerks on falling asleep or isolated brief episodes of sleep paralysis.
62. Refer urgently adults with symptoms suggestive of new-onset epileptic seizures in sleep for neurological assessment in line with the NICE guideline on epilepsies.
63. For adults with excessive sleepiness:
- use the Epworth score together with history of obstructive symptoms in sleep to assess the likelihood of sleep apnoea
 - refer in accordance with local policy
 - if appropriate, offer advice on weight reduction, alcohol consumption and smoking cessation, in line with NICE guidance on obesity, alcohol-use disorders, and smoking and tobacco.
64. Refer adults with narcolepsy, with or without cataplexy, for neurological assessment.
65. Consider referring adults with persistent symptoms suggestive of sleep behaviour disorders (such as agitated or violent movements that are more complex than a simple jerking motion) for neurological assessment.
66. Be aware that sudden-onset distortion of sense of smell or taste in adults is rarely associated with structural neurological abnormality and usually resolves within a few months.
67. Refer adults with transient, repetitive smell or taste hallucinations to have a neurological assessment for epilepsy.
68. Consider neuroimaging for adults with unexplained loss of sense of smell or taste that lasts more than 3 months.
69. Do not routinely refer adults with loss of sense of smell or taste and normal neuroimaging.
70. Do not routinely refer adults who lose their sense of smell or taste immediately after a head injury.
71. Refer urgently adults with sudden-onset speech or language disturbance to have an assessment for a vascular event, in line with local stroke pathways and following the recommendations on prompt recognition of symptoms of stroke and TIA in the NICE guideline on stroke and transient ischaemic attack in over 16s.

72. For adults with progressive slurred or disrupted speech:
- refer for an assessment for neuromuscular disorders, in line with the recommendations on recognition and referral in the NICE guideline on motor neurone disease
 - refer urgently if there is any evidence of swallowing impairment
 - refer immediately if there is breathlessness at rest or when lying flat.
73. Consider referring adults with isolated and unexplained persistent dysphonia (a quiet, hoarse or wobbly voice) to have an assessment for laryngeal dystonia (involuntary contractions of the vocal cords) if hoarseness caused by structural abnormality or malignancy has been excluded by ear, nose and throat examination.
74. Be aware that persistent dysphonia in adults may be a presenting symptom of a neurological condition such as Parkinson's disease. For recommendations on the diagnosis and management of Parkinson's disease, see the NICE guideline on Parkinson's disease in adults.
75. Be aware that anxiety disorder and functional neurological disorders are the most common causes of minor word-finding difficulties in adults and people with a diagnosis of anxiety disorder or functional neurological disorder made by a specialist might not need a referral.
76. Do not routinely refer adults with tics (involuntary movements that can be temporarily suppressed at the expense of mounting inner tension) unless the tics are troublesome or accompanied by additional progressive neurological symptoms .
77. Consider referring adults with a tic disorder for psychological therapy if the disorder distresses them.
78. Consider referring adults who have completed psychological therapy for a tic disorder to have a neurological assessment if their symptoms are severe and the disorder continues to distress them, but tell the person that:
- there are not many medicines available to treat a tic disorder
 - the medicines that are available don't always work very well and can have serious side effects.
79. Do not routinely refer adults with isolated involuntary movements of the eyelid unless the movements:
- cause involuntary tight eye closure of both eyes (blepharospasm) or
 - have persisted for more than 3 months.
80. In adults with involuntary movements of the face, neck, limbs or trunk that cannot be temporarily suppressed by mental concentration:
- refer for neurological assessment or
 - refer to neurology or an eye clinic according to local provision, if the person has involuntary tight eye closure of both eyes (blepharospasm).
81. Do not routinely refer people with small involuntary muscular twitches (fasciculations) unless these are associated with muscle wasting and weakness or muscle rigidity.

82. Refer adults with suspected parkinsonian tremor, other asymmetric tremor, or tremor associated with stiffness, slowness, balance problems or gait disorders for neurological assessment before treatment in line with the NICE guideline on Parkinson's disease in adults.
83. Suspect essential tremor in an adult with symmetrical postural tremor and no symptoms of parkinsonism.
84. In adults with suspected essential tremor:
 - review regular medication
 - check thyroid function
 - assess alcohol consumption using a tool such as AUDIT (Alcohol Use Disorders Identification Test), in line with the NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence.

Refer for neurological assessment only if the symptoms are disabling and first-line treatment as specified in the British national formulary is ineffective or not tolerated.

85. Consider referring adults with troublesome tremor of the head to a movement disorder clinic.
86. Follow the principles in the NICE guideline on patient experience in adult NHS services relating to communication, information and shared decision making.
87. Advise adults with suspected neurological conditions to:
 - check the government's information on driving with medical conditions to find out whether they might have a condition that needs to be notified to the DVLA (Driver and Vehicle Licensing Agency)
 - consider telling their employer, school or college if their symptoms might affect their ability to work or study.
88. Refer urgently children who present with discrete episodes of loss of awareness (mid-activity vacant spells) or of attention and concentration difficulties in line with the NICE guideline on epilepsies.
89. Be aware that medicines commonly used to treat epilepsy in children can adversely affect concentration and memory.
90. Refer children with concentration and memory difficulties that interfere with learning, school progress or behaviour to community paediatric or paediatric neurodevelopmental services for assessment.
91. Be aware that some children with attention and concentration difficulties do not have hyperactivity.
92. Refer urgently children with new-onset blackouts (transient loss of consciousness) accompanied by seizure markers for neurological assessment, in line with the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.
93. Refer urgently children with mid-activity vacant spells or behavioural outbursts associated with altered consciousness or amnesia for the events to have a paediatric assessment.
94. Refer urgently all children aged under 12 years with blackouts for paediatric assessment.

95. Do not routinely refer children aged over 12 years with blackouts if there are clear features of vasovagal syncope, even if associated with brief jerking of the limbs. See recommendation 1.1.4.3 on uncomplicated faint in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.
96. For children who have blackouts, seizures or amnesia for events after a head injury, follow the recommendations on pre-hospital assessment, advice and referral to hospital in the NICE guideline on head injury.
97. For children with unexplained acute confusion:
 - arrange an emergency transfer to hospital and
 - measure blood glucose.
98. Be aware that acute confusion in children can be a symptom of meningitis, encephalitis or poisoning. If infection is suspected, follow the recommendations on identifying people with suspected sepsis and face-to-face assessment of people with suspected sepsis in the NICE guideline on sepsis.
99. For children with acute confusion who have a non-blanching rash or other signs or symptoms suggestive of meningococcal septicaemia follow the recommendations on suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) in the NICE guideline on meningitis (bacterial) and meningococcal septicaemia in under 16s.

For other signs and symptoms of meningococcal septicaemia, see bacterial meningitis and meningococcal septicaemia in children and young people – symptoms, signs and initial assessment.

100. Be aware that isolated dizziness in children is unlikely to be a symptom of a brain tumour if there are no accompanying symptoms or signs.
101. Be aware that dizziness in children is often a symptom of migraine and may be the predominant feature.
102. Be aware that in older children (usually aged over 8 years), dizziness related to change in posture is often caused by postural hypotension.
103. In children with dizziness, examine the ears for any signs of infection, inflammation or eardrum perforation.
104. For children with recurrent episodes of dizziness:
 - consider referring for cardiological assessment if there are any factors that might suggest a cardiac cause, such as blackouts (transient loss of consciousness), a family history of cardiomyopathy or unexplained sudden death, or palpitations
 - if there are episodes of dizziness with a fixed symptom pattern, be alert to the possibility of epilepsy as the cause and follow the recommendations in the NICE guideline on epilepsies.

For recommendations on headaches or migraine in children aged over 12 years, see the NICE guideline on headaches in over 12s.

105. Refer immediately children aged under 12 years with headache for same-day assessment, according to local pathways, if they have any one of the following:
 - headache that wakes them at night
 - headache that is present on awakening in the morning

- headache that progressively worsens
 - headache triggered or aggravated by coughing, sneezing or bending down
 - headache with fever and features of meningism
 - headache associated with vomiting
 - headache associated with ataxia
 - headache associated with change in conscious level or pervasive lethargy
 - headache occurring within 5 days of a head injury
 - headache associated with squint or failure of upward gaze ('sunsetting').
106. Refer urgently all children aged under 4 years with headache for neurological assessment.
107. Perform or request fundoscopy for all children with recurrent headache and refer urgently for neurological assessment if there are abnormalities.
108. For all children with recurrent headache:
- be aware that hypertension might be the cause
 - measure the child's blood pressure and check the measurement against blood pressure reference ranges adjusted for age and height
 - refer children if headaches are consistently worsened by upright posture and relieved by lying down.
109. Do not routinely refer children with migraine unless it is affecting their school life, social life or family activities or they have one of the features listed in recommendation 104.
110. Be aware that emotional stress is a strong trigger of migraine and chronic, daily headache in children. Ask the child and their parent or carer about specific learning problems, bullying at school and stress in the family.
111. Ask about analgesic use in children with recurrent headache to ensure that medicine use is not excessive and to assess the likelihood of medication overuse headache. See the NICE guideline on headaches in over 12s for more information on medication overuse headache.
112. Refer urgently to paediatric services children with dysmorphic features and developmental delay.
113. For all children under 4 years with suspected abnormal head shape or size:
- take 3 consecutive measurements of the child's head circumference at the same appointment, using a disposable paper tape measure
 - plot the longest of the 3 measurements on a standardised growth chart, corrected for gestational age
 - if the child's head circumference is below the 2nd centile, refer for paediatric assessment.
- Offer follow-up measurements if needed, according to clinical judgement and taking the child's age into account.
114. For children with a head circumference measurement that differs by 2 or more centile lines from a previous measurement on a standardised growth chart (for example, an increase from the 25th to the 75th centile, or a decrease from the 50th to 9th centile):

- refer to paediatric services for assessment and cranial imaging to exclude progressive hydrocephalus or microcephaly or
 - refer urgently to paediatric services if the child also has any of the following signs or symptoms of raised intracranial pressure:
 - tense fontanelle
 - sixth nerve palsy
 - failure of upward gaze ('sunsetting')
 - vomiting
 - unsteadiness (ataxia)
 - headache.
115. For children with a head circumference above the 98th centile that has not changed by more than 2 centile lines from the previous measurement on a standardised growth chart, who are developing normally and who have no symptoms of raised intracranial pressure:
- note the head size of the biological parents, if possible, to check for familial macrocephaly
 - if familial macrocephaly is likely, do not routinely refer the child in the absence of any other problem.
116. For babies aged under 1 year whose head is flattened on one side (plagiocephaly):
- be aware that positional plagiocephaly (plagiocephaly caused by pressure outside the skull before or after birth) is the most common cause of asymmetric head shape
 - measure the distance between the outer canthus of the baby's eye and the tragus of their ear on each side
 - if the measurements differ, confirm positional plagiocephaly and do not routinely refer if the baby is developing normally
 - if the measurements are the same, suspect unilateral premature closure of lambdoid suture and refer to paediatric services.
117. Advise parents or carers of babies with positional plagiocephaly that it is usually caused by the baby sleeping in one position and can be improved by changing the baby's position when they are lying, encouraging the baby to sit up when awake, and giving the baby time on their tummy.
118. For babies aged under 1 year with acute-onset hypotonia (floppiness), examine the baby for signs of cardiac failure, enlargement of the liver or kidneys, pyrexia or an altered level of consciousness, and refer immediately to paediatric services.
119. For babies under 1 year with hypotonia (floppiness) that has been present for weeks or months:
- if the baby is weak (for example, feeding and breathing difficulties), refer urgently to paediatric services or
 - the baby is not weak and has no signs of intercurrent illness, consider referring in line with looking for signs of cerebral palsy in the NICE guideline on cerebral palsy under 25s.

120. Refer immediately children with sudden-onset or rapidly progressive (hours to days) limb or facial weakness for neurological assessment.
121. Refer urgently children with progressive limb weakness for neurological assessment.
122. Refer children with limb weakness that is part of a developmental disorder to paediatric services, in line with looking for signs of cerebral palsy in the NICE guideline on cerebral palsy under 25s.
123. For boys with limb weakness, see recommendations 125 and 127 on motor development delay and motor development regression in boys.
124. Refer immediately children with new-onset gait abnormality to acute paediatric services.
125. Refer children to a child development service, and consider referring for physiotherapy or occupational therapy, in line with the recommendations in the NICE guideline on cerebral palsy in under 25s, if they:
 - are not sitting unsupported by 8 months (corrected for gestational age) or
 - are not walking independently by 15 months (girls) or 18 months (boys) (corrected for gestational age) or
 - show early asymmetry of hand function (hand preference) before 1 year (corrected for gestational age).
126. If the child is a boy, consider measuring creatinine kinase level to exclude Duchenne muscular dystrophy before the boy has had a specialist review.
127. Refer children with motor developmental regression to a paediatric neurodevelopmental service or paediatric neurology depending on locally agreed pathways .
128. If the child is a boy, consider measuring creatine kinase level to exclude Duchenne muscular dystrophy before the boy has had a specialist review.
129. Refer immediately children with abnormal neck posture and a recent head or neck trauma to an emergency department for assessment, and follow recommendations 1.2.9 and 1.2.10 on cervical immobilisation in the NICE guideline on head injury and recommendation 1.1.4 on spinal immobilisation in the NICE guideline on spinal injury.
130. In children with abnormal neck posture, check whether painful cervical lymphadenopathy is the cause.
131. Refer children who develop abnormal limb posture that has no musculoskeletal cause for neurological assessment.
132. Be aware that abnormal head tilt in children can be a symptom of posterior fossa tumour.
133. Refer urgently children who have tingling accompanied by other peripheral nervous system symptoms such as weakness, bladder dysfunction or bowel dysfunction for neurological assessment.
134. Be aware that tingling in children may be the first symptom of an acute polyneuropathy (Guillain–Barré syndrome) or other neuro-inflammatory conditions. If the child has features suggesting motor impairment, refer urgently for neurological assessment.

135. Refer children with isolated tingling, altered sensation or paraesthesia for neurological assessment if the symptoms are episodic and are not associated with compression of a nerve. For more information see the recommendations on diagnosis and investigations in the NICE guideline on epilepsies.
136. Do not routinely refer children for neurological assessment of temporary tingling or numbness if there is a clear history of the symptom being triggered by activities known to cause nerve compression, such as carrying a heavy backpack or sitting with crossed legs.
137. Be aware that in children hyperventilation is a common cause of transient tingling in the limbs.
138. Refer urgently children with neuromuscular disorders who have early morning headaches or new-onset sleep disturbance for a respiratory assessment.
139. Refer urgently children who have symptoms suggestive of new-onset epileptic seizures in sleep for neurological assessment.
140. Refer children with symptoms suggestive of narcolepsy, with or without cataplexy, for neurological assessment or a sleep clinic assessment according to local pathways.
141. Refer children with symptoms of sleep apnoea to ear, nose and throat or paediatric respiratory services, as appropriate, and offer advice on weight loss if the child is obese.
142. Refer children aged over 5 years with new-onset night terrors and children with night terrors that persist after age 12.
143. Reassure parents or carers of children aged under 5 years who have night terrors, repetitive movements, sleep talking or sleep walking that these are common in healthy children and rarely indicate a neurological condition.
144. Offer advice on sleep hygiene to parents or carers of children with insomnia, and consider referring to a health visitor if the child is aged under 5 years.
145. Consider referring children with sleep disorders associated with neurodevelopmental disorders or learning disabilities to community paediatric services.
146. Be aware that sleep disorders in children may be a symptom of gastro-oesophageal reflux or constipation. See the recommendations on diagnosing and investigating gastro-oesophageal reflux disease in the NICE guideline on gastro-oesophageal reflux disease in children and young people, and the NICE guideline on constipation in children and young people.
147. Refer urgently children with new-onset slurred or disrupted speech that is not attributable to prescribed medicines, recreational drugs or alcohol for neurological assessment.
148. Consider referring children aged over 2 years with abnormal speech development to speech and language services.
149. Be aware that delay or regression in speech and language in children can be a symptom of autism. Follow the recommendations on recognising children and young people with possible autism and referring children and young people to the autism team in the NICE guideline on recognition, referral and diagnosis of autism spectrum disorder in under 19s.

150. Refer immediately children with new-onset squint that occurs together with loss of red reflex in one or both eyes to ophthalmology services.
151. Refer immediately children with new-onset squint that occurs together with ataxia, vomiting or headache to acute paediatric services.
152. Refer urgently children with paralytic squint for neurological assessment, even in the absence of other signs and symptoms of raised intracranial pressure.
153. Refer children with non-paralytic squint to ophthalmology services.
154. Refer immediately children who have sudden-onset chorea, ataxia or dystonia for neurological assessment.
155. Do not routinely refer children with simple motor tics that are not troublesome to the child.
156. Advise parents or carers of children with a tic disorder to discuss the disorder with the child's school, emphasising that the tic is an involuntary movement and the child should not be reprimanded for it.
157. Do not offer medicine for motor tics in children without specialist referral and advice (see recommendation 160).
158. Be aware that tics and stereotypies (repetitive or ritualistic movements such as body rocking) are more common in children with autism or a learning (intellectual) disability.
159. For children with a tic disorder that has a significant impact on their quality of life, consider referring according to local pathways, as follows:
 - referral to mental health services if the tic disorder is associated with symptoms of anxiety or obsessive compulsive behaviour
 - referral to the neurodevelopmental team if the tic disorder is associated with symptoms suggestive of autism or attention deficit hyperactivity disorder
 - referral for neurological assessment if the tic disorder is severe.
160. Refer urgently children presenting with tremor for neurological assessment if:
 - they have additional neurological signs and symptoms such as unsteadiness or
 - the onset of the tremor was sudden.
161. Be aware that isolated postural tremor in children may be a side effect of sodium valproate or a beta-adrenergic agonist.
162. Consider thyroid function tests for children with postural tremor and other symptoms or signs suggestive of thyroid overactivity.
163. Refer children with postural tremor for occupational therapy only if the tremor is affecting activities of daily living such as writing, eating or dressing.

2 Introduction

Neurological conditions account for more than 1 in 10 GP consultations, around 10% of emergency medical admissions (excluding stroke), and result in disability for 1 in 50 of the UK population.²¹ It has been estimated that 2–3% of children are living with special needs or some level of disability,² with most being neurological in origin.

Onset, progression, prevalence and severity vary across different neurological conditions. Some neurological conditions are present at birth, while others begin during childhood or adulthood. Some conditions can recover completely, some relapse, some remain static, and others can cause deterioration leading to premature death. Some are common, such as migraine (which affects 1 in 5 women and 1 in 15 men) and others are rare, such as Guillain–Barré syndrome (which affects about 1,200 people in the UK per year). Most neurological disorders have an impact on the person's quality of life, and some cause serious disability that substantially affects family and carers.

Neurological symptoms in primary care may be difficult to interpret, which can make diagnosing neurological conditions difficult and the decision about whether to refer for a specialist opinion or for investigation challenging. People often present with symptoms that are medically unexplained (functional symptoms), which may mimic physical disease. Up to one-fifth of new neurology outpatients have functional symptoms.¹⁹ Interpretation of the examination of the nervous system to determine the significance of physical signs and distinguish functional from organic symptoms sometimes requires a high level of skill, and referral for a neurology assessment may be appropriate to undertake this.

Current practice

People with suspected neurological conditions often need referral to a specialist to be diagnosed and treated. However, some referrals are unnecessary as the neurological condition can be managed adequately in primary care. Some people with neurological conditions are initially misdiagnosed or have a delayed referral to a specialist resulting in tardy treatment or adverse outcomes. A report from the Neurological Alliance²² in 2014 found that over 40% of people with a neurological condition had to see their primary care physician 5 or more times before being referred to a specialist. By 2016 this has worsened to 42%, which corresponds to the period over which this guideline was being developed. These referral issues sometimes stem from a lack of support and knowledge among non-specialists about the extensive and growing field of clinical neurology and neurosurgery. It is impractical for a generalist to keep abreast of the range of neurological treatments available and sometimes to appreciate the significance of neurological symptoms. The decision to refer to secondary care is therefore often difficult and may be contentious. This guideline aims to facilitate these decisions.

People suspected of having, and people living with, chronic neurological conditions may have additional information needs, including understanding the type of investigations that need to be done, the diagnostic possibilities and their prognostic implications. Some of this must be provided in primary care and some will require specialist knowledge and assistance. Psychiatric symptoms, including anxiety and depression, are common in patients with neurological symptoms, and patients may benefit from psychological support before, during and after diagnosis.

Neurological specialist services are generally under-provided in England and Wales, with the number of neurologists below the European average²⁶ and a disproportionate concentration of neurologists around London. A report from the Public Accounts Committee noted variation in both the access to health services for those with neurological condition and variation in quality of neurological services around the country.⁷ Neurological emergency admissions have increased. Against this backdrop, it is important that neurological referrals are targeted effectively to facilitate prompt access for those at greatest need and that unnecessary and inappropriate referrals to specialist services are minimised.

Policy, legislation, regulation and commissioning

Many specialist professional and charitable bodies have produced guidance for specific neurological conditions, but there is a lack of overarching accessible guidance on referral available for neurological conditions aimed at the generalist physician. This lack of support, particularly for uncommon neurological conditions, was highlighted by the National Audit Office¹⁰ report on services for people with neurological conditions. The report recommended that “the Department [of Health] should instruct NICE to develop a generic quality standard covering other neurological conditions”. The UK Strategy for Rare Diseases³ (Department of Health) highlights issues with delays to diagnosis and aims to improve the overall patient journey from first contact with the NHS.

Aim of the guideline

The guideline aims to provide information to non-specialists about referral of the common and important neurological ‘presentations’ in non-specialist settings, for example to primary and emergency care. It is not intended as a substitute for a textbook, and the guideline committee accepted that a high level of competence in neurological examination would not be expected of a generalist.

Scope of the guideline

Because of the vast potential breadth of neurological conditions, the scope (appendix A) concentrated on more common presentations of neurological symptoms, with indications for referral to specialist care. If recognition or referral was already covered in existing NICE guidance, the guideline cross-refers.

Criteria (symptoms, signs, risk factors and red flags) representing need for referral were identified, and the urgency of referral is indicated where appropriate. We have highlighted where investigations are appropriate before referral.

Expected readership

- Healthcare professionals in primary and secondary care.
- Neurology departments.
- People using services, their family members and carers, and the public.

3 Development of the guideline

3.1 What is a NICE guideline?

NICE guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. These may also include elements of social care or public health measures. We base our guidelines on the best available research evidence with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patients and health professionals.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a guideline committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The ‘NICE guideline’ lists the recommendations.
- ‘Information for the public’ is written using suitable language for people without specialist medical knowledge.
- NICE Pathways bring together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is to produce a guideline on the assessment, diagnosis and referral of suspected neurological conditions.

3.3 Who developed this guideline?

A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members developed this guideline (see the list of guideline committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by Richard Grünewald in accordance with guidance from NICE.

The group met approximately every 5 to 6 weeks during the development of the guideline. At the start of the guideline development process, all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix B.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information specialists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

This guideline will cover children, young people and adults who present in non-specialist settings with symptoms suggestive of a neurological condition. Children aged 5 years and under have been identified as a subgroup needing specific consideration. For further details, please refer to the scope in appendix A and the review questions in section 4.3.

3.3.2 What this guideline does not cover

This guideline does not cover neonates (infants aged 28 days and under).

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE guidelines:

- [Chronic fatigue syndrome/myalgic encephalomyelitis \(or encephalopathy\): diagnosis and management](#). NICE guideline CG53. August 2007
- [Meningitis \(bacterial\) and meningococcal septicaemia in under 16s: recognition, diagnosis and management](#). NICE guideline CG102. June 2010.
- [Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence](#). NICE guideline CG115. February 2011.
- [Autism spectrum disorder in under 19s: recognition, referral and diagnosis](#). NICE guideline CG128. September 2011.
- [Patient experience in adult NHS services: improving the experience of care for people using adult NHS services](#). NICE guideline CG138. February 2012.
- [Headaches in over 12s: diagnosis and management](#). NICE guideline CG150. September 2012.
- Falls in older people: assessing risk and prevention. NICE guideline CG161. June 2013.
- [Head injury: assessment and early management](#). NICE guideline CG176. January 2014.

- [Transient loss of consciousness \('blackouts'\) in over 16s](#). NICE guideline CG109. September 2014.
- [Multiple sclerosis in adults: management](#). NICE guideline CG186. October 2014.
- [Obesity: identification, assessment and management](#). NICE guideline CG189. November 2014.
- [Gastro-oesophageal reflux disease in children and young people: diagnosis and management](#). NICE guideline NG1. January 2015.
- [Suspected cancer: recognition and referral](#). NICE guideline NG12. June 2015.
- [Coeliac disease: recognition, assessment and management](#). NICE guideline. NG20. September 2015
- [Epilepsies: diagnosis and management](#). NICE guideline CG137. February 2016.
- [Motor neurone disease: assessment and management](#). NICE guideline NG42. February 2016.
- [Spinal injury: assessment and initial management](#). NICE NG41. February 2016.
- [Sepsis: recognition, diagnosis and early management](#). NICE guideline NG51. July 2016.
- [Low back pain and sciatica in over 16s: assessment and management](#). NICE guideline NG59. November 2016.
- [Cerebral palsy in under 25s: assessment and management](#). NICE guideline NG62. January 2017.
- [Neuropathic pain in adults: pharmacological management in non-specialist settings](#). NICE guideline CG173. February 2017.
- [Stroke and transient ischaemic attack in over 16s](#). NICE guideline CG68. March 2017.
- [Constipation in children and young people: diagnosis and management](#). NICE guideline CG99. July 2017.

Related NICE guidance currently in development

- [Parkinson's disease in over 20s: diagnosis and management](#). NICE guideline. Publication expected July 2017.
- [Attention deficit hyperactivity disorder \(update\)](#). NICE guideline. Publication expected February 2018.
- [Dementia: assessment, management and support for people living with dementia and their carers](#). NICE guideline. Publication expected June 2018.
- [Brain tumours \(primary\) and brain metastases in adults](#). NICE guideline. Publication expected July 2018.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. There were unusual methodological challenges for this guideline: i) the majority of the review questions focused on the initial presentations which might raise suspicion of a number of possible neurological diagnoses, instead of the traditional diagnostic questions on signs and symptoms of a single, specific condition; ii) the large number of neurological conditions covered by the guideline; and iii) the sparsity or lack of published evidence. A mixture of alternative approaches, together with NICE standard methodology where possible, were adopted to address these challenges. Where systematic reviews of evidence have been undertaken, NICE standard methodology was used in accordance with the NICE guidelines manual, 2014 version,¹¹ a description of which is outlined in section 4.2.

The challenges that arose for each key area of the scope, and the methods chosen to address these, are summarised below:

- For questions on symptoms, initial literature searches retrieved extremely large numbers of papers of very limited relevance for inclusion, or with no relevance at all. There was a lack of high quality evidence in the key areas the guideline is covering and there was likely to be limited available evidence due to the relative rarity of neurological conditions.
- For questions on examinations and investigative tests, there was limited available evidence because general examination techniques are accepted practice and either free or low cost, so they are unlikely to be a research priority. In addition, clinicians will have already examined the patient to some extent before they suspect a neurological condition and will be familiar with standard practice examination techniques from their medical training.
- For the question on information and support for patients, there would be difficulty developing a focused protocol due to a very broad population of this guideline population that covers a large number of neurological conditions. Therefore, it would be difficult to identify and give guidance on specific support and needs for these patients.

Therefore, an alternative approach was undertaken and is summarised below:

- Prior to the first guideline committee meeting, the Chair (adult neurologist) and a committee member (paediatric neurologist) drafted an initial list of the signs and symptoms for which patients are currently referred to them for neurological assessment, based on their knowledge and expertise.
- During the first 2 committee meetings, committee members discussed the circumstances under which referrals should and should not be made (based on their knowledge and expertise), considering both red and green flags, and identifying areas of uncertainty, contention and disagreement.
- The committee then categorised the initial list of signs and symptoms based on consideration of whether an evidence review would add value. Decisions took into account whether the sign or symptom is being recognised already by non-specialists, whether there are issues with inappropriate referrals, whether there is disagreement about patients being referred or not, and whether there is a limited lack of published evidence based on their knowledge in the field.
- The list of signs and symptoms was then split into 4 categories based on the committee's discussions, and a mix of committee consensus and evidence reviews was used to formulate draft recommendations. A summary of the committee's decisions and rationales is provided in appendix O.

The 4 categories were as follows:

1. Category 1: signs and symptoms for which there are current issues of over-referral or under-referral, where based on their knowledge and expertise the committee were in agreement that

the optimal referral advice is clear and non-contentious and where an evidence review would not change this or add value. The committee drafted the recommendations for these signs and symptoms by consensus and no systematic reviews of evidence were undertaken.

2. Category 2: signs and symptoms for which it is unclear in which circumstances patients should be referred. Systematic evidence reviews were carried out for these signs and symptoms.
3. Category 3: signs and symptoms covered by recognition and referral recommendations in existing NICE guidance. The committee signposted to these recommendations where appropriate.
4. Category 4: signs and symptoms that are not prioritised for inclusion within the guideline either because current referral patterns are already working well or the presentation is too infrequent to require national guidance.

As the draft recommendations for signs and symptoms in category 1 are based on the committee's knowledge and expertise and had not been produced with the benefit of an evidence review, the committee agreed that further validation from other external experts is necessary. This further validation was conducted through a targeted engagement exercise with a sample of expert advisors (outlined in section 4.1 below) which took place prior to the main stakeholder consultation.

Draft recommendations for signs and symptoms in categories 2 and 3 were not included in the targeted engagement exercise. Standard guideline methodology was followed for the signs and symptoms in category 2 (see sections 4.2). Recommendations in category 3 consist of cross-references to published NICE recommendations. Both categories 2 and 3 did not require feedback from expert advisors as these were in line with standard methodology.

As indicated at the start of this section, the committee judged that there was limited value in undertaking evidence reviews for most of the questions on investigative tests and all the questions on information for patients. Therefore, NICE agreed that the committee could make recommendations for these questions by consensus.

4.1 Targeted engagement exercise with external experts:

The targeted engagement exercise focussed on draft recommendations for referral (or non-referral) of signs and symptoms in category 1. Once the committee had formulated draft consensus recommendations for the identified questions, the targeted engagement exercise provided an opportunity for expert advisors to ratify and suggest changes to the recommendations for inclusion in the final draft of the guideline before the main consultation.

The targeted engagement exercise is summarised below:

1. The targeted engagement exercise took place towards the end of the development phase. An online survey using modified RAND rating for agreement was run for 4 weeks, from 23 January to 17 February 2017.
2. Recruitment of external experts: recruitment took place in late autumn 2016. A formal open recruitment process was followed. An advertisement was posted on the NICE website for 1 month, which explained the reasons for recruitment and highlighted the time commitment and input required. Key stakeholder organisations including the Association of British Neurologists, British Paediatric Neurology Association, Primary Care Neurology Society, Royal College of GPs and the Royal College of Emergency Medicine, and other specialist societies were notified of the advertisement. External experts were invited to apply with their CV and to declare any conflicting interests. The Chair and Guideline Lead checked external experts based on their level of expertise and the relevance of their role. External experts were asked to sign consent and confidentiality forms. The list of expert advisors is listed in appendix P.

3. Constituency of external experts: The aim was to recruit approximately 30 external experts to account for withdrawal and non-responders and to include both adult and paediatric neurology specialists and non-specialists including primary care physicians.
4. Online survey using modified RAND rating for agreement: An online survey was developed asking external experts whether they agreed with the draft recommendations. If they did not agree, external experts were asked to provide comments on their reasoning (and if possible, alternative suggestions or wording) for the committee's consideration.
5. Results and analysis:
 - a. There were 43 external experts in total consisting of the following expertise: 9 adult neurologists (20.9%), 7 paediatric neurologists (16.3%), 9 general practitioners (20.9%) and 18 other professionals including paediatricians, psychiatrists and physiotherapists (41.9%).
 - b. The external experts were given the option of commenting on either the adult or the children's recommendations or both. Fifteen external experts (34.9%) provided feedback on adult recommendations, 21 external experts (48.8%) provided feedback on the children's recommendations and 7 external experts (16.3%) provided feedback on recommendations for both age groups.
 - c. The committee agreed that the threshold for agreement was 75%, which is a threshold that is widely used for other consensus methods such as Delphi and RAND and was determined to be a good threshold for agreement in a recent systematic review by Diamond et al (2014)⁴. However, the results showed that although most recommendations reached the 75% agreement threshold, many external experts had provided very helpful comments that would improve the clarity and content of the recommendations. Therefore, the committee revisited the majority of the recommendations in light of the external experts' feedback. A summary of the feedback from the targeted engagement exercise and the actions the committee took for each recommendation is included in the 'recommendations and link to evidence' sections under 'other considerations'.
6. Following the targeted engagement exercise, the revised draft recommendations were submitted for the main consultation with all stakeholders along with the other recommendations in categories 2 and 3.

All results from the targeted engagement exercise are available in appendix S.

4.2 Evidence reviews

Sections 4.2, 4.3, 4.4 and 4.5 describe the process used to identify and review clinical evidence (summarised in Figure 1), section 4.6 describes the process used to identify and review the health economic evidence, and section 4.7 describes the process used to develop recommendations.

Figure 1: Step-by-step process of review of evidence in the guideline



4.3 Developing the review questions and outcomes

Review questions were developed using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy and using population, presence or absence of factors under investigation and outcomes for clinical prediction reviews. This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the committee’s development of the recommendations. The NGC technical team drafted the review questions, and the committee refined and validated them. The questions were based on the key clinical areas identified in the scope (appendix A).

A total of 10 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

For questions on category 2 symptoms, the committee wanted to consider any studies that determine whether a certain sign or symptom accompanying a main presenting symptom (for example, hearing loss in the presence of dizziness) is indicative of a neurological condition that requires onward referral for a specialist assessment. Therefore, measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC and AUC were considered as the main outcomes of interest. However, the committee was aware that there was limited evidence available in this area; therefore, the committee considered clinical prediction studies where a multivariate analysis was conducted and adjusted odds ratios for outcomes of

interest were presented. Hence, some of the clinical questions were reviewed using a mix of diagnostic and clinical prediction strategies.

Table 1: Review questions on category 2 symptoms

Chapter	Type of review	Review questions	Outcomes
5.2.1 Dizziness and vertigo in adults	Diagnostic and clinical prediction	In adults and young people who present with dizziness or vertigo, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ central nervous system causes such as posterior circulation strokes and other (migraines, tumours) ○ peripheral vestibular disorders, including posterior semi-circular canal dehiscence, BPPV, and labyrinthitis ○ cardiovascular disorders (presyncope, postural hypotension) ○ functional disorders ○ vertebrobasilar insufficiency.
5.2.2 Dizziness and vertigo in adults	Diagnostic	In people with suspected (or under investigation for) new onset of vertigo or dizziness, is the HINTS (Head-Impulse—Nystagmus—Test-of-Skew) test effective in identifying whether there is a central nervous system cause, as indicated by the reference standard, MRI?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value
5.3 Atraumatic facial pain in adults	Diagnostic and clinical prediction	In adults who present with atraumatic facial pain, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ carotid and vertebral artery dissection ○ cluster headache ○ dental pain ○ max sinusitis ○ migraine facial pain ○ occipital neuralgia ○ temporal arteritis ○ tension headache ○ TMJ dysfunction ○ trigeminal neuralgia.

Chapter	Type of review	Review questions	Outcomes
5.8.2 Memory tests in adults	Diagnostic	In adults under 40 with suspected (or under investigation for) memory failure, what is the negative predictive value of neuropsychological assessments in ruling out organic memory failure?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value
5.10 Sensory symptoms such as tingling or numbness	Diagnostic and clinical prediction	In people (adults, young people and children) who present with tingling or altered sensation in the body, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ compression neuropathy (for example, carpal tunnel syndrome and Meralgia parasthetica) ○ demyelination ○ drug toxicity – chemotherapy, alcohol, platinum-based drugs ○ functional (hyperventilation) ○ mononeuropathy multiplex ○ peripheral neuropathy ○ radiculopathy ○ seizures ○ small fibre neuropathy ○ TIAs ○ tethering of the spinal cord.
5.15 Tremor in adults	Diagnostic and clinical prediction	In adults and young people who present with tremor, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ cerebellar tremors ○ drug-related tremors ○ dystonic tremor (task-specific tremor) ○ essential tremor ○ neuropathic tremor ○ parkinsonism ○ physiological tremor ○ primary orthostatic tremor ○ psychogenic tremors ○ thyroid disorder.

Chapter	Type of review	Review questions	Outcomes
7.2 Blackouts and paroxysmal events in children	Diagnostic and clinical prediction	In children and babies who present with paroxysmal events, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ behavioural (that is, temper tantrums, breath-holding attacks and emotional disorders) ○ cardiac disorders – long QT, left ventricular outflow obstruction ○ epilepsy ○ reflex anoxic seizures ○ vasovagal syncope or postural hypotension.
7.5 Headaches in children	Diagnostic and clinical prediction	In children under 12 who present with headache, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ brain tumour ○ chronic daily headaches ○ hydrocephalus ○ idiopathic intracranial hypertension ○ intracranial infection ○ migraine ○ nocturnal hypoventilation ○ raised intracranial pressure ○ sinusitis ○ venous sinus thrombosis.
7.6 Head shape or size abnormalities in children	Diagnostic and clinical prediction	In children and babies who present with abnormal head shape or size, what is the accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological problems?	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive/negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ microcephaly ○ familial macrocephaly ○ hydrocephalus ○ positional plagiocephaly ○ single suture synostosis ○ multiple suture synostosis

Chapter	Type of review	Review questions	Outcomes
			<ul style="list-style-type: none"> ○ syndromic synostosis ○ growing skull fracture.
7.9.2 Motor developmental delay in children	Diagnostic	In children and infants under 10 years of age who present with motor developmental delay, is a creatine kinase (CK) test accurate in identifying whether muscular dystrophy is present as compared to no test (and as indicated by the reference standard, diagnosis at follow-up)?	Main outcomes: <ul style="list-style-type: none"> ● Sensitivity (%) and specificity (%) ● Area under the ROC curve (AUROC) – measure of predictive accuracy ● Positive/negative predictive value

4.4 Searching for clinical evidence

4.4.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.¹¹ Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed. All searches were conducted in Medline and Embase, and additional searches made in The Cochrane Library for diagnostic test questions. Searches were run between 3 June 2016 and 19 October 2016. No papers published after 19 October 2016 were considered.

Search strategies were quality assured by crosschecking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight any additional studies. Searches were quality assured by a second information specialist before being run. The questions, the study types applied, the databases searched, the years covered and the date each search was run can be found in appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- NHS Evidence Search (www.evidence.nhs.uk).

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken.

Due to the broad population of the guideline and the inclusion of non-randomised trials, initial evidence searches retrieved significantly large numbers of abstracts (tens of thousands for each question). Therefore, to make the most efficient use of time and resources, the searches had to be specific. The committee was aware of a recent widely agreed classification that was published by the Neurological Intelligence Network (NIN)¹⁷ and which used the International Classification of Diseases codes (ICD10 2015) to define the conditions included in adult neurology in England. The committee used this classification to map out each sign and symptom to the relevant conditions, which were

then used to narrow down the populations in the search strategy and hence obtain more precise and focused abstracts. For conditions relating to childhood conditions, the paediatric specialists on the committee used the NIN list as a basis for producing a list of relevant conditions for children. The conditions and population included for each search strategy are listed in the protocols in appendix C and in the search strategies in appendix G.

4.4.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to suspected neurological conditions in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA) with no date restrictions, (NHS EED ceased to be updated after March 2015). Additionally, the search was run on Medline and Embase using a health economic filter, from January 2015, to ensure recent publications that had not yet been indexed by the economic databases were identified. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in appendix G. All searches were updated on 9 March 2017. No papers published after this date were considered.

4.5 Identifying and analysing clinical evidence

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in appendix C).
- Critically appraised relevant studies using the appropriate study design checklist as specified in the NICE guidelines manual.¹¹ [Clinical prediction studies were critically appraised using NGC checklists](#). Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
 - o Clinical prediction data were meta-analysed where appropriate and reported in GRADE-like profile tables.
 - o Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers, and a senior research fellow double sifted those for complex review questions (for example, clinical prediction reviews). Any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
 - o papers were included or excluded appropriately
 - o a sample of the data extractions
 - o correct methods were used to synthesise data
 - o a sample of the risk of bias assessments.

4.5.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies were based on the criteria defined in the review protocols, which can be found in appendix C. Excluded studies by review question (with the reasons for their

exclusion) are listed in appendix L. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- children, young people and adults who present to non-specialist settings with symptoms suggestive of a neurological condition.

The key population exclusion criterion was:

- neonates (infants aged 28 days and under).

Conference abstracts were not automatically excluded from any review. The abstracts were initially assessed against the inclusion criteria for the review question and further processed when a full publication was not available for that review question. If the abstracts were included, the authors were contacted for further information. No relevant conference abstracts were identified for this guideline. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.5.2 Type of studies

For diagnostic accuracy review questions, diagnostic RCTs, cross-sectional studies and retrospective cohort studies were considered for inclusion. For clinical prediction review questions, only prospective and retrospective cohort studies that conducted a multivariate analysis including at least some of the predictors and key confounders identified in the protocols were included. Case-control studies were not included.

4.5.3 Methods of combining clinical studies

4.5.3.1 Data synthesis for diagnostic test accuracy reviews

Diagnostic test accuracy measures used in the analysis were area under the receiver operating characteristics (ROC) curve (AUC) and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice, this varies amongst studies. If a test has a high sensitivity, then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a specificity of 97% will only incorrectly diagnose 3% of people who do not have the condition as positive. For most of the reviews in this guideline, sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications, which can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Coupled forest plots of sensitivity and specificity with their 95% CIs across studies were produced for each test, using RevMan5.²⁰ In order to do this, 2x2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given or else were derived from raw data or calculated from the set of test accuracy statistics.

Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS software.²⁵ The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere.^{18,23,24} The bivariate method uses logistic regression on the true

positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity, specificity and confidence regions were plotted (using methods outlined by Novielli 2010.¹⁶) Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots and pooled diagnostic meta-analysis plots.

4.5.3.2 Data synthesis for clinical prediction reviews

Odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs), with their 95% CIs, for the effect of the pre-specified clinical prediction factors were extracted from the studies. Studies were only included if the confounders the committee pre-specified were either matched at baseline or were adjusted in multivariate analysis.

Studies of lower risk of bias were preferred, taking into account the analysis and the study design. In particular, prospective cohort studies were preferred if they reported multivariate analyses that adjusted for the key confounders that the committee identified at the protocol stage for that outcome.

Data were not combined in meta-analyses for clinical prediction studies.

4.5.4 Appraising the quality of evidence by outcomes

4.5.4.1 Diagnostic studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see appendix H in the NICE guidelines manual 2014¹¹). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Table 2):

- patient selection
- index test
- reference standard
- flow and timing.

Table 2: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) or reference standard or who were excluded from the 2x2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the	Is the reference standard likely to correctly classify	Was there an appropriate interval between index test(s) and reference standard?

Domain	Patient selection	Index test	Reference standard	Flow and timing
		reference standard?	the target condition?	
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
		Were all patients included in the analysis?		
Risk of bias; (high/low/unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.5.4.1.1 *Inconsistency*

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the sensitivity or specificity (based on the most important outcome for each particular review question) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold the committee set (the threshold above which it would be acceptable to recommend a test). For example, the committee might have set a threshold of 90% sensitivity as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example, 50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0–50%, 50–90% and 90–100%).

4.5.4.1.2 *Imprecision*

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the diagnostic meta-analysis, if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only 1 study contributed to the evidence, the 95% CI around the single study. As a general rule (after discussion with the committee), a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.5.4.1.3 *Overall grading*

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, –1 or –2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to –8 (the worst possible). However, scores were capped at –3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. Quality rating started at High for prospective and retrospective cross-sectional studies, and each major

limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment. Each of these studies started at High and the overall quality became Moderate, Low or Very Low if the overall score was -1, -2 or -3 points respectively. The significance of these overall ratings is explained in Table 3. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Table 3: Overall quality of outcome evidence in modified GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.5.4.2 Clinical prediction reviews

A modified GRADE methodology was used for clinical prediction studies, considering risk of bias, indirectness, inconsistency and imprecision.

The quality of evidence for risk prediction studies was evaluated according to the criteria given in Table 4. This table was adapted from the Quality In Prognosis Studies tool (QUIPS)⁵. If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then a quality rating was presented for each study.

Table 4: Description of quality elements for prospective studies (adapted from the QUIPS tool)

Domain	Risk of bias clinical prediction studies	Response and score
Selection bias	Was there a lack of reported attempts made to achieve some group comparability between the risk factor and non-risk factor groups? (ignore if 2 or more risk factors considered)	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Was there a lack of consideration of any of the key confounders, or was this unclear? Note that if the study can show that a particular confounder was not at risk of causing bias (for example, by being well-matched at baseline between groups), then this confounder does not have to be adjusted for a multivariate analysis.	Exclude.
	Was there a lack of consideration of non-key plausible confounders, or was this unclear? Note that if the study can show that a particular confounder was not at risk of causing bias (for example, by being well-matched at baseline between groups), then this confounder does not have to be adjusted for a multivariate analysis.	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	If the outcome is categorical: Were there <10 events per variable included in the multivariable analysis? If the outcome is continuous: Were there <10 people per variable included in the multivariable analysis?	Consider if this was moderate, high or very high risk of bias if answer was 'yes' to either.
	Was it very clear that 1 group was more likely to have had more outcomes occurring at baseline than another group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
Detection bias	Was there a lack of assessor blinding AND the outcome was not completely objective?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.

Domain	Risk of bias clinical prediction studies	Response and score
	Were the risk factors measured in a way that would systematically favour either group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Were the outcomes measured in a way that would systematically favour either group?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	If there were multiple raters, was there lack of adjustment for systematic inter-rater measurement errors, or was inter-rater reliability unreported?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Was there an excessively short follow-up, such that there was not enough time for outcomes to occur?	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
Attrition bias	Was there >10% group differential attrition (for reasons related to outcome) and there was no appropriate imputation? (if 1 risk factor) or	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
	Was there >10% overall attrition (for reasons related to outcome) and there was no appropriate imputation? (if > 1 risk factor).	Consider if this was moderate, high or very high risk of bias if answer was 'yes'.
For each domain make a judgement of risk of bias (for example, very high if there are 2 moderate boxes and a high box).		
Sum these domain risks to form an overall rating of risk of bias (for example, no risk, serious risk or very serious risk).		

The risk of bias rating was assigned per study for each combination of risk factor or outcome. When studies were pooled, the overall risk of bias for all studies covering a specific risk factor or outcome was determined by a weighted mean of the ratings across the studies (no risk = 0; serious risk = -1 and very serious risk = -2). The weighting depended on the weighting used in the meta-analysis, as in intervention reviews. Where a meta-analysis had not been conducted, a simple average was used.

4.5.4.2.1 Indirectness

Indirectness refers to the extent to which the populations, risk factors and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews, as explained for intervention reviews. As for risk of bias, each outcome had its indirectness assessed within each study first. For each paper, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example, in terms of population), indirectness was given a 'serious' rating of -1, but if there was indirectness in 2 or more sources (for example, in terms of population and risk factor), the indirectness was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weights in the meta-analysis.

4.5.4.2.2 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When heterogeneity existed within an outcome (chi-squared $p < 0.1$, or $I^2 > 50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of -1 if the I^2 was 50–74% and a 'very serious' score of -2 if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an $I^2 < 50\%$), the committee considered this and considered whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory

factors. In such a situation, the quality of evidence was not downgraded for those emergent outcomes.

4.5.4.2.3 Imprecision

The criteria applied for imprecision were based on the confidence intervals around the estimate of association between the risk factor/predictor and the outcome (condition of interest). The decision to downgrade was discussed with the committee and was based on the interpretations of the width of the confidence intervals and how certain the committee was in drawing a conclusion (that is, how certain that there is no association, or a positive association, or a negative association (protective) between the risk factor/predictor and the outcome (condition of interest).

4.5.4.2.4 Overall grading

Quality rating started at High for prospective studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for diagnostic reviews above. For clinical prediction reviews, prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually inappropriate for these types of review for ethical or pragmatic reasons. Furthermore, if the study looked at more than 1 risk factor of interest then randomisation would be inappropriate, as it can only be applied to 1 of the risk factors.

4.5.5 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- an indication of the direction of clinical importance (if 1 treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of the evidence (GRADE overall quality).

4.6 Identifying and analysing evidence of cost effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. However, the committee will also need to be increasingly confident in the cost effectiveness of a recommendation as the cost of implementation increases. Therefore, the committee may require more robust evidence on the effectiveness and cost effectiveness of any recommendations that are expected to have a substantial impact on resources; any uncertainties must be offset by a compelling argument in favour of the recommendation. The cost impact or savings potential of a recommendation should not be the sole reason for the committee's decision.¹¹

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- Undertook a systematic review of the published economic literature.
- Considered options for new cost-effectiveness analysis in priority areas.

4.6.1 Literature review

The health economists identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers would then have been obtained, reviewed against inclusion and exclusion criteria and critically appraised where relevant. However, for this guideline, a review of the health economic search results did not lead to the identification of any potentially relevant studies. Therefore, none were ordered or critically appraised. A second health economist reviewed and confirmed the decision not to order any full papers.

4.6.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2000 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.6.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, the health economist undertook a new health economic analysis in selected areas. The committee considered the priority areas for a new analysis after the formation of the review questions and consideration of the existing health economic evidence.

Due to the absence of economic and clinical evidence regarding individual review questions, no review questions were selected for original economic analysis.

Instead, a brief cost-impact analysis was conducted of the cost of neurological outpatient appointments (appendix N). This looked at the costs of adult and child neurology appointments and the current total annual cost of such appointments to the NHS.

This information was then used in each of the evidence reviews as a comparison point by which any changes to current practice included in the recommendations made in that review could be judged in terms of changes to cost impact, particularly with respect to any recommendations that might be expected to increase the number of referrals by GPs to neurology services for assessments, and hence to increase the total cost of neurology services compared to current practice. This is discussed in the recommendations and link to evidence tables in each section of the guideline.

4.6.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.¹² In general, an intervention was considered to be cost effective (given that the estimate was considered plausible) if either of the following criteria applied:

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.¹²

When QALYs, or life years gained, are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.6.4 In the absence of health economic evidence

When no relevant published health economic studies were found and a new analysis was not prioritised, the committee made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.7 Developing recommendations

Over the course of the guideline development process, the committee was presented with:

- Evidence tables of the clinical evidence reviewed from the literature. All evidence tables are in appendix H.
- Summaries of clinical and health economic evidence and quality (as presented in chapters 5-7).
- Forest plots and summary ROC curves (appendix K).
- A description of the methods and results of the cost-impact analysis undertaken for the guideline (appendix N).

Recommendations were drafted based on the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was completed either formally in an economic model or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences) and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations

were agreed through discussions in the committee. The committee also considered whether the uncertainty was sufficient to justify a delay in making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 4.7.1 below).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention (referral in this guideline) if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effects and others are not. In these circumstances, the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example, the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see section 9.2 in the 2014 NICE guidelines manual¹¹).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.7.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

Although research questions were debated, in the end, the committee did not make any future research recommendations. This was partly because many of the questions had not been the subject of a literature search (see reasons in section 4), and therefore the committee could not be absolutely certain that questions had not been addressed already. In addition, the practical difficulties of research into presenting symptoms made it, in the committee's judgement, unlikely that the projects would be commissioned.

4.7.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.7.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.7.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.7.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Part 1: Adults aged over 16 – signs, symptoms and investigative tests

5.1 Blackouts in adults

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.1.1 Recommendations and link to evidence (consensus statements 10 to 16 in appendix S)

<p>Recommendations</p>	<ol style="list-style-type: none"> 1. Refer urgently adults with new-onset blackouts (transient loss of consciousness), accompanied by features that are strongly suggestive of epileptic seizures, for neurological assessment in line with the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s. 2. Do not routinely refer adults with blackouts if there are clear features of vasovagal syncope, even if associated with brief jerking of the limbs. See recommendation 1.1.4.3 on uncomplicated faint in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for adults because the NICE guideline on transient loss of consciousness ('blackouts') in over 16s (CG109) covers non-specialist settings and provides comprehensive recommendations on recognition and referral. The committee therefore decided to cross-refer to this guideline.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 1 – Blackouts accompanied by seizure markers</p> <p>A blackout associated with seizure markers may indicate the onset of epilepsy. Seizure markers include:</p> <ul style="list-style-type: none"> • a bitten tongue • confusion following the event • head-turning to one side during TLOC • no memory of abnormal behaviour that was witnessed before, during or after TLOC by someone else • prodromal <i>déjà vu</i> or <i>jamais vu</i> • prolonged limb-jerking (note that brief seizure-like activity can often occur during uncomplicated faints) • unusual posturing. <p>Seizure markers also include episodic fixed pattern involuntary behaviours or hallucinations and brief motor phenomena (for example stiffening or jerking of part of the body) which may or may not be associated with impairment of consciousness. Brief limb jerks in full consciousness and momentary blank spells can also be features of epilepsy in adults.</p> <p>The committee had the benefit of being able to cross-refer to the NICE guideline on transient loss of consciousness, which includes a consideration of suspected epilepsy. Uncontrolled epileptic seizures could lead to injury or death, and new onset epilepsy can be the presenting feature of yet undiagnosed brain pathology. As such, urgent referral for assessment and treatment is advised.</p>

	<p>Recommendation 2 – Transient loss of consciousness (TLOC) and vasovagal syncope</p> <p>Vasovagal syncope is common and can often be diagnosed through the history or augmented by an eyewitness account. It requires minimal investigation unless accompanying ‘red flag’ features are present (NICE TLOC guideline CG 109). Of note, some jerking of limbs is common during a vasovagal episode. This alone should not be understood as indicating epilepsy or another serious pathology. Management is summarised in NICE TLOC guidance (CG 109).</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee felt that the recommendations would not change the number of referrals given that they appear in other NICE guidance, and hence there will be no change from current costs.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>Both these recommendations received a high level of agreement ranging from 77.8% to 88.9%. Some helpful, minor adjustments to the wording were made following suggestions from the targeted engagement exercise group. Most importantly, responders indicated that these recommendations would only apply to people with a first presentation who have not been previously assessed by specialists. Therefore, ‘new onset’ was added to the recommendation to make this clear. For the sake of clarity, the original 3 recommendations have been edited into the current 2.</p>

5.2 Dizziness and vertigo in adults

Dizziness is a common complaint in A&E departments and in primary care. Although many cases have a benign self-limiting cause, the symptom can also be the presenting feature of a serious medical condition. The term dizziness encompasses a variety of different symptoms, including light-headedness, weakness, and true vertigo. For vertigo, the challenge is to differentiate benign peripheral vertigo from the potentially more serious central vertigo, which may be the result of a posterior circulation stroke. Unfortunately, focal neurologic deficits on examination may be absent in posterior circulation stroke, and people with dizziness are therefore frequently sent for CT scans to exclude stroke. This is costly; moreover, CT scans are insensitive in detecting infarcts in the brainstem or cerebellum. MRI is more reliable than CT, but less readily available and at least as expensive. A rapid, bedside test to help differentiate central from peripheral vertigo would therefore have great value; the HINTS examination has been developed to address this need.

HINTS stands for Head Impulse, Nystagmus, and Test of Skew. It is a 3-part procedure. It has been proposed that a negative HINTS test (that is an abnormal head impulse test plus no nystagmus or direction-fixed horizontal nystagmus, plus no skew deviation), makes a central aetiology unlikely and further scanning is unnecessary.

The aim of the first part of the review is to identify signs and symptoms that, if presenting with dizziness or vertigo, would indicate a neurological condition that requires referral for further specialist assessment.

The aim of the second part of the review was to evaluate the accuracy of HINTS test in diagnosing a central nervous system cause of new onset vertigo or dizziness. In other words, how accurate is the test at distinguishing central causes (that is, damage to the brainstem) such as stroke or MS from peripheral causes due to problems with the inner ear.

5.2.1 Dizziness

5.2.1.1 Review question: In adults and young people who present with dizziness or vertigo, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological conditions?

For full details, see review protocol in appendix C.

Table 5: Characteristics of review question

Population	Adults and young people who present to a non-specialist with dizziness
Predictor variables under consideration	<ul style="list-style-type: none"> • Ataxia • Brisk reflexes • Chronic imbalance • Extensor plantar responses • Fullness in the ear • Hallpike test • Head thrust • Headache • Hearing loss • HINTS test • Intermittency • Limb weakness • Nystagmus • Postural dizziness • Skew deviation • Tinnitus • Vomiting
Confounding factors	Any of the predictors listed above
Outcomes	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ cardiovascular disorders (presyncope, postural hypotension) ○ central nervous system causes such as posterior circulation strokes and other (migraines, tumours) ○ functional disorders ○ peripheral vestibular disorders, including posterior semi-circular canal dehiscence, benign paroxysmal positional vertigo (BPPV), and labyrinthitis ○ vertebrobasilar insufficiency.
Study design	<ul style="list-style-type: none"> • Prospective and retrospective cohorts • Systematic reviews of the above

5.2.1.2 Clinical evidence

One retrospective cohort study was included in the review¹³. Evidence from this is summarised in the clinical evidence profile below. See also the study selection flow chart in appendix E, forest plots in appendix K, Grade tables in appendix J, study evidence tables in appendix H and exclusion list in appendix L.

Note that the outcome definition in this study differed from our protocol. The study assessed predictors of the composite outcome of serious neurological disease, defined as any of the following: ischemic stroke, transient ischaemic attack (TIA), intracerebral haemorrhage, subarachnoid haemorrhage, subdural haemorrhage, epidural haemorrhage, brain neoplasm, seizure, demyelinating disease, and brain abscess or meningitis. Additionally, some outcomes of interest in our protocol, such as benign paroxysmal positional vertigo, migraine, and presyncope, were included within the 'other diagnoses' outcome category in this study. These factors equate to serious indirectness of the study outcome.

Summary of included studies

Table 6: Summary of studies included in the review (cross reference evidence tables)

Study	Population	Analysis	predictor variable(s)	Confounders	Outcomes	Limitations
Navi et al. 2012 ¹³	Single cohort from retrospective record review n=907 Number of events (serious neurological diagnoses)=49	Multivariate logistic regression	Relevant variables included in MVA: <ul style="list-style-type: none"> • imbalance • isolated dizziness • focal examination abnormalities 	<ul style="list-style-type: none"> • age • imbalance as the triage symptom • isolated dizziness • previous stroke • focal examination abnormalities 	Composite of serious neurological diagnoses (not time-to-event)	Indirect outcome definition Very high risk of selection bias Possible detection bias

Table 7: Clinical evidence summary: Serious neurological diagnoses versus other diagnoses

Risk factors	Number of participants (studies)	Imprecision	Quality of the evidence (GRADE)	Effect and CI in single study
Focal examination abnormality	907 (1 study)	No serious imprecision	VERY LOW ^{a,b}	Adjusted OR [95% CI]: 5.9 [3.1, 11.2]
Imbalance	907 (1 study)	No serious imprecision	VERY LOW ^{a,b}	Adjusted OR [95% CI]: 5.9 [2.3, 15.2]
Isolated dizziness	907 (1 study)	No serious imprecision	VERY LOW ^{a,b}	Adjusted OR [95% CI]: 0.2 [0.0, 0.7]

a) Very serious risk of bias – very high risk of selection bias (not all plausible confounders considered and less than 10 events per variable) and possible detection bias (lack of adjustment for inter-rater measurement errors for risk factors but data abstraction objective).

a) Serious indirectness – outcome definition does not match our protocol and misclassification of final diagnosis possible.

5.2.1.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the health economic study selection flow chart in appendix F.

5.2.1.4 Evidence statements

Clinical

Very low quality evidence from a multivariate analysis in 1 study of 907 people showed that abnormality on focal examination and imbalance as a triage symptom were both associated with increased risk of having a serious neurological diagnosis compared to people without these findings.

Conversely, isolated dizziness as the presenting symptom was associated with a reduced risk of having a serious neurological diagnosis compared to people presenting with dizziness alongside other symptoms.

Economic

No relevant economic evaluations were identified.

5.2.1.5 Recommendations and link to evidence

Recommendations	3. For adults with sudden-onset dizziness and a focal neurological deficit such as vertical or rotatory nystagmus, new-onset unsteadiness or new-onset deafness: <ul data-bbox="590 414 1380 672" style="list-style-type: none">• if the person has diabetes, check for and treat hypoglycaemia• if the person does not have diabetes, or treating hypoglycaemia does not resolve the symptoms, and benign paroxysmal positional vertigo or postural hypotension do not account for the presentation, refer immediately to exclude posterior circulation stroke, in line with the NICE guideline on stroke and transient ischaemic attack in over 16s. 4. Be aware that dizziness in adults with no imbalance or other focal neurological deficit is unlikely to indicate a serious neurological condition. 5. For adults with transient rotational vertigo on head movement: <ul data-bbox="590 907 1396 1422" style="list-style-type: none">• offer the Hallpike manoeuvre to check for benign paroxysmal positional vertigo (BPPV) if a healthcare professional trained in its use is available. If there is no healthcare professional trained in the Hallpike manoeuvre available, refer in accordance with local pathways.• if BPPV is diagnosed, offer the canalith repositioning manoeuvre (such as the Epley manoeuvre) if a healthcare professional trained in its use is available and if the person does not have unstable cervical spine disease. If there is no healthcare professional trained in a canalith repositioning manoeuvre, or the person has unstable cervical spine disease, refer in accordance with local pathways.• be aware that BPPV is common after a head injury or labyrinthitis. 6. Be alert to the possibility of vestibular migraine (migraine-associated vertigo) in adults who have episodes of dizziness that last between 5 minutes and 72 hours and a history of recurrent headache. 7. Be aware that, for adults who have been diagnosed with a functional neurological disorder by a specialist, recurrent dizziness might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline. 8. Advise adults with recurrent dizziness and a diagnosed functional neurological disorder that their dizziness will fluctuate and might increase during times of stress.
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	9. Refer adults with recurrent fixed-pattern dizziness associated with alteration of consciousness to have an assessment for epilepsy in line with the NICE guideline on epilepsies.
Rationale for categorising symptoms	This symptom was prioritised for an evidence review because it is a commonly presenting symptom with numerous causes, some benign and some indicating a potentially serious neurological disease. A key issue is how to differentiate central nervous system causes from peripheral vestibular disorders. The committee agreed that an evidence review to support their decision-making would be helpful.
Relative values of different outcomes	Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of dizziness are indicative of a neurological condition that requires referral for a specialist assessment. Sensitivity is more important than specificity because the consequences may be missing a patient with a serious neurological condition such as stroke. Specificity remains important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the clinical prediction factors of interest were considered.
Quality of evidence	The included retrospective cohort study had the following biases and indirectness in relation to our review question: <ul style="list-style-type: none"> • risk of selection bias: not all plausible confounders considered (headache, vomiting, nystagmus and intermittency missing) and less than 10 events per variable • risk of detection bias: lack of adjustment for inter-rater measurement errors for risk factors • indirectness of population: the sample was people presenting with dizziness, vertigo or imbalance (not solely dizziness) • indirectness of outcome: outcome definition does not match our protocol and misclassification of final diagnosis possible. <p>The committee noted that conditions included within our protocol as outcomes were within the ‘other diagnosis’ category in the analysis of the included study. Therefore, the effects seen relate to the clinical prediction value of the identified factors for relatively severe or malignant conditions rather than the full spectrum of neurological conditions.</p> <p>However, given the clear findings in line with clinical experience and the overall good study design that were seen from the available evidence, the very low quality rating did not preclude making recommendations.</p>
Trade-off between clinical benefits and harms	Dizziness is a term used to refer to a subjective sensation of spinning (vertigo), to a more vague sensation of unsteadiness and sometimes to a feeling of light-headedness or pre-syncope. Recommendation 3 – Sudden onset dizziness with focal neurological deficit The committee relied on the evidence for increased risk for serious neurological diagnosis among those presenting with imbalance or focal neurological deficit, along with its own clinical experience, to recommend that people with these presentations should be referred immediately for further investigation. However, it was noted that hypoglycaemia could be a cause for these symptoms and that such a diagnosis should be excluded promptly because simple immediate treatment is available which can reduce the risk of permanent neurological damage.

The evidence demonstrated that both focal abnormality on neurological examination, and imbalance as a triage symptom, were associated with an increased risk of having a serious neurological diagnosis. Conversely, isolated dizziness as the presenting symptom, without other symptoms or signs on examination was associated with a reduced risk of having a serious neurological illness.

Recommendation 4 – Isolated dizziness

The committee noted the available evidence indicates a low risk of serious neurological diagnoses among people presenting with isolated dizziness and agreed that this was in line with their own clinical experience. Whilst it is difficult to recommend against neurological referral in all instances of isolated dizziness (for example, if the symptom is intrusive and common alternative explanations have been excluded) the committee felt that it would be useful to point out that if this is the only symptom and there are no neurological signs, a significant neurological disease is very unlikely. This should lead to a reduction in inappropriate referrals.

Recommendation 5 – Recognition and treatment of benign paroxysmal positional vertigo (BPPV)

This recommendation is based on committee consensus. In people with vertigo triggered by head movement, the Hallpike manoeuvre is a widely accepted diagnostic test for BPPV. The committee noted that many people experience rapid symptomatic relief following a canalith repositioning manoeuvre (for example, the Epley manoeuvre). This is a simple and low risk intervention that can be offered in primary care. If the symptoms improve immediately, referral is generally unnecessary. The manoeuvre can be repeated after an interval if the symptoms recur, or the people can be instructed on how to perform it themselves.

Recommendation 6 – Vestibular migraine

The committee noted that vestibular migraine is a condition that responds readily to migraine treatment. The diagnosis should be considered if the episodes are recurrent, and the additional presence of the classical headaches is another obvious clue. The International Headache Society have agreed diagnostic criteria for vestibular migraine which stipulate that the vertigo is more than fleeting, lasting at least 5 minutes, but resolves within 72 hours (Cephalgia 2013; 33:629-808). If it is recognised, vestibular migraine can generally be managed without referral to secondary care neurology services.

Recommendation 7 – Recurrent dizziness as a feature of functional disorder

The committee noted that the symptoms of functional neurological disorders might mimic a wide range of physical neurological disorders. Dizziness and imbalance are a common symptom of functional neurological disorder, and if recognized, it may be more appropriate to manage the person's functional neurological disorder without referral to neurology services.

Recommendation 8 – Anxiety influencing functional neurological disorder

Functional symptoms are complaints that are not primarily explained based on physical or physiological abnormalities. They may mimic neurological disorders. Diagnosis may depend on exclusion of a medical explanation of the symptoms, and require a high level of clinical expertise and judgement. Functional symptoms can complicate a medically explained illness and cause difficulties in diagnosis and delineation. The committee noted that anxiety or a functional neurological disorder might not require a referral to neurology services; instead, the committee advised assuring people with such fluctuating symptoms that the symptoms were part of a functional neurological disorder and offering psychological support if appropriate.

	<p>Recommendation 9 – Recurrent fixed-pattern sensory hallucinations and dizziness</p> <p>The committee noted that the occasional presentation of epilepsy can be stereotyped as experiential symptoms including dizziness. When recognized, this should be managed according to NICE guidelines on epilepsy, that is, by prompt referral to epilepsy specialist services.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs of an outpatient visit costing £175 and a paediatric outpatient visit costing £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. These estimates were a starting point for the committee to consider whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that immediate referral of sudden-onset dizziness with a focal neurological deficit was crucial to the individual's health should they be experiencing a stroke. Therefore, this is highly likely to be a cost-effective use of NHS resources, as it would lead to better outcomes for those referred.</p> <p>The committee noted that recurrent dizziness episodes might not always warrant referral as they can be managed without the need of specialist input. This would generate cost savings to the NHS by avoiding referrals that will have no impact on the individual's health.</p> <p>Finally, the committee also agreed that if epilepsy is suspected then a referral for assessment of epilepsy represents a cost-effective use of resources as appropriate diagnosis and management will lead to a significant improvement in the individual's health.</p>
Other considerations	<p>These recommendations were not subject to the targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.</p>

5.2.2 HINTS test

5.2.2.1 Review question: In people with suspected (or under investigation for) new onset of vertigo or dizziness, is the HINTS (Head-Impulse—Nystagmus—Test-of-Skew) test effective in identifying whether there is a central nervous system cause, as indicated by the reference standard, MRI?

For full details, see review protocol in appendix C.

Table 8: Characteristics of review question

Population	All people with new onset vertigo or dizziness suspected (or under investigation for) stroke or MS
Target condition	Stroke or MS
Index test	HINTS
Reference standard	MRI
Statistical measures	<p>The following diagnostic accuracy measures of the HINTS test if available:</p> <ul style="list-style-type: none"> • 2x2 tables • Specificity • Sensitivity • Positive or negative predictive value

	<ul style="list-style-type: none"> • ROC curves and area under the curve
Study design	Cross sectional, prospective and retrospective cohort studies to be considered. Case-control studies will only be included if there is no other evidence as they are highly biased.

5.2.2.2 Clinical evidence

Four studies were included in the review;^{1,8,9,14,15} these are summarised in Table 9 below. Evidence from these is summarised in the clinical evidence profile below (Table 10). See also the study selection flow chart in appendix E, sensitivity and specificity forest plots in appendix K, study evidence tables in appendix H and exclusion list in appendix L.

5.2.2.2.1 Summary of included studies

Table 9: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Chen 2011 ¹	HINTS versus MRI	n=24 patients with AVS with cardiovascular risk factors	Stroke	Very high risk of bias because of patient selection (very small sample size; sampling from a high-risk population)
Kattah 2009 ⁸	HINTS versus MRI	n=101 consecutive patients with AVS with ≥1 stroke risk factors	Central lesion	Very high risk of bias because of patient selection (sampling from a high-risk population) and index test (in most cases, the index test results were interpreted with knowledge of the results of the reference standard)
Kerber 2015 ⁹	HINTS versus MRI	n=272 patients with dizziness (n=202 had full HINTS test)	Stroke	High risk of bias (unclear whether the index test results were interpreted with knowledge of the results of the reference standard)
Newman-Toker 2013 ¹⁴	HINTS versus MRI	n=190 patients with AVS with ≥1 stroke risk factors	Stroke	Very high risk of bias because of patient selection (sampling from a high-risk population) and index test (in some cases, the index test results were interpreted with knowledge of the results of the reference standard)

Table 10: Clinical evidence summary: diagnostic test accuracy for HINTS

HINTS	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity % [(95% CI)]	Specificity % [(95% CI)]	Quality
HINTS (Pooled estimates)	4	517	Very serious risk of bias ^a	Serious inconsistency ^b	No serious indirectness ^c	No serious imprecision ^d	96% [80%,100%]	83% [40%,98%]	VERY LOW

- (a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias
- (b) Inconsistency was assessed by inspection of the sensitivity and specificity plots. Particular attention was placed on the sensitivity threshold. The evidence was downgraded by 1 increment because the pooled estimate varied across 2 areas: where specificity values of individual studies are both above and below 50% indicating that these may be due to chance alone
- (c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect
- (d) Imprecision was assessed according to the range of confidence interval around the summary sensitivity and specificity point from the diagnostic meta-analysis. The evidence was considered precise as the range of the confidence interval was between 0-20%.

5.2.2.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.2.2.4 Evidence statements

Clinical

Very Low quality evidence from 4 studies (n=517) showed that the pooled estimate of the sensitivity of the HINTS test at excluding stroke or central lesions was 96% (83%, 100%) and the pooled estimate of specificity was 83% (40%, 98%).

Economic

No relevant economic evaluations were identified.

5.2.2.5 Recommendations and link to evidence

Recommendations	<p>10. For adults with sudden-onset acute vestibular syndrome (vertigo, nausea or vomiting and gait unsteadiness) a HINTS (head impulse–nystagmus–test-of-skew) test should be performed if a healthcare professional with training and experience in the use of this test is available.</p> <p>11. For adults with sudden-onset acute vestibular syndrome who have had a HINTS test:</p> <ul style="list-style-type: none"> • be aware that a negative HINTS test makes a diagnosis of stroke very unlikely • refer immediately for neuroimaging if the HINTS test shows indications of stroke (a normal head impulse test, direction-changing nystagmus or skew deviation). <p>12. Refer immediately adults with sudden-onset acute vestibular syndrome in whom benign paroxysmal positional vertigo or postural hypotension do not account for the presentation, in line with local stroke pathways, if a healthcare professional with training and experience in the use of the HINTS test is not available.</p>
Relative values of different diagnostic measures	Measures of diagnostic accuracy including sensitivity, specificity, 2x2 tables, positive or negative predictive values, receiver operating curves and area under the curve were considered outcomes of interest. The committee agreed that the most important outcome measures for decision-making were sensitivity and the negative predictive value (NPV) because the aim of the test is to rule out people who do not have stroke effectively. If the test is not sensitive enough, the consequences of missing people who may have a stroke are very serious. Therefore, the probability that a person with a negative HINTS test result actually does not have stroke needs

	<p>to be high. A threshold of 95% was chosen as MRI, which is the best available reference standard is known to have a sensitivity of about 80–95%.</p>
Quality of the clinical evidence	<p>Four studies including 517 participants were included in this review. The results showed that the pooled estimate of sensitivity of the HINTS test at excluding stroke or central lesions was 96% (83%, 100%) and the corresponding specificity was 83% (40%-98%). The median NPV was 97.5% (range 94%-100%).</p> <p>However, the studies were at high risk of selection bias due to the inclusion of people from a high-risk population who had known risk factors. In addition, in some studies, the HINTS tests was interpreted with the knowledge of the results of the reference standard, and the people included were highly selected and not representative of primary care.</p> <p>The committee considered that sensitivity was more important than specificity and set a threshold of 95%. Although the pooled estimate of the sensitivity of the HINTS tests across the 4 included studies was above this threshold, the uncertainty around this estimate ranged from 83% (below the threshold) to 100 % above the threshold. This is probably due to the much lower sensitivity and specificity of 1 of the included studies (83% and 44% respectively). The reasons for these lower values were explored but none seemed to explain this inconsistency. The committee agreed that these overall results were still within the same ranges of sensitivities and specificities of MRI. Therefore, HINTS could still be a good alternative to MRI in excluding central lesions in a population similar to that included in the studies and when performed by someone trained in its use and interpretation.</p>
Trade-off between clinical benefits and harms	<p>The committee determined that the evidence suggested that the HINTS test was broadly as sensitive and specific as MRI in excluding acute stroke or central lesions in people with sudden onset vertigo.</p> <p>It is non-invasive and does not have any risks or associated untoward effects. Therefore, the committee felt that this would be a reasonable alternative to undertaking an MRI scan. However, the evidence suggested that this was only applicable to situations where clinicians were trained in employing the HINTS test. The committee also noted that these results will not be applicable to the whole population with dizziness normally seen in primary care, and it was appreciated that expertise in undertaking the HINTS test is not usual in primary care, although more widely available in Accident and Emergency departments. The studies were conducted in a selected population seen in secondary or tertiary care (who would be more likely to have a central cause of vertigo) and presenting with true vertigo accompanied by unsteadiness and nausea rather than isolated dizziness (a sometimes vague symptom). The committee recognised that a negative HINTS test does not mean a negative finding on 1 of the components of the test but of the cumulative finding for all components (that is, the combination of the head impulse, nystagmus and test of skew findings). It is important to note that, for example, a negative (normal) head impulse does not mean a negative HINTS test. This further highlights the need for this test to be carried out only by clinicians who are well trained in its use and interpretation.</p> <p>It is also important to note that in situations where people are suspected of having dizziness due to a central cause and no clinicians trained in the HINTS test are available, it is advisable not to delay MRI scans or attempt to administer the HINTS test if the only available clinicians are not proficient in its use or interpretation.</p>
Trade-off between net clinical effects and costs	<p>The clinical evidence showed the sensitivity and specificity were within the acceptable thresholds agreed by the committee. The HINTS test is a fairly low cost test to conduct with the main resource impact coming from the time taken to conduct the test properly. Therefore, if conducted well, the committee agreed it could safely exclude stroke. This would prevent further expensive downstream tests, which would represent a cost saving to the health service.</p>

Other considerations	<p>The committee accepted the value of the HINTS test in helping exclude a stroke, but in accordance with other recommendations in this guideline added a second part to the recommendation emphasising the need for rapid referral onto a stroke pathway if any component of the test is positive.</p> <p>These recommendations were not subject to the targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.</p>
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5.3 Facial pain, atraumatic

5.3.1 Review question: In adults who present with atraumatic facial pain, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?

The aim of the review was to identify signs and symptoms that, if presenting with atraumatic facial pain, would indicate a suspected neurological condition that requires referral for further specialist assessment. Typically, this would differentiate between trigeminal neuralgia, which can be managed in primary care, and other conditions that would need to be referred for specialist assessment.

For full details, see review protocol in appendix C.

Table 11: PICO characteristics of review question

Population	Adults who present to a non-specialist with atraumatic facial pain
Presence / absence of predictor	<p>The committee identified the following predictors in people who present to a non-specialist with atraumatic facial pain for inclusion in the review:</p> <ul style="list-style-type: none"> • double vision • electric shock – elicited by stimulating the face • fatigue and malaise • fever • history of polymyalgia rheumatica • jaw claudication • quality of pain • scalp tenderness • vision loss.
Outcomes	<p>Main outcomes:</p> <ul style="list-style-type: none"> • sensitivity (%) and specificity (%) • area under the ROC curve (AUROC) – measure of predictive accuracy • positive and negative predictive value <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ carotid and vertebral artery dissection ○ cluster headache ○ dental pain ○ max sinusitis ○ migraine facial pain ○ occipital neuralgia ○ temporal arteritis ○ tension headache ○ temporomandibular joint disorders (TMJ) dysfunction

Population	Adults who present to a non-specialist with atraumatic facial pain
	o trigeminal neuralgia.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis
Key confounders	Any of the predictors listed above

5.3.2 Clinical evidence

No relevant clinical studies were identified. See study selection flow chart in appendix E and the excluded studies list in appendix L.

5.3.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.3.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant health economic studies were identified.

5.3.5 Recommendations and link to evidence

Recommendations	<p>13. Refer urgently adults with facial pain associated with persistent facial numbness or abnormal neurological signs for neuroimaging.</p> <p>14. Refer adults with unilateral facial pain that is triggered by touching the affected part of the face (trigeminal neuralgia) and is refractory to treatment, in line with the NICE guideline on neuropathic pain in adults.</p> <p>15. For adults with scalp tenderness or jaw claudication suggestive of temporal arteritis, consider blood tests and follow local pathways for suspected giant cell (temporal) arteritis. Be aware that a normal ESR (erythrocyte sedimentation rate) does not exclude a diagnosis of giant cell arteritis.</p>
Rationale for categorising symptoms	This is a common presentation in primary care. Although people with atraumatic facial pain are often treated for trigeminal neuralgia, which can be managed in primary care, there are other instances when atraumatic facial pain should be referred. Therefore, a key issue is to identify signs and symptoms that help differentiate trigeminal neuralgia from other causes of facial pain that require

	referral to a specialist. The committee agreed that an evidence review to support their decision-making would be helpful.
Relative values of different outcomes	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of facial pain are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications, which can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
Quality of the clinical evidence	No clinical evidence was identified for inclusion in this review. The recommendations are based on committee consensus.
Trade-off between clinical benefits and harms	<p>Recommendation 13 – Facial pain with abnormal neurological signs</p> <p>Isolated facial pain is a common symptom and mostly the symptom is self-limiting and benign. Dental and facial sinus pain are common causes. The presence of persistent numbness accompanied by abnormal neurological signs on examination, such as sensory loss in the face which is persistent or progressive, an abnormality of eye movement or facial weakness, in people with facial pain suggests the presence of a mass lesion. Urgent neuroimaging according to the NICE guideline on suspected cancer is appropriate when these additional signs are detected.</p> <p>Recommendation 14 – Trigeminal neuralgia</p> <p>Trigeminal neuralgia is characterised by severe, stimulation-sensitive, shock-like pain in the distribution of the trigeminal nerve. People with trigeminal neuralgia do not necessarily need referral and can be managed in primary care according to the NICE guideline on neuropathic pain in adults. It is appropriate to refer people with more resistant pain to neurology services for assessment and treatment. Non-neurologic facial pain is commonly inappropriately attributed to trigeminal neuralgia but does not respond well to treatment of neuropathic pain.</p> <p>Recommendation 15 – Temporal arteritis</p> <p>Temporal arteritis can be difficult to diagnose and because of the risk of permanent neurological damage associated with untreated disease it should always be considered as a cause of headache and facial pain in older people. The diagnosis is usually confirmed by typical clinical features and abnormal blood tests such as elevated erythrocyte sedimentation rate, elevated C-reactive protein and abnormal liver function tests. It is exceptionally rare under the age of 50 years. People with symptoms suggestive of temporal arteritis should be treated urgently because of the risk of irreversible damage to eyesight and stroke. Where there is uncertainty about the diagnosis, because of atypical clinical features or inconsistent blood test results, they should be referred urgently for consideration of a diagnostic temporal artery biopsy.</p>
Trade-off between net clinical effects and costs	The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these

	<p>estimates as a starting point for the considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>Due to the seriousness of the symptom, the committee felt urgent referral is warranted in these specified cases. This is in line with current protocols; therefore, it is not believed to represent a dramatic shift in practice and should not lead to a significant increase in referrals.</p>
Other considerations	<p>The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.</p>

5.4 Gait unsteadiness

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.4.1 Recommendations and link to evidence (consensus statement 234 to 244 in appendix S)

Recommendations	<p>16. For recommendations on assessing sudden-onset unsteady gait in adults, see the NICE guideline on stroke and transient ischaemic attack in over 16s.</p> <p>17. Refer urgently adults with rapidly (within days to weeks) progressive unsteady gait (gait ataxia) for neurological assessment.</p> <p>18. Refer adults with gradually progressive unsteady gait (gait ataxia) for neurological assessment and:</p> <ul style="list-style-type: none"> • take an alcohol history and follow the recommendations in the NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. • Check thyroid function • Check for vitamin B12 and folate deficiency • consider serological testing for gluten sensitivity as recommended in the NICE guideline on coeliac disease. <p>19. Refer adults who have difficulty initiating and coordinating walking (gait apraxia) to neurology or an elderly care clinic to exclude normal pressure hydrocephalus.</p> <p>20. For adults with unsteadiness of gait who are at risk of falling, follow the recommendations on multifactorial falls risk assessment in the NICE guideline on falls in older people and consider referring to a falls prevention team.</p>
Rationale for categorising symptoms	<p>This symptom was not prioritised for an evidence review because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change this.</p>

	<p>Diagnosis of the various different causes of unsteadiness demands clinical skills, but the requirement for referral is non-contentious once the type of unsteadiness is recognised.</p>
Trade-off between benefits and harms	<p>Unsteadiness of gait can be caused by either gait ataxia or gait apraxia. Ataxia of gait is caused by impaired voluntary co-ordination of movement, whereas apraxia of gait is a difficulty in correctly sequencing the automatic components (including balance, gait initiation, stride length and speed) necessary to walk. The committee recognised that it is difficult to distinguish unsteadiness due to ataxia from unsteadiness due to apraxia. Therefore, differentiation may require referral for an expert assessment.</p> <p>Recommendation 16 – Sudden-onset unsteady gait</p> <p>Sudden onset of unsteady gait can signify a vascular event such as stroke, especially if it is an isolated symptom. The committee therefore agreed that referrals should be urgent. The committee noted the NICE guideline on stroke (CG68) and agreed to cross-refer.</p> <p>Recommendation 17 – Rapidly progressive unsteadiness of gait</p> <p>Rapidly progressive unsteadiness of gait (ataxia) that presents and progresses over a course of days or weeks is an unusual presentation and should be referred on the 2-week neurology pathway. The most common cause in a young person is multiple sclerosis (MS). The differential diagnoses for rapidly progressive ataxia includes brain tumour, paraneoplastic syndrome, atypical infections (for example, herpes zoster and legionella), autoimmune disorders and very rare conditions (for example, acute disseminated encephalomyelitis [ADEM]). These may require a quick diagnosis in order to treat the condition in the best manner; thus, people presenting with rapidly progressive gait ataxia should be referred to neurology urgently.</p> <p>Clinicians should be aware that cancer is a risk in this population. Ovarian, breast and lung cancer can cause paraneoplastic syndromes, which can present with neuromuscular symptoms. Tests such as chest radiographs and pelvic ultrasounds can be used to search for cancers that may be driving a suspected paraneoplastic syndrome, but under these circumstances, the committee considered that referral to a specialist for a differential diagnosis in these rapidly progressive cases is more important than non-specialists undertaking investigative tests.</p> <p>Recommendation 18 – Gradually progressive unsteady gait (gait ataxia)</p> <p>Unsteady gait is common in the elderly but true gait ataxia is rare. It can be caused by cerebellar or proprioceptive sensory lesion due to peripheral neuropathy or spinal cord (dorsal column) pathology. These may be of sporadic or genetic origin and require a neurological assessment. An accurate diagnosis is important to look for treatable causes. However, the committee also wished to highlight some simple measures, which could be taken while awaiting a secondary care appointment.</p> <p>Longstanding alcohol use can often lead to gait ataxia. Some people may not volunteer a history of excessive alcohol use, and assessment of alcohol intake can be problematic. Adults with gait ataxia and a history of excessive alcohol use should also be referred to neurology because, in a significant minority, the ataxia will be due to a condition not related to their alcohol intake.</p> <p>Ataxia can be the presenting feature of an inflammatory neuropathy and treatable with immunomodulatory medicines. There will usually be some weakness, which can be distal or proximal, and deep tendon reflexes will be depressed. The clinical diagnosis is confirmed with nerve conduction studies.</p> <p>The nutritional status of people with progressive gait ataxia is important and can be assessed using full blood count, vitamin B12 and folate tests prior to attending secondary care clinics. Test results can also help to expedite a diagnosis and optimise nutritional status prior to a neurological assessment. Occult coeliac disease</p>

	<p>should be considered as a cause of B12 and folate deficiency. This is particularly important for vitamin B12 and folate as malabsorption or deficiency can cause sensory ataxia due to peripheral neuropathy and spinal cord or dorsal column pathology.</p> <p>Gluten sensitivity is one of the most common treatable causes of sporadic gait ataxia. It can present at any age and may be overlooked by non-specialists. If gluten sensitivity is suspected, the person should be referred for a gastroenterology opinion and associated nutritional deficiencies addressed at the same time as neurological referral for gait ataxia. The NICE coeliac guideline recommends considering tests for coeliac disease in people with unexplained neurological symptoms, particularly peripheral neuropathy or ataxia (NICE guideline on Coeliac disease: recognition, assessment and management, NG20).</p> <p>Recommendation 19 – Normal pressure hydrocephalus</p> <p>The committee wanted to raise awareness of normal pressure hydrocephalus (NPH) amongst both GPs and other non-specialists. Normal pressure hydrocephalus is a potentially treatable cause of gait apraxia and can easily be overlooked. It can also manifest with cognitive loss and urinary incontinence, and people with these features should be referred to a specialist with relevant expertise for consideration of a NPH diagnosis (local service arrangements may vary). A significant improvement in gait following lumbar puncture is usually required for diagnosis. Treatment options include ventricular shunting or repeated lumbar puncture. Surgery requires a certain level of fitness, and the gait disorder is more likely to improve than cognitive dysfunction. Therefore, the referral of very frail people and individuals with advanced cognitive decline may not be appropriate although referral to an elderly care or falls clinic and repeated lumbar puncture remains an option.</p> <p>Recommendation 20 – Preventing falls</p> <p>Unsteadiness of gait is more prevalent in older people, in whom it often has a multifactorial aetiology. While an early neurological assessment is important in younger people, if the patient is older and has multiple comorbidities, a referral to an elderly care or falls clinic may be more appropriate. The elderly care or falls clinic will refer to neurology if necessary. The guideline committee agreed that the recommendations on multifactorial falls risk assessment for people aged over 65 in the NICE guideline on falls in older people are applicable to adults aged under 65 who are at risk of falling.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current best practice, and that, viewed along with the rest of this guideline, the recommendations should not increase the total number of referrals or NHS costs.</p> <p>The committee agreed that all individuals would be offered serological testing at some point in the pathway, so this did not represent an incremental cost if it was merely conducted sooner. The committee also agreed that such test results could expedite a diagnosis and optimise a referral, meaning that they could improve health outcomes.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p>

There was a very high level of agreement with this set of recommendations ranging from 81.3% to 100%. There were suggestions to remove gluten sensitivity testing from recommendation 18. However, the committee felt that it was important to include this as it is one of the most common and treatable causes of sporadic gait ataxia, which is easily missed by both specialists and non-specialists. The committee felt that this should remain in the recommendation and provided further detail above to support this.

5.5 Handwriting difficulties

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.5.1 Recommendations and link to evidence (consensus statement 17 to 21 in appendix S)

Recommendations	<p>21. Refer adults who have sudden-onset difficulty with handwriting that has no obvious musculoskeletal cause for a neurological assessment according to local stroke pathways.</p> <p>22. Ask adults who have difficulty with handwriting that has no obvious musculoskeletal cause to demonstrate their handwriting and:</p> <ul style="list-style-type: none"> • if they have a problem with generating language rather than hand function, refer for neurological assessment • if their handwriting is small and slow, consider referring for possible Parkinson’s disease • if their difficulty is specific to the task of handwriting and examination shows no other abnormalities, consider referring for possible focal dystonia. •
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review because the committee agreed that adults who have new-onset difficulty writing should always be referred. It was felt that most healthcare professionals would agree that the referral decision is uncontentious; therefore, an evidence review in this area is unlikely to change that.
Trade-off between benefits and harms	<p>There are many neurological reasons for people to have writing difficulties besides those caused by weakness, which is covered elsewhere in this guideline. Examples of this include movement disorders (such as Parkinson’s disease) and task-based dystonias (such as writer’s cramp). Cognitive deficits (including those associated with dementia) that affect executive function and language can make it difficult for some people to write.</p> <p>Recommendation 21 – Sudden-onset writing difficulty</p> <p>Isolated difficulty in writing is a relatively unusual manifestation of a stroke. However, in the event of a very sudden onset of writing difficulties (that is, illegible writing that has no musculoskeletal explanation), it would be important to consider this possibility, and the committee therefore recommend referral using the relevant local pathway.</p> <p>Recommendation 22 – Demonstrating writing</p> <p>Patients may be concerned that their handwriting has changed to become less legible. By asking the patient to demonstrate writing, non-specialists can garner</p>

	<p>additional information that may help to clarify a potential diagnosis and determine whether the person needs to be referred for a suspected neurological condition.</p> <p>Parkinson’s disease can occasionally present with writing difficulties, typically small writing (micrographia), and if this symptom is dominant, other features of Parkinson’s disease should be sought, including asymmetric slowness of rapid repetitive movements, a history of anosmia or REM behaviour sleep disorder. A referral for confirmation of the diagnosis and management advice should be made to a neurologist or a care of the elderly physician, in line with local pathways.</p> <p>Dystonia is a task-specific movement disorder, and standard neurological examination of the hand and arm usually reveals no abnormality. Recognition of dystonia is currently sub-optimal, and there are often long delays before neurologists see people with this condition. The committee therefore considered it important to raise awareness amongst non-specialists about the possibility of focal dystonia as a diagnosis as well as the need for referral for neurological assessment. People in whom dystonia is suspected could be referred directly to a movement disorders clinic if available; otherwise, they can be referred to the local neurology service.</p> <p>Cognitive deficits (including those associated with dementia) that affect executive function and language can make it difficult for some people to write and may be interpreted as a writing difficulty. Such people may benefit from referral for assessment to a neurology clinic or, where language difficulties occur in older people in the context of other cognitive features suggestive of dementia, a memory clinic. Be aware that ambivalence, poverty of speech and disorganised language can be the presenting features of a primary psychiatric disorder.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs when an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considerations whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>People with writing difficulties may seek advice from a general practitioner, but such symptoms are uncommon in general practice. The approach to interpreting the symptoms may be unfamiliar, and the symptoms may sometimes be misinterpreted or considered likely to be emotionally generated. Difficulty with writing can be caused by tremor, dystonia of the hand or Parkinson’s disease. In each case, the problem may compromise the patient’s ability to work or undertake other manual tasks. Such difficulties with writing may be considered as untreatable or the underlying neurological disorder may remain unrecognised. Prompt referral to a neurologist may facilitate diagnosis and symptomatic treatment. This improvement in quality of life would ensure referral was a cost-effective use of NHS resources.</p> <p>Although the committee felt this might increase referrals it is not a symptom commonly seen in GP practices; therefore, the increase in referrals will not be significant.</p>
<p>Other considerations</p>	<p>Difficulty writing is more commonly due to a mechanical problem, particularly due to musculoskeletal disorders, and these should be excluded before considering a referral to a neurology service. The committee therefore draws attention to this in both recommendations.</p> <p>Targeted engagement exercise</p> <p>The committee discussed the results of the targeted engagement exercise, which showed that 66.7% of the 18 participants who responded to this section agreed with</p>

	<p>recommendation 21, 22.2% requested revisions and 11% (2 participants) disagreed. It was thought that the original wording of the recommendations needed clarification that not all people with a new of onset difficulty writing should be referred but only those where there were no obvious musculoskeletal causes. The committee agreed and amended the recommendations accordingly.</p> <p>There was no disagreement with recommendation 22, but 50% of the 18 participants who responded requested some revisions on the link to Parkinson’s disease, the differentiation between difficulty writing and language as well as the differences in local services for which the committee provided further details in the table above and made minor edits to the recommendation.</p>
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5.6 Headaches in adults

For advice on referral for headaches in adults, see the [NICE guideline on headaches in over 12s \(in particular see recommendations 1.1.1 and 1.1.2\)](#).

5.7 Limb or facial weakness in adults

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.7.1 Recommendations and link to evidence (consensus statement 84 to 105 in appendix S)

Recommendations	<p>23. Be aware that sudden-onset weakness, even in restricted distribution (for example, sudden hand weakness), may be caused by a stroke or transient ischaemic attack. See the NICE guideline on stroke and transient ischaemic attack in over 16s for recommendations on assessing sudden-onset limb or facial weakness in adults.</p> <p>24. Refer immediately adults with rapidly (within 4 weeks) progressive symmetrical limb weakness for neurological assessment and assessment of bulbar and respiratory function.</p> <p>25. Refer immediately, in line with local pathways, adults who have severe low back pain radiating into the leg and new-onset disturbance of bladder, bowel or sexual function, or new-onset perineal numbness, to have an assessment for cauda equina syndrome.</p> <p>26. Refer urgently adults with rapidly (within hours to days) progressive weakness of a single limb or hemiparesis for investigation, including neuroimaging, in line with the recommendation on brain and central nervous system cancers in adults in the NICE guideline on suspected cancer.</p> <p>27. For adults with slowly (within weeks to months) progressive limb or neck weakness:</p>
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- refer for assessment of neuromuscular disorders in line with the recommendations on [recognition and referral](#) in the NICE guideline on motor neurone disease
- refer urgently if there is any evidence of swallowing impairment
- refer immediately if there is breathlessness at rest or when lying flat

28. Be aware that lower limb claudication symptoms in adults with adequate peripheral circulation might be caused by lumbar canal stenosis and need specialist assessment and imaging.

29. Be aware that, for adults who have been diagnosed with a functional neurological disorder by a specialist, recurrent limb weakness might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.

30. Advise adults with limb or facial weakness ascribed to a functional neurological disorder that their limb or facial weakness might fluctuate and evolve over time and might increase during times of stress.

31. For adults with clear features of compression neuropathy and no features of a nerve root lesion (radiculopathy^a) of the radial nerve, common peroneal nerve or ulnar nerve:

- refer to orthotic services for a splint
- review the symptoms after 6 weeks, and refer for neurological assessment if there is no evidence of improvement

For adults with features of radiculopathy see the section on cervical or lumbar radiculopathy.

32. Advise adults with compression neuropathy to avoid any activity that might lead to further pressure on the affected nerve.

33. Do not routinely refer adults with an uncomplicated episode of Bell's palsy (unilateral lower motor neurone pattern facial weakness affecting all parts of the face and including weakness of eye closure) and no evidence of another medical condition such as middle ear disease.

34. Advise adults with Bell's palsy about eye care, and that the rate of improvement is variable and maximum recovery can take several months.

a Irritation or damage to a nerve root as it exits the spinal canal, most commonly by mechanical compression from a prolapsed intervertebral disc or degenerative arthritis of the spine. Less frequently, infections need to be considered (e.g. herpes zoster, Lyme disease). Symptoms include neck or low back pain radiating into a limb, tingling (paraesthesia), reduced/absent deep tendon reflex(es) and weakness in the distribution of the nerve root.

	<p>35. Consider referring adults with Bell's palsy who have developed symptoms of aberrant reinnervation (including gustatory sweating or jaw-winking) 5 months or more after the onset of Bell's palsy for neurological assessment and possible treatment.</p>
Rationale for categorising symptoms	<p>This symptom was not prioritised for an evidence review for adults or children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change this. The committee also noted relevant recommendations in existing NICE guidance covering recognition and referral.</p>
Trade-off between benefits and harms	<p>Recommendation 23 – Sudden onset limb weakness</p> <p>Sudden onset transient limb weakness could indicate a vascular event such as a transient ischaemic attack (TIA) even if it is present only in a restricted distribution, for example, hand weakness. The NICE stroke guideline provides recommendations for recognition and referral. Stroke or TIA should also be considered in unexplained isolated hand weakness of sudden onset, which, in the absence of a history of trauma, is sometimes incorrectly attributed to a compression neuropathy.</p> <p>Recommendation 24 – Rapidly progressive symmetrical weakness</p> <p>Rapidly progressive lower motor neurone weakness could be an indication of Guillain-Barré syndrome (GBS), which progresses rapidly over the course of days – up to 4 weeks. Such symptoms may be a feature of other acute neuromuscular disorder (for example, myasthenia gravis), in which case other features may be found such as double vision or drooping of the eyelids that can fluctuate during the course of the day. These are highly treatable but potentially life-threatening conditions, as they can affect the respiratory muscles causing respiratory failure requiring intensive levels of supportive care in a hospital setting. The committee noted that the initial presenting features of neuromuscular disorders may not be recognised by non-specialists and people might be inappropriately reassured. GPs should feel confident to re-refer for immediate neurological re-assessment, where there is concern about progressive symptoms as respiratory compromise may rapidly ensue.</p> <p>Rapidly progressive upper motor neurone symmetrical weakness could be an indication of spinal cord compression or demyelination. This may require treatment to preserve function and so requires an immediate referral for neurological assessment, including cervical spine imaging.</p> <p>Recommendation 25 – Cauda equina syndrome</p> <p>Cauda equina syndrome is an emergency requiring immediate assessment for imaging and consideration of surgical decompression. The committee noted that identical symptoms are common in the context of, or as a new presentation of, functional neurological disorder but these people still require emergency imaging.</p> <p>Recommendation 26 – Rapidly progressive weakness of a single limb or hemiparesis</p> <p>Rapidly progressive (hours to days) weakness of a single limb or hemiparesis indicates potentially serious neurological disease and would require referral for urgent assessment, including neuroimaging in line with the recommendations on brain and central nervous system cancers in adults in the NICE guideline on Suspected cancer: recognition and referral – NG12.</p> <p>Recommendation 27 – Slowly progressive weakness</p> <p>Slowly progressive lower motor neurone weakness could be due to a global weakness of muscle. Appropriate haematological investigations for causes of myositis and myopathy should be conducted before referral. A routine referral is acceptable.</p>

Slowly progressive weakness could also be indicative of anterior horn cell disease, such as motor neurone disease. The typical rate of disease progression and currently available treatment options requires a prompt rather than urgent neurological review. Accurate diagnosis is important in order to initiate appropriate multidisciplinary supportive care, which may include physiotherapy, occupational therapy and respiratory support.

People with slowly progressive weakness should be kept under review by the referrer until they see a neurologist. Occasionally, people's conditions can deteriorate rapidly (over weeks), and these people may be more appropriately managed through an acute hospital admission. In addition, the Committee recognised that a more urgent referral is required when slowly progressive weakness includes signs of bulbar involvement, with the attendant risk of aspiration, or of respiratory impairment. The recommendation was designed to cover these possibilities.

Recommendation 28 – Lumbar canal stenosis

Limb weakness that comes on after walking and improves with rest (claudication), in which vascular causes have been excluded, requires a referral for a specialist assessment of possible lumbar canal stenosis. Depending on local pathways, this could be to an extended scope practitioner, neurosurgeon or orthopaedic surgeon. Because of variation in local pathways a directed referral recommendation was not possible.

Recommendation 29 – Recurrent limb weakness

Functional symptoms are complaints that are not primarily explained based on physical or physiological abnormalities. They may mimic neurological disorders. Diagnosis may depend on exclusion of a medical explanation of the symptoms and require a high level of clinical expertise and judgement. Functional symptoms can complicate a medically-explained illness and cause difficulties in diagnosis and delineation. Recurrent episodes of limb weakness, hemiparesis or paraparesis are not uncommon in people with an existing functional neurological disorder; and with other disorders for example, chronic fatigue syndrome and fibromyalgia. The committee considered it inappropriate to refer people with such episodes for investigation after each episode, and considered that psychological support would often be more appropriate than a neurological services re-investigation. The committee emphasised that normal and symmetrical tone and deep tendon reflexes significantly reduce the likelihood of an underlying organic disorder. A recommendation which covered these considerations was thought likely to help GPs to direct these patients to more appropriate channels than neurology services.

Recommendation 30 – Advice for suspected functional neurological disorders

As functional neurological symptoms usually fluctuate and evolve with time, the committee agreed that it was important to address the nature of the condition with people with this condition in order to allay concern about the presence of physical illness and to reduce pressure for onward referral for further specialist opinion.

Recommendation 31 and 32 – Suspected compression neuropathy

Compression neuropathies can be suspected based on a suggestive history of prolonged pressure on the nerve and the pattern of weakness and numbness. Such neuropathies are expected to improve spontaneously without treatment within 6 weeks in most cases, although a splint may be required to support and preserve functionality in a weak wrist or dropped foot during recovery. Where a history of compression is unclear, or where there is evidence of progressive neurological deficit, urgent referral is required to exclude mononeuritis multiplex, a condition that may require systemic treatment.

Reducing pressure or trauma on the affected nerve can increase the chance of recovery. Some activities to be avoided include leg crossing, sleeping on a sore

	<p>shoulder, excessive kneeling, leaning on elbows, and sleeping deeply following ingestion of alcohol and sedatives.</p> <p>Recommendations 33, 34 and 35 – Unilateral lower motor neurone facial nerve (Bell’s) palsy</p> <p>A diagnosis of unilateral lower motor neurone facial nerve palsy (Bell’s palsy) is usually straightforward. Lyme disease should be considered in areas where it is endemic.</p> <p>The presentation is sometimes confused with stroke. However, unilateral lower motor neurone facial nerve palsy (Bell’s palsy) affects all divisions of the facial nerve, including the forehead and weakens eye closure on 1 side. The condition usually evolves over hours, but may be present on waking. Primary care clinicians can diagnose Bell’s palsy without referring to neurology, and offer high-dose steroids if seen within 72 hours of onset. Corneal exposure may be managed with taping the eyelids shut or lubrication.</p> <p>Although the outcome is usually excellent, recovery is frequently incomplete. Aberrant re-innervation of the facial nerve can lead to a number of troublesome symptoms, including gustatory sweating or jaw-winking. These symptoms can occur months after the initial recovery period. As there are potential management techniques for these symptoms available in secondary care, including botulinum toxin injections, these people need to be referred to a neurologist.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. These estimates were the committee’s starting point for considering whether its recommendations caused additional referrals that would significantly affect the cost impact of the NHS.</p> <p>The committee acknowledged the cost of an outpatient referral for neurological problems as £178 for adults and £285 for children. Therefore, the committee only recommended referral of an individual when it was felt that this would lead to sufficiently great health benefits to compensate for the additional pressures placed on neurological services. The committee also acknowledged the additional costs that would be incurred following referral but that these would constitute a cost-effective use of NHS resources, meaning that individuals would not be placed on treatment pathways that were not cost effective.</p> <p>The committee suggested that an individual should not be referred where it was felt that there would be no, or minimal, reductions in health, thus justifying a reduction in referrals which would lead to cost savings.</p> <p>The committee did not feel that the recommendations for face and limb weakness would change the number of referrals or increase costs to the health service. The committee felt that cost savings may arise through an ending of unnecessary referral for diagnosis of Bell’s palsy, which can be successfully managed in primary care.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p> <p>Recommendation 33 on non-referral of isolated Bell’s palsy scored 70.6% agreement. Some responders to the targeted engagement exercise were concerned that no treatment advice for Bell’s palsy is included in the recommendations. This has been omitted because to include such recommendations would require a full evidence review of the available treatment options, which is beyond the scope of this guideline. The consensus of the committee is that current standard treatment is appropriate, including local measures (for example, eye protection) and high dose prednisolone, offered early in the disease course.</p>

	<p>There was some disagreement (5.9%, 1 participant) on recommendation 25. It was thought that this recommendation was not helpful and should not be included in the guideline as it wasn't clear what the recommendation addressed. The committee felt that it was important to keep this recommendation and refined the wording and LETR to support it and explain the reasoning further in the LETR.</p> <p>Recommendation 29 achieved 58.8% agreement. A suggestion was made to change the wording of 'functional disorders' to 'patient weakness describes may not be explained anatomically'. However, the committee preferred to keep the original wording as it was more concise and they wanted to raise awareness of 'functional disorders' and the suggested wording may not be clear enough.</p> <p>All other recommendations had a high level of agreement ranging from 76.5% to 88.2% and therefore remained unchanged.</p>
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5.8 Memory failure and cognitive deterioration in adults

5.8.1 Memory failure and cognitive deterioration

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.8.1.1 Recommendations and link to evidence (consensus statement 129 to 141 in appendix S)

<p>Recommendations</p>	<p>36. For adults aged under 50 with memory problems and no other neurological signs:</p> <ul style="list-style-type: none"> • do not routinely refer if brief testing shows memory function to be normal and symptoms are consistent with concentration difficulties • be aware that memory problems or concentration difficulties can be caused by: <ul style="list-style-type: none"> ○ recreational, and some prescription, drugs ○ alcohol ○ affective disorders ○ stress. <p>For more information see initial assessment in non-specialist settings in the NICE guideline on dementia.</p> <p>37. Be aware that, for adults who have an anxiety disorder or have been diagnosed with a functional neurological disorder by a specialist, memory problems and concentration difficulties might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.</p> <p>38. Do not routinely refer adults for neurological assessment if they have concentration difficulties associated with myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome or fibromyalgia.</p>
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	<p>39. For guidance on referring adults with progressive memory problems see initial assessment in non-specialist settings in the NICE guideline on dementia.</p> <p>40. Do not routinely refer adults with a single episode of dense amnesia (inability to recall the recent past or form new memories) if:</p> <ul style="list-style-type: none"> • the episode lasts less than 8 hours and • there is complete recovery and • there are no features suggestive of an epileptic seizure (see seizure markers for suspected epilepsy in the NICE guideline on transient loss of consciousness [‘blackouts’] in over 16s). <p>Advise the person that they have probably had an episode of transient global amnesia and that the recurrence rate is low.</p> <p>41. Refer adults with recurrent episodes of dense amnesia to have an assessment for epileptic amnesia.</p>
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for adults or children because the committee considered the referral decision to be non-contentious and an evidence review was unlikely to change this.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 36 – Adults under 50</p> <p>Neurodegenerative disorders affecting memory are rare in those under 50, but complaints of memory and concentration difficulties relatively common. Brief screening tests for memory impairment are not validated for this age group, but if normal, this should provide reassurance to the clinician.</p> <p>The committee wished to highlight common causes of difficulty in concentration that could potentially be addressed in primary care without referral to neurology services. These include use of recreational drugs and excessive use of alcohol and periods of stress.</p> <p>Difficulty with concentration is a common symptom seen in hypervigilance, anxiety, depression and functional neurological disorder and can present with the complaint of memory failure. The committee did not consider that a neurological referral would be appropriate for concentration difficulties alone. Where there are concerns about changes in behaviour or progressive deterioration in cognitive function affecting different domains, such as language, numeracy or physical skills, referral is appropriate.</p> <p>Recommendations 37–38 – Chronic fatigue syndrome, fibromyalgia and functional neurological disorder</p> <p>Functional symptoms are complaints that are not primarily explained based on physical or physiological abnormalities. They may mimic neurological disorders. Diagnosis may depend on exclusion of a medical explanation of the symptoms, and require a high level of clinical expertise and judgement. Functional symptoms can complicate a medically explained illness and cause difficulties in diagnosis and delineation. The committee also considered that people may benefit from an explanation that functional symptoms are commonly accompanied by problems with concentration and memory, and that this may reduce the overall load on clinical services.</p> <p>Difficulties with memory and concentration are a core diagnostic criterion for chronic fatigue syndrome and myalgic encephalopathy (CFS/ME) and may be present</p>

in people with fibromyalgia and functional neurological disorder. People with CFS/ME should be referred according to local pathways (see CG53).

The committee considered that a referral for neurological assessment in these cases is not necessary, unless the cognitive difficulties have a significant impact on everyday life. However, this patient population may still need medical or psychological support, depending on the nature of their condition, where reassurance is not enough, and the symptom has a significant impact on everyday life. The committee discussed that access to clinical health psychology can be limited but wanted to point out that, where pain is a prominent accompanying symptom (for example, fibromyalgia or chronic, daily headache), a pain clinic may have appropriate resources. Some patients with functional neurological disorder may benefit from referral for specialist physiotherapy.

A recommendation which covered these considerations was thought likely to help GPs to direct these patients to more appropriate channels than neurology services.

Recommendation 39 – Progressive memory problems, progressive behavioural change and progressive cognitive difficulties

Memory disorders can occasionally affect younger adults; cognitive problems are rarely the presenting symptoms of multiple sclerosis. Although these can initially present with isolated disorders of memory, which can be confused with concentration difficulties, they progress to involve multiple domains of cognitive function, and the appearance of these additional features indicates the need for referral.

Early onset dementia can be familial, so a history of first or second degree relative with onset of dementia under the age of 50 years should prompt consideration of referral for assessment. These disorders require referral for diagnosis, management and sometimes genetic counselling.

The committee recognised that progressive cognitive impairment, while rare in younger adults, may represent a serious neurological condition and require specialist referral depending on local clinical pathways. In order to reduce the misinterpretation of the more common functional memory impairment, which tends to be fluctuating rather than static or progressive, the opinion of a witness should be sought and the symptom confirmed by reassessment of the person at an interval of at least a month.

Recommendation 40 – Single dense amnesia with complete recovery

Short-lived, episodic isolated memory problems can indicate a diagnosis of transient global amnesia (TGA), transient epileptic amnesia (TEA) or functional neurological disorder. If no seizure markers are present, epilepsy is unlikely to be the cause. The committee noted that the NICE guideline on blackouts for over 16s (TLOC, CG109) defines seizure markers, and the committee agreed to cross-refer.

The committee also noted that a witness account of repetitive questioning with preserved consciousness during the amnesic episode is necessary to diagnose the TGA accurately.

Episodes of TGA are usually dense and brief. The committee discussed the time frame for episodes of transient, dense amnesia and agreed that most attacks last between 1 and 8 hours based on a review by Warlow and Hodges.⁶

A single episode of dense amnesia with no other alarming features has a very low recurrence rate. The committee therefore concluded that reassuring the person that it was probably an episode of TGA of an unknown cause is appropriate and that a referral is not necessary at the first presentation if the person has fully recovered.

Recommendation 41– Recurrent episodes of dense amnesia

TGA is characterised by episodes of dense amnesia that are brief (less than 2 hours). If TGA is suspected, an urgent referral for a neurological assessment is appropriate.

	Although TGA can recur, this is not typical and therefore needs specialist review if it occurs more than once to exclude TEA.
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations did not represent a change from current best practice, and the recommendations will not increase the number of referrals. The committee felt that referrals may decrease as some current unnecessary referrals due to identifiable causes, such as stress, could be avoided. In this case, the recommendations would be cost saving.</p>
Other considerations	<p>The committee discussed concerns about lack of familiarity with the diagnosis of transient global amnesia; feedback from the targeted engagement exercise raised this, suggesting that most in primary care would not be confident about not referring someone who presents with this alarming symptom. The committee acknowledged this. However, TGA is a clinical diagnosis, which does not require investigation or treatment, and if reassurance can be provided at first presentation this will be beneficial to the affected person as well as preventing an ultimately unnecessary outpatient episode. The committee therefore recommended against referral, hoping to raise awareness of this presentation.</p> <p>Targeted engagement exercise</p> <p>There was a high level of agreement with this set of recommendations ranging from 76.5% to 94.1%. There were several important points raised regarding recognition of this patient group that the committee discussed and included in the rationales for further clarification.</p> <p>Recommendation 36 was changed after the targeted engagement exercise as the committee felt that the use of recreational drugs, excessive use of alcohol and stress had been missed out in the original recommendation</p>

5.8.2 Memory tests

A systematic review of published evidence has been conducted for this topic.

5.8.2.1 Review question: In adults under 50 with suspected (or under investigation for) memory failure, what is the negative predictive value of neuropsychological assessments in ruling out organic memory failure?

There is value in reviewing whether there is a simple test that can be used in primary care to distinguish functional and early onset memory loss. There may also be brief cognitive assessment that can be undertaken in primary care, which may increase appropriate referrals.

The aim of this review was to evaluate the accuracy of a neuropsychological assessment, in particular the negative predictive value in ruling out organic memory failure in young adults suspected of early onset dementia.

For full details, see review protocol in appendix C.

Table 12: Characteristics of review question

Population	All adults under 50 having a memory assessment including those with suspected or under investigation for memory failure, anxiety and depression, chronic fatigue syndrome, fibromyalgia, and pain syndromes
Target condition	Early onset dementia
Index tests	<ul style="list-style-type: none"> • 6CIT test • ACE-3 questionnaire • Mini-mental exam • GP-COG • Mini COG • 7-minute screen
Reference standard(s)	<ul style="list-style-type: none"> • Clinical examination • Specialist diagnosis of dementia
Statistical measures	<ul style="list-style-type: none"> • Sensitivity and negative predictive value would be the most important outcomes, as we are looking for tests that would rule out memory failure. However, the committee is also interested in any of the following diagnostic accuracy measures: <ul style="list-style-type: none"> ○ 2×2 tables ○ specificity ○ ROC curves and area under the curve ○ repeatability (intra-tester reliability) <p>If the data is available, the committee is interested in the difference in diagnostic accuracy of shorter tests compared to longer ones.</p>
Study design	Cross-sectional studies, cohort studies, case series (including both retrospective and prospective analyses). Case-control studies will only be included if there is no other evidence, as they are biased.

5.8.2.2 Clinical evidence

No relevant clinical studies investigating the diagnostic accuracy of the listed index tests for identifying early-onset dementia were identified.

5.8.2.3 Economic evidence**Published literature**

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.8.2.4 Recommendations and link to evidence

Recommendations	No recommendations
Relative values of different diagnostic measures	<p>Sensitivity and negative predictive value were considered to be the most important outcomes for this review as the aim is to find the most accurate test at ruling out memory failure. However, the committee was also interested in any of the following diagnostic accuracy measures:</p> <ul style="list-style-type: none"> • 2×2 tables • Specificity

	<ul style="list-style-type: none"> • ROC curves and area under the curve • Repeatability (intra-tester reliability).
Quality of the clinical evidence	No evidence was identified for this review. The committee considered whether to include indirect evidence from older people. It was decided that this would not be applicable to this patient group because the prevalence of dementing conditions is much higher in the older group and any evidence is likely to be confounded by the natural cognitive decline that occurs with aging.
Trade-off between clinical benefits and harms	<p>The committee determined that there was no evidence on which to recommend any brief cognitive screening tool as an aid to identifying organic memory disorders in younger adults.</p> <p>The principal memory impairment diagnoses in adults under the age of 40 or 50 are functional memory disorder, which is very common compared to organic dementing conditions which are very rare. There was no evidence any of the screening tests were sensitive or specific for the diagnoses of dementing conditions in this age group.</p> <p>Because the incidence of dementia is so low, it would be difficult to undertake a research study to develop a screening tool.</p>
Trade-off between net clinical effects and costs	No recommendations were made; hence, there will be no change to current NHS resource use or costs.

5.9 Posture distortion in adults

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.9.1 Recommendations and link to evidence (consensus statement 22 to 32 in appendix S)

<p>Recommendations</p>	<p>42. Suspect cervical dystonia in adults who have persistent abnormalities of head or neck posture, with or without head tremor, especially if the symptom improves when the person touches their chin with their hand.</p> <p>43. Do not offer cervical imaging to evaluate suspected cervical dystonia in adults.</p> <p>44. Be aware that dystonia in adults can affect other parts of the body (for example, it can cause writer's cramp or in-turned posture of the foot).</p> <p>45. Refer adults with suspected dystonia to have an assessment for diagnosis and possible botulinum toxin treatment.</p> <p>46. Be aware that antipsychotic and antiemetic medicines can trigger or exacerbate dystonia in adults.</p>
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for adults because the committee considered the referral decision to be uncontentious and an evidence review is unlikely to change the decision.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 42 – Cervical dystonia</p> <p>Cervical dystonia is the most common type of dystonia and is characterised by a tendency of the neck to twist, flex, extend or be pulled laterally. Head tremor is a common feature of cervical dystonia; however, cervical dystonia can present without tremor. Painful lesions and nerve root irritation in the neck can also cause pain and muscle spasm but cervical dystonia can be painful, so the presence or absence of pain is not discriminatory. People with dystonia sometimes find that temporary relief from muscle spasm is achieved by touch or light pressure, classically to the chin. Postural abnormalities of the head and neck that could be due to cervical dystonia require a referral to a neurologist if sufficiently troublesome.</p> <p>Recommendation 43 – Cervical imaging</p> <p>Non-specialists may incorrectly assume that cervical nerve entrapment causes persistent distorted neck posture; thus, cervical imaging is inappropriately requested. The diagnosis of dystonia is based on clinical features rather than imaging. Neuroimaging is usually non-contributory. The delay in waiting for imaging results prolongs the time taken for people to access specialist treatment and incurs unnecessary medical costs. If imaging is appropriate, a neurologist will order it after referral.</p> <p>Recommendation 44 – Dystonia</p> <p>The muscle group affected with dystonia may cause involuntary muscle contractions resulting in a change in posture or distortion of a limb. Some focal dystonias are task-specific and only become apparent when that specific activity is undertaken, for example, writing in writer's cramp. Others are characterised by involuntary contractions of the eyes, tongue, face, neck, trunk, limbs or larynx, which can be sustained or fluctuating (spasmodic). Other examples include oculogyric crisis, tongue twisting or protrusion and in-turning of the ankle. The committee was unable to capture every possibility within the recommendation and chose to couch this in general terms aimed at reminding healthcare professionals of the possibility of dystonia.</p>

	<p>Recommendation 45 – Assessment for botulinum toxin treatment</p> <p>Non-specialists may misinterpret distortions of neck and foot posture and not refer to neurology or inappropriately refer to orthopaedic specialists first. Idiopathic dystonia is the most common cause of such abnormalities and is responsive to treatment with botulinum toxin. Spasticity associated with stroke, structural lesions of the brain and spinal cord, and cerebral palsy are also sometimes responsive to botulinum toxin injections. Secondary dystonia (or acquired dystonia) can arise from specific underlying neurodegenerative conditions or medication. This requires a specialist review for assessment, as the relationship between medication and dystonia is complex and often the discontinuation of medication is not an effective solution by itself.</p> <p>Recommendation 46 – Antipsychotic and antiemetic medication</p> <p>A variety of movement disorders can occur as a side effect to anti-psychotic and some antiemetic (for example, metoclopramide, prochlorperazine) medications, typically within a few days of initiation of treatment. These include acute dystonic reactions, motor restlessness (akathisia) and parkinsonism. If this happens, the prescriber of the medication should review it and consider symptomatic treatment with anticholinergic agents or benzodiazepines. Tardive dyskinesias and dystonias are involuntary movements of the face, lips, tongue, trunk and limbs that occur after a delay following treatment with antipsychotic medication. These medications are used widely, and the possibility that they have caused dystonia may not be recognised, generating an inappropriate neurology referral. The committee considered that a recommendation pointing out the possibility of an iatrogenic cause might reduce some unnecessary referrals.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for consideration of whether its recommendations caused additional referrals that would significantly cost impact the NHS.</p> <p>The committee is recommending that diagnosis of dystonia should be based on clinical features rather than imaging. The reduction in imaging will create cost savings for the NHS without having a negative impact on health.</p> <p>As dystonia can be treated, the committee felt that a strong recommendation concerning referral should be made, as this will have a positive impact on the individual's quality of life. The committee also felt that the symptom is sometimes inappropriately referred to orthopaedic specialists first which, in this case, represents an inappropriate use of NHS resources. The suggested assessment of botulin toxin ensures that the individual is assessed and, if appropriate, initiated on the most appropriate treatment pathway in the most timely and cost-effective manner.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p> <p>As the committee anticipated, there was no contention with this set of recommendations and the large majority of those consulted agreed with them. The level of agreement ranged from 83–94.4 %. The recommendation on antipsychotic and antiemetic medication exacerbating dystonia received 72.2 % agreement from a total of 18 participants, which was slightly below the threshold (27.8% thought it needed revision). Comments were mainly requesting clarifications on why these drugs may exacerbate dystonia and what the prescriber could do pending the review by neurological services. The committee felt that this would be too much</p>

	detail in a recommendation and therefore added further information to the relevant LETR section.
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5.10 Sensory symptoms including tingling or numbness in adults

5.10.1 Review question: In people who present with tingling or altered sensation in the body, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?

For full details, see review protocol in appendix C.

Component	Description
Population	<p>People presenting to a non-specialist with tingling or altered sensation in the body stratified into the following 2 groups:</p> <ul style="list-style-type: none"> • adults, young people and children (>5 years) • children (<5 years old) and babies
Predictor variables under consideration	<p>The committee identified the following predictors in people presenting to a non-specialist with tingling or altered sensation in the body for inclusion in the review:</p> <ul style="list-style-type: none"> • alcohol use • diabetes • distribution of symptoms (for example, peripheral or particular nerve) • duration of symptoms • loss of reflexes • pain • periodicity (transience) and focality • sensory loss • vitamin deficiencies • weakness.
Outcomes	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive values <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ compression neuropathy (for example, carpal tunnel syndrome and Meralgia parasthetica) ○ demyelination ○ drug toxicity – chemotherapy, alcohol, platinum-based drugs ○ functional (hyperventilation) ○ mononeuropathy multiplex ○ peripheral neuropathy ○ radiculopathy ○ seizures ○ small fibre neuropathy ○ TIAs ○ tethering of the spinal cord.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis

Component	Description
Key confounders	Any of the predictors listed above

5.10.2 Clinical evidence

No relevant clinical studies were identified.

5.10.3 Economic evidence

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

5.10.4 Evidence statements

Clinical

No relevant economic evaluations were identified.

Economic

No relevant economic evaluations were identified.

5.10.5 Recommendations and link to evidence

Recommendations	<p>47. Assess sudden-onset transient unilateral numbness in adults in line with the NICE guideline on stroke and transient ischaemic attack in over 16s.</p> <p>48. Refer immediately adults with rapidly progressive (within hours to days) symmetrical numbness and weakness or imbalance to have a neurological assessment.</p> <p>49. Refer urgently adults with recurrent, brief (less than 2 minutes), fixed-pattern disturbances of sensation to have an assessment for epilepsy.</p> <p>50. Refer adults with persistent, distally predominant altered sensation in the limbs, and brisk deep tendon reflexes, to have an assessment for possible brain or spine disease.</p> <p>51. Suspect migraine with aura in adults who have sensory symptoms that occur with or without headache and:</p> <ul style="list-style-type: none"> • are fully reversible and • develop over at least 5 minutes and • last between 5 and 60 minutes. <p>For recommendations on diagnosing and managing migraine with aura, see the NICE guideline on headaches in over 12s.</p>
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- 52. For adults with persistent, distally predominant ('stocking' or 'glove and stocking') altered sensation in the limbs and depressed deep tendon reflexes:**
- be alert to the possibility of peripheral neuropathy and consider checking:
 - vitamin B12 deficiency
 - thyroid function
 - for evidence of coeliac disease in line with the [NICE guideline on coeliac disease](#).
 - renal function
 - blood glucose
 - ESR (erythrocyte sedimentation rate)
 - alcohol consumption, using a tool such as AUDIT (Alcohol Use Disorders Identification Test), in line with the [NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence](#)
 - if no causes of peripheral neuropathy are found, refer for neurological assessment.
- 53. Be aware that, for adults who have been diagnosed with a [functional neurological disorder](#) by a specialist, recurrent numbness and tingling might be part of the disorder and the person might not need re-referral if there are no new neurological signs. New symptoms in adults who have been diagnosed with a functional neurological disorder by a specialist should be assessed as described in the relevant sections of this guideline.**
- 54. Advise adults with tingling and a diagnosis of functional neurological disorder that the tingling might fluctuate and evolve over time and could increase at times of stress.**
- 55. Refer in line with local pathways if symptoms of carpal tunnel syndrome are severe or persistent after initial management.**
- 56. Reassure adults with unilateral or bilateral numbness, tingling or pain in the distribution of the lateral cutaneous nerve of the thigh (meralgia paraesthetica) that the condition is benign and might improve spontaneously. Consider referring for pain management only if the symptoms are severe.**
- 57. Do not routinely refer adults with symptoms of cervical radiculopathy that have remained stable for 6 weeks or more unless:**
- pain is not controlled with analgesics or
 - the symptoms are disabling or
 - one of the following factors is present:
 - age under 20

	<ul style="list-style-type: none"> ○ gait disturbance ○ clumsy or weak hands or legs ○ brisk deep tendon reflexes (triceps and lower limbs) ○ extensor plantar responses ○ new-onset disturbance of bladder or bowel function. <p>58. Do not routinely refer adults with symptoms of lumbar radiculopathy that have remained stable for 6 weeks or more unless pain is not controlled with analgesics or symptoms are disabling, in line with the NICE guideline on low back pain and sciatica in over 16s.</p> <p>59. Do not routinely refer adults with recurrent episodes of tingling or sensory disturbance in the limbs that are present on waking from sleep and last less than 10 minutes.</p>
<p>Rationale for categorising symptoms</p>	<p>Altered sensation is a common presentation in primary care and there is uncertainty as to when people should be referred. Key issues are determining which clinical features are indicative of functional neurological disorders and which features indicate physical disease. It is also important to determine how urgently these symptoms require specialist assessment. The committee agreed that an evidence review to support their decision-making would be helpful.</p>
<p>Relative values of different outcomes</p>	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of sensory symptoms are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications that can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
<p>Quality of the clinical evidence</p>	<p>No evidence was identified for this review. These recommendations are based on committee consensus.</p>
<p>Trade-off between clinical benefits and harms</p>	<p>Recommendation 47 – Sudden-onset loss of sensation</p> <p>Sudden-onset unilateral transient sensory symptoms raise the possibility of stroke or TIA and require urgent assessment and possibly immediate referral (see NICE CG68).</p> <p>Recommendation 48 – Rapidly progressive symmetrical numbness</p> <p>Rapidly progressive symmetrical numbness may indicate the development of post infective polyneuropathy, a rapidly progressive syndrome that may result in respiratory failure. Immediate neurological assessment is required for respiratory support and treatment.</p> <p>Recommendation 49 – Disturbances of sensation</p> <p>Disturbances of sensation even without loss of consciousness may be a result of epileptic seizures. Although not the most common presentation of epilepsy, it is important not to miss this diagnosis and referral should follow the recommendations of NICE CG 137.</p> <p>Recommendation 50 – Possible brain or spine disease</p>

Sensory disturbance in the limbs can be caused by lesions in the central nervous system (brain and spinal cord), for example, those caused by multiple sclerosis or tumours. In contrast to sensory disturbance caused by damage to peripheral nerves, those caused by lesions of the brain or spinal cord characteristically produce exaggerated deep tendon reflexes and extensor plantar responses (rather than depressed deep tendon reflexes and flexor plantar responses as found in neuropathies). The presence of exaggerated deep tendon reflexes and extensor plantar responses should trigger referral in people with undiagnosed neurological disease.

Recommendation 51 – Migraine aura

Tingling and sensory distortion can occasionally be part of the aura of migraine and may be misconstrued as suggestive of stroke. Typical aura features include visual symptoms such as flickering lights, spots or lines, or partial loss of vision as well as numbness or tingling which usually spreads gradually from its starting point to adjacent body parts over a period of a few minutes, in contrast to stroke, which comes on very rapidly. Sensory migraine aura may be associated with speech and language disturbance. It is important to be aware of the possibility of migraine (see also CG150).

Recommendation 52 – Suspected neuropathy

Distally predominant sensory loss may be caused by nerve damage (neuropathy). This should be suspected if it has a 'glove and stocking' distribution covering the distal parts of the affected limbs and if the deep tendon reflexes are depressed. If reflexes are brisk, then neuropathy is very unlikely, and a central nervous system cause should be considered. The committee considered that a straightforward screening for common causes of neuropathy would facilitate direction of the patient to the most appropriate service, which may not be neurology in the first instance. If people have diabetes, gluten sensitivity or alcohol excess, they may need referral to the appropriate non-neurological specialist service. In other cases, neurological referral for diagnostic clarification will be appropriate.

Recommendation 53–54 – Recurrent numbness and tingling

Functional symptoms are complaints that are not primarily explained by physical or physiological abnormalities. They may mimic neurological disorders. Diagnosis may depend on exclusion of a medical explanation of the symptoms and require a high level of clinical expertise and judgement. Functional symptoms can complicate a medically explained illness and cause difficulties in diagnosis and delineation.

Transient sensory symptoms are common in functional neurological disorders. The committee considered that these might not require neurological assessment, although this will depend on the experience of the healthcare professional to whom the symptom is presented, and their certainty regarding the diagnosis. People with functional disorder may require medical or psychological support for their condition. The committee considered that people with functional disorder might benefit from an understanding that their symptoms are likely to fluctuate and evolve with time and acceptance of this may reduce the overall load on clinical services.

Recommendation 55 – Carpal tunnel syndrome

Carpal tunnel syndrome is caused by compression of the median nerve at the wrist, which produces pain in the arm, often at night, and sensory symptoms in the palm of the hand and sometimes hand weakness. It is a common condition and, providing the diagnosis is considered, a provisional diagnosis can be made without necessarily requiring referral to neurology for confirmation. Many regions have well-established management pathways for this common condition (which may avoid the involvement of neurological services) and referral should follow these local arrangements.

Recommendation 56 – Meralgia parasthetica

	<p>This common entrapment neuropathy gives rise to symptoms of numbness and pain in the outer aspects of the thigh. People with meralgia parasthetica should be reassured that the symptoms will usually improve with time and may benefit from weight loss and simple analgesia. Symptoms are largely self-limiting and do not normally require referral.</p> <p>Recommendation 57 – Cervical radiculopathy</p> <p>Compressive cervical radiculopathy is usually caused by disc herniation, osteophytes arising in cervical spondylosis, or a combination of the 2. Stable compressive radiculopathy can be managed conservatively in the first instance, with analgesia and physical therapy or exercise. It usually settles spontaneously within a few weeks. Referral is required if surgery is to be considered for progressive or unrelenting symptoms or if there are atypical features suggesting damage to the spinal cord (myelopathy). Urgent surgical referral should be considered if there are symptoms or signs of myelopathy or spinal cord involvement with, for example, gait disturbance, brisk deep tendon reflexes, extensor plantar responses or disturbance of bladder or bowel function. Clumsy or weak hands could indicate a high cervical or intrinsic cord lesion and again should be referred urgently for specialist assessment and imaging.</p> <p>Recommendation 58 – Lumbar radiculopathy</p> <p>This is a common condition of nerve root entrapment and usually settles spontaneously within a few weeks. Stable lumbar radiculopathy is usually managed conservatively and does not require referral unless there are progressive unrelenting or disabling symptoms or symptoms of conus or cauda equina involvement (for example, bladder or bowel dysfunction or perineal numbness in the case of cauda equina involvement). Urgent referral is required if surgery is to be considered or if there are signs of cauda equina compromise. For guidance on management of low back pain with or without sciatica, see NICE NG59.</p> <p>Recommendation 59 – Transient tingling on waking from sleep</p> <p>Transient tingling on waking is usually caused by nerve compression related to sleeping posture. It recovers rapidly and many people who experience this symptom will not report it. Those who do should be reassured that it does not represent a serious illness. It does not require referral to a neurologist.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations were generally similar to current practice. Taken together, they would be likely to reduce the total number of referrals by reducing some current unnecessary referrals. This will consequently be cost saving.</p>
<p>Other considerations</p>	<p>The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise (which only applied to recommendations where no evidence review was undertaken).</p>

5.11 Sleep disorders in adults

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.11.1 Recommendations and link to evidence (consensus statement 162 to 174 in appendix S)

Recommendations	<p>60. Offer advice on sleep hygiene to adults with insomnia.</p> <p>61. Do not routinely refer adults with insomnia, jerks on falling asleep or isolated brief episodes of sleep paralysis.</p> <p>62. Refer urgently adults with symptoms suggestive of new-onset epileptic seizures in sleep for neurological assessment in line with the NICE guideline on epilepsies.</p> <p>63. For adults with excessive sleepiness:</p> <ul style="list-style-type: none"> • use the Epworth score together with history of obstructive symptoms in sleep to assess the likelihood of sleep apnoea • refer in accordance with local policy • if appropriate, offer advice on weight reduction, alcohol consumption and smoking cessation, in line with NICE guidance on obesity, alcohol-use disorders, and smoking and tobacco. <p>64. Refer adults with narcolepsy, with or without cataplexy, for neurological assessment.</p> <p>65. Consider referring adults with persistent symptoms suggestive of sleep behaviour disorders (such as agitated or violent movements that are more complex than a simple jerking motion) for neurological assessment.</p>
Rationale for categorising symptoms	<p>This symptom was not prioritised for an evidence review for adults because the committee considered the referral decision to be non-contentious and unlikely to be changed by an evidence review. The committee recognised that sleep disorders in children are a common presentation and considered that there is a need for guidance for non-specialists on where to refer.</p>
Trade-off between benefits and harms	<p>Recommendation 60 – Sleep hygiene advice for insomnia</p> <p>Difficulty sleeping is not usually a neurological problem and the committee also noted that most forms of insomnia do not require medical treatment. However, people with insomnia may be referred inappropriately to sleep clinics, which can place a strain on these services. Insomnia can be addressed by improved sleep hygiene, about which advice is easily accessible to non-specialists.</p> <p>Recommendation 61 – Benign sleep phenomena</p> <p>Brief involuntary movements in sleep (such as hypnic jerks, which happen when falling asleep and being jerked awake) are common. People with such symptoms should be reassured that they do not indicate an underlying neurological disease and do not need referral unless severe. Some people find sleep hygiene measures helpful in managing these symptoms</p>

Isolated brief episodes of sleep paralysis are also benign but should prompt enquiry about symptoms of narcolepsy.

Recommendation 62 – Sleep epilepsy

While seizures from sleep may remain unrecognised for long periods and may result in only minor injuries, the risk of sudden unexpected death in epilepsy is substantial in this group. The committee noted the existing NICE epilepsy guideline, which recommends that people who have had a seizure be referred after their first seizure to see an epileptic management specialist as soon as possible. This includes night time seizures. The committee therefore reflected the existing guidance in this recommendation.

Symptoms suggestive of nocturnal epilepsy include tonic clonic movements, stertorous breathing, tongue biting, urinary incontinence, postictal drowsiness, and confusion.

Recommendation 63 – Excessive sleepiness

The Epworth score is an appropriate, simple, well-established measure for screening people with excessive sleepiness.

Raising awareness amongst non-specialists of the possibility of obstructive sleep apnoea as a diagnosis should help to reduce inappropriate referrals to neurology. Local policies and pathways will generally already be in place for referral of sleep apnoea based on a person's Epworth score, although the committee noted that local thresholds might vary. Some sleep disorders such as sleep apnoea and excessive sleepiness can be reduced with advice on weight reduction, and in some areas dietary advice is recommended as a first-line response. Limiting alcohol and smoking can also increase sleep quality. Clinicians should refer to national guidance regarding alcohol consumption and smoking cessation

Sleep services will identify narcolepsy if it is present, but the committee noted that good communication does not always exist between neurology and sleep services, which may create a disservice to those in need of care. Clinicians should refer according to local policies unless there is a strong suspicion that the person has narcolepsy or another serious neurological condition

Recommendation 64 – Narcolepsy with or without cataplexy

Although narcolepsy and cataplexy are rare conditions, the committee felt it was important to highlight these conditions to raise awareness amongst non-specialists that these could be potential diagnoses. Symptoms suggestive of narcolepsy include excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis and cataplexy. Cataplexy should be suspected in people complaining of transient muscle weakness triggered by emotion (for example, laughter, anger and grief).

Recommendation 65 – Sleep behaviour disorders

Sleep behaviour disorders vary in severity and on rare occasions can endanger life if they cause a person to undertake potentially harmful behaviours while asleep. People with complex and severe sleep behaviour disorders should be referred, but milder forms may not necessitate referral to neurology. The committee agreed that clinical judgement should be used to determine the appropriateness of a referral on an individual basis; therefore, the committee decided upon a recommendation to consider referral. The committee recognised that clinicians sometimes face pressure from people to refer, and a weaker recommendation may help to emphasise that milder sleep behaviour disorders do not always need to be referred.

People with REM sleep behaviour disorder (RBD) are at increased risk of future Parkinson's disease and related neurodegenerative conditions. The committee noted that people with such sleep behaviour disorders may present at sleep clinics first but they will then be referred to neurology.

<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit costs £175 and a paediatric outpatient visit costs £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current practice; therefore, the recommendations will not increase the number of referrals. The committee recommended referral in situations where there is a standard treatment pathway in place that will enable individuals to cope better with their symptoms. In addition, as sleep disorders can be chronic, the committee believed that appropriate timely referral and treatment may prevent future, unscheduled healthcare utilisation.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p> <p>Recommendations 60 and 61 received 100% agreement and recommendation 64 had 93.8% agreement. Therefore, the committee did not discuss these recommendations; they remain unchanged.</p> <p>Recommendation 63 received 81.3% agreement. The participants highlighted that the Epworth score on its own should not be the sole criteria for referral. The committee felt that this was a simple test and that local policies which are generally already in place use this score as a basis for referral. There was also some doubt about whether there was evidence to suggest that weight loss helps with sleep apnoea. However, the committee felt that in their experience this was helpful as a first-line response.</p> <p>Recommendation 62 reached 75% agreement. However, 6.3% (1 participant) disagreed and 18.8% (3 participants) suggested revisions. The participants did not agree with the use of the term ‘nocturnal epilepsy’ stating that these types of seizures were not necessarily linked to particular time of day or night but occur with sleep. Therefore, the committee changed the wording to ‘epileptic seizures in sleep’. The participants also highlighted that people fulfilling these criteria are at high risk of sudden unexpected death from epilepsy (SUDEP) and therefore should be referred urgently. The committee agreed and changed the wording of the recommendations to reflect that.</p> <p>Recommendation 64 reached 87.5% agreement but 6.3% (1 participant) disagreed stating that these people should be referred to sleep specialists. The committee felt that these people would be best seen for neurological assessment and therefore did not change the recommendation.</p>

5.12 Smell or taste problems

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.12.1 Recommendations and link to evidence (consensus statement 116 to 128 in appendix S)

<p>Recommendations</p>	<p>66. Be aware that sudden-onset distortion of sense of smell or taste in adults is rarely associated with structural neurological abnormality and usually resolves within a few months.</p>
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	<p>67.Refer adults with transient, repetitive smell or taste hallucinations to have a neurological assessment for epilepsy.</p> <p>68.Consider neuroimaging for adults with unexplained loss of sense of smell or taste that lasts more than 3 months.</p> <p>69.Do not routinely refer adults with loss of sense of smell or taste and normal neuroimaging.</p> <p>70.Do not routinely refer adults who lose their sense of smell or taste immediately after a head injury.</p>
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for adults because the committee considered the referral decision to be non-contentious and an evidence review was unlikely change this.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 66 – Sudden-onset distortion of sense of smell or taste</p> <p>Sudden-onset distortion of sense of smell or taste is usually idiopathic and unlikely to indicate the presence of a neurological condition. Idiopathic dysgeusia is particularly common in the first trimester of pregnancy, and it is also commonly seen in people undergoing chemotherapy.</p> <p>The committee noted that there is an issue in current practice regarding excessive imaging and referral for this symptom. The committee hopes that reassuring non-specialists that neurological assessment is unnecessary will help to reduce the number of inappropriate referrals.</p> <p>Recommendation 67 – Transient fixed-pattern taste or smell hallucinations</p> <p>The committee discussed the presentation of recurrent positive olfactory symptoms (olfactory hallucinations). These are unlikely to be associated with a brain tumour but can be a manifestation of temporal lobe epilepsy auras (that is, focal seizures), particularly if they are brief and stereotyped and should prompt the search for a witness account of an accompanying loss of awareness or other feature suggestive of epilepsy. People with recurrent olfactory hallucinations should therefore be referred for a neurological assessment.</p> <p>Recommendation 68 – Unexplained persistent loss of sense of smell or taste</p> <p>Progressive loss of sense of smell or taste can be a rare presentation of an olfactory groove meningioma or frontal lobe tumour. The vast majority of people presenting with progressive loss of sense of smell or taste will not have a brain tumour but imaging should be considered if the symptom is unexplained and persistent. Referral to an Ear, Nose and Throat specialist, may be required to exclude a local cause of sensory loss first. The committee considered that a loss of sense of smell that did not appear to have a rhinological cause could not be attributed to normal aging or neurodegenerative disease and should trigger neuroimaging if it persisted beyond 3 months without sign of recovery. This symptom is of particular concern in younger people. The committee noted that urgent neuroimaging should be undertaken where progressive loss of sense of smell or taste presents with other neurological deficits such as headaches, memory dysfunction or personality change in line with cancer guidelines. It was also highlighted that progressive loss of sense of smell or taste in older people can be an accompaniment of neurodegenerative disorders affecting the olfactory bulb (for example, Parkinson’s disease) but neuroimaging is usually unhelpful in these circumstances.</p>

	<p>Recommendation 69 – Loss of sense of smell or taste and normal neuroimaging</p> <p>Loss or distortion of sense of smell is a common referral to neurological services, but it only rarely has a serious neurological cause. It could be age-related, associated with Parkinson’s or Alzheimer’s disease or caused as a side effect of treatments such as chemotherapy. The committee therefore believe that neuroimaging is usually not required; if neuroimaging has been performed and the results are normal, the committee considered that referral to neurology is not necessary.</p> <p>Recommendation 70 – Loss of sense of smell or taste after a head injury</p> <p>Loss of sense of smell or taste is extremely common after a head injury and, although distressing, does not warrant referral. Impaired olfactory function following a head injury is an indication of damage of the fine olfactory nerve connections as they pass through the cribriform plate. It does not correlate with post-traumatic amnesia and is not a marker of a more extensive brain injury. Post-traumatic anosmia is untreatable and usually permanent so referral for neurological assessment is unnecessary if this is the only symptom present.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>There is a cost implication for recommending neuroimaging for progressive loss of sense of smell or taste; however, the NICE guideline on suspected cancer (NG12) already recommends urgent neuroimaging in the event of progressive, sub-acute loss of central neurological function (recommendation 1.9.1).</p> <p>Overall, the committee agreed that the recommendations did not represent a change from current practice. These recommendations will not increase the number of referrals or the costs to the health service.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p> <p>There was a high level of agreement with this set of recommendations, ranging from 76.5% to 94.1%. Although there was a very low level of disagreement with some recommendations, the committee felt that they raised important issues and warranted some consideration and discussion.</p> <p>The level of disagreement with recommendation 70 was 5.9% (1 participant). It was felt that not referring people for imaging who have had a recent head injury may miss otherwise unidentified frontal fractures. The committee considered this but did not think it warranted a change in the recommendation when anosmia is the only symptom.</p> <p>The level of disagreement with recommendation 68 was also 5.9% (1 participant). There was concern that this may lead to an increase in referrals for imaging. The committee believed this would not be the case, as this is in line with the suspected cancer guideline and the cost implications have already been considered. There was no change to the recommendation but further detail was provided in the trade-off between clinical benefits and costs section.</p> <p>The level of disagreement with recommendation 69 was also 11.8% (2 participants). One participant expressed concern that this recommendation also indirectly suggests referral for imaging. The committee had already addressed this in recommendation 68 so no further action was taken. The other reason for disagreement was that this recommendation may miss people with</p>

neurodegenerative disorders, but the committee felt that referring people with loss of smell and no other neurological features was unnecessary.

5.13 Speech, swallowing and language problems in adults

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.13.1 Recommendations and link to evidence (consensus statement 198 to 208 in appendix S)

Recommendations	<p>71. Refer urgently adults with sudden-onset speech or language disturbance to have an assessment for a vascular event, in line with local stroke pathways and following the recommendations on prompt recognition of symptoms of stroke and TIA in the NICE guideline on stroke and transient ischaemic attack in over 16s.</p> <p>72. For adults with progressive slurred or disrupted speech:</p> <ul style="list-style-type: none"> • refer for an assessment for neuromuscular disorders, in line with the recommendations on recognition and referral in the NICE guideline on motor neurone disease • refer urgently if there is any evidence of swallowing impairment • refer immediately if there is breathlessness at rest or when lying flat. <p>73. Consider referring adults with isolated and unexplained persistent dysphonia (a quiet, hoarse or wobbly voice) to have an assessment for laryngeal dystonia (involuntary contractions of the vocal cords) if hoarseness caused by structural abnormality or malignancy has been excluded by ear, nose and throat examination.</p> <p>74. Be aware that persistent dysphonia in adults may be a presenting symptom of a neurological condition such as Parkinson’s disease. For recommendations on the diagnosis and management of Parkinson’s disease, see the NICE guideline on Parkinson’s disease in adults.</p> <p>75. Be aware that anxiety disorder and functional neurological disorders are the most common causes of minor word-finding difficulties in adults and people with a diagnosis of anxiety disorder or functional neurological disorder made by a specialist might not need a referral.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for adults because the committee considered the referral decision to be uncontentious and an evidence review is unlikely to change the decision.
Trade-off between benefits and harms	<p>Recommendation 71 – Sudden onset of speech disturbance</p> <p>New onset transient speech disturbance could indicate a vascular event such as a transient ischaemic attack. The NICE stroke guideline (CG68) provides recommendations for recognition and referral.</p> <p>Recommendation 72 – Progressive slurred speech</p> <p>Progressive disruption of speech over a period of months could indicate motor neurone disease (MND) because it is often associated with swallowing difficulties.</p>

Myasthenia gravis can also present with progressive slurred speech and swallowing difficulties; although, unlike in MND, these fluctuate significantly, are usually worse after chewing and towards the end of the day and are often accompanied by double vision or drooping of the eyelids. Other causes of progressive slurred speech include ataxia, extrapyramidal and dementing disorders.

Although MND prognosis is not influenced greatly by early diagnosis, the committee considered that a prompt referral should be made, partly to consider other diagnoses such as myasthenia gravis, which is highly treatable, and also to enable people with MND to access vital support services to maintain their independence and quality of life for as long as possible, including services such as physiotherapy, occupational therapy and respiratory support. It also enables people to make provision to prepare for the rapid progression of the disease, such as accessing home or vehicular adaptations, communication aids, or services such as voice banking which enables people to record their own voice for when they lose the ability to speak. In addition, there are safety considerations because people with bulbar difficulties may also run into problems with chewing and swallowing. The committee noted the recommendations on recognition and referral in the NICE guideline on MND (NG42) and agreed to cross-refer.

People with slowly progressive speech disturbance should be kept under review by the referrer until they are seen by a neurologist. Occasionally, people's conditions can deteriorate rapidly (over days to weeks), and these people may require an urgent hospital admission.

Recommendation 73 – Persistent dysphonia

People with an unexplained new onset hoarse voice over the age of 45 years, particularly in smokers, should be referred urgently to ENT for exclusion of malignancy (see NICE NG12), and the committee agreed that this is an important first step.

In the absence of structural abnormalities identified by ENT services, dysphonia is commonly mislabelled as a functional neurological disorder. However, a quiet or wobbly voice can be a symptom of a neurological condition such as Parkinson's or laryngeal dystonia. When dysphonia is accompanied by dysarthria or dysphagia, motor neurone disease and myasthenia gravis should be considered

People who present with dysphonia are usually appropriately referred to ENT first for exclusion of ENT causes. In the absence of laryngeal pathology and signs of parkinsonism, laryngeal dystonia should be considered and, depending on local pathways, referred to specialist ENT or neurology for diagnosis and consideration of botulinum toxin treatment.

The committee felt it was important to highlight potential neurological causes for non-specialists to bear in mind when assessing people whose symptoms persist despite no obvious problem being found on ENT examination. Examination for dysarthria and of the lower cranial nerves may be revealing. Dysphonia can be an early presenting symptom of a significant neurological condition such as Parkinson's. In addition, a prompt diagnosis of laryngeal dystonia – while not an indicator of a more serious neurological condition – could increase the quality of life for those who present with the disabling voice condition. When dysphonia is accompanied by dysarthria or dysphagia, motor neurone disease and myasthenia gravis should be considered.

Recommendation 74 – Parkinson's disease

Parkinson's disease can occasionally present with dysphonia, typically a quiet voice. This is not appreciated by all clinicians, and the committee considered that it was appropriate to raise awareness of this as a presenting symptom to facilitate more prompt diagnosis. If this symptom is dominant, other features of Parkinson's disease should be sought, including asymmetric slowness of rapid repetitive movements, a

	<p>history of anosmia or REM behaviour sleep disorder. A referral for confirmation of the diagnosis and management advice should be made to a neurologist or a care of the elderly physician, in line with local pathways.</p> <p>Recommendation 75 – Minor word-finding difficulties</p> <p>Functional symptoms are complaints that are not primarily explained based on physical or physiological abnormalities. They may mimic neurological disorders. Diagnosis may depend on exclusion of a medical explanation of the symptoms and require a high level of clinical expertise and judgement. Functional symptoms can complicate a medically explained illness and cause difficulties in diagnosis and delineation. Minor word-finding difficulties are a very common presentation in functional neurological disorders, including anxiety states. The symptom may wax and wane and is often more apparent to the patient than to observers. The committee agreed that anxiety disorder should be considered in someone with word-finding difficulties that are not progressive or accompanied by other symptoms. Referral for psychological support may be appropriate. Common symptoms that may coincide with word-finding difficulties in people with anxiety include migraine, headaches, tingling, fatigue, memory and concentration difficulties. People may be unaware that they are experiencing functional symptoms or that functional symptoms may be exacerbated at times of stress.</p> <p>The committee noted that isolated word-finding difficulties can rarely be the presenting symptom of semantic dementias, such as primary progressive aphasia. These are extremely rare conditions that would be distinctive because, rather than fluctuating, there are progressive language difficulties, for example, in reading and comprehension. In due course, impairments will become apparent in other cognitive domains, such as memory and orientation, suggestive of Alzheimer’s disease, or behaviour, indicating possible frontotemporal dementia.</p> <p>Word-finding difficulty causes undue distress in some cases, and the committee decided that a recommendation to raise awareness of functional disorder as a common cause might help GPs reassure patients and prevent some inappropriate referrals.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, the first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations did not represent a change from current best practice, and that, viewed along with the rest of this guideline, the recommendations will not increase the total number of referrals or NHS costs.</p> <p>The committee believed that the recognition of and potential referral for laryngeal dystonia would represent a cost-effective use of resources in some cases as potential treatment options can improve quality of life and may also highlight a potential neurological cause. Therefore, referral should be considered on an individual basis for these people.</p>
<p>Other considerations</p>	<p>Targeted engagement exercise</p> <p>There was a high level of agreement with this set of recommendations ranging from 75–93.8%. Therefore, the recommendations remained mostly unchanged except for minor refinement of the wording to make them clearer.</p>

5.14 Tics and involuntary movements in adults

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

5.14.1 Recommendations and link to evidence (consensus statement 54 to 66 in appendix S)

Recommendations	<p>76. Do not routinely refer adults with tics (involuntary movements that can be temporarily suppressed at the expense of mounting inner tension) unless the tics are troublesome or accompanied by additional progressive neurological symptoms .</p> <p>77. Consider referring adults with a tic disorder for psychological therapy if the disorder distresses them.</p> <p>78. Consider referring adults who have completed psychological therapy for a tic disorder to have a neurological assessment if their symptoms are severe and the disorder continues to distress them, but tell the person that:</p> <ul style="list-style-type: none"> • there are not many medicines available to treat a tic disorder • the medicines that are available don't always work very well and can have serious side effects. <p>79. Do not routinely refer adults with isolated involuntary movements of the eyelid unless the movements:</p> <ul style="list-style-type: none"> • cause involuntary tight eye closure of both eyes (blepharospasm) or • have persisted for more than 3 months. <p>80. In adults with involuntary movements of the face, neck, limbs or trunk that cannot be temporarily suppressed by mental concentration:</p> <ul style="list-style-type: none"> • refer for neurological assessment or • refer to neurology or an eye clinic according to local provision, if the person has involuntary tight eye closure of both eyes (blepharospasm). <p>81. Do not routinely refer people with small involuntary muscular twitches (fasciculations) unless these are associated with muscle wasting and weakness or muscle rigidity.</p>
Rationale for categorising symptoms	A tic is a sudden, repetitive, non-rhythmical movement or vocalisation, which can be temporarily suppressed at the expense of mounting inner tension. This symptom was not prioritised for an evidence review for adults because the committee considered the referral decision to be uncontentious and an evidence review is unlikely to change the decision.
Trade-off between benefits and harms	<p>Recommendation 76 – Transiently suppressible movements</p> <p>Tic disorder is a relatively common disorder in adults and mild forms frequently remain undiagnosed. Isolated tic disorder is benign and not indicative of neurodegenerative disease. Treatment and management options are limited. The drug treatment of the tic requires taking medication of limited efficacy and with</p>

significant side effects, for example, anti-dopaminergic drugs such as risperidone, tetrabenazine or botulinum toxin injections. There is no neurosurgical option.

Tics should be differentiated from other fleeting movements such as hemifacial spasm (a condition caused by irritation of the facial nerve producing simultaneous contraction of muscles in half the face) and blepharospasm (a form of dystonia condition causing involuntary persistent bilateral eye closure).

The committee noted that, once they receive a clear explanation, adults most often decide they are better off without treatment, unless it has a severe impact on their quality of life (for example, reduced social interaction, job performance or increased pain). Tics are generally managed most effectively by controlling stress. There is little value in referring to secondary care except for confirmation of the diagnosis. The committee therefore agreed upon a recommendation of 'do not refer' providing there are no other neurological signs or symptoms.

Recommendation 77 – Referral for psychological therapy

Anxiety and distress is a common comorbidity of tic disorder. The committee noted that, in these circumstances, a psychology referral may be appropriate, and clinical judgement should be used to determine appropriate circumstances. Treatment may reduce the psychological impact of the disorder including help with associated comorbid psychiatric conditions such as obsessive compulsive and anxiety disorder. For particularly disabling tics, and where this is available, psychologists may be able to offer habit-reversal therapy, for which some efficacy has been demonstrated.

Recommendation 78 – Following psychological therapy

In people with very severe or socially disabling tics, medical treatment can occasionally be justified. A neurological referral would then be appropriate in order to explore further treatment options. It would be appropriate to warn the patient that there are few drug options, they are of limited efficacy, and involve a risk of serious side effects.

Recommendation 79 – Involuntary movements confined to the eyelids

Conditions treatable with botulinum toxin injections, such as blepharospasm, involuntary tight closure of both eyes, and hemifacial spasm, where there is distortion of other parts of the face on the same side as the eye closure, are often mistaken for tics. In contrast to tics, these are outside any voluntary control and cannot be suppressed.

Minor, insuppressible and flickering movements confined to one eyelid (myokymia) are a widely experienced self-limiting normal phenomenon, even more common with sleep-deprivation and stress. These involuntary eyelid movements can sometimes continue for months in which case, if they are distressing, a referral is justifiable.

Recommendation 80 – Involuntary movements that cannot be suppressed

Involuntary movements that cannot be suppressed could represent a number of neurological disorders, for example hemifacial spasm, tremor, chorea, epileptic myoclonus or tight eye closure of both eyes (blepharospasm). These movement disorders require a neurological assessment and diagnosis, and may require treatment in a movement disorder clinic to relieve symptoms.

Tight eye closure (blepharospasm) can be a form of dystonia in adults. It may be mild, but often causes significant disability through interference with vision. Treatment options, such as botulinum toxin injections, are available, which can be offered following a neurological or ophthalmological assessment.

Recommendation 81 – Involuntary muscular contractions (fasciculations) associated with muscle wasting and weakness or muscle rigidity

Muscle fasciculation is usually an innocent phenomenon, and is especially common in the calf muscles. As it is sometimes an indicator of serious underlying

	neuromuscular disease, it may cause patient concern. When indicating neuromuscular disease it is accompanied by weakness, muscle wasting or muscular rigidity (stiffness). In the absence of such features, it is usually appropriate to reassure the patient and review after an interval.
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considerations of whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee acknowledged that tic disorders are a common symptom that is presented in general practice. The committee believe that the recommendations would reduce overall referrals to neurology and would ensure that only those who stand to benefit from further interventions are referred. This would reduce costs to the NHS without compromising treatment for those who could benefit from treatment.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>Of the 18 participants who commented on recommendation 76, 77.8% agreed with the recommendation where as 5.6% (1 participant) disagreed, as it did not seem clear why referral for psychological therapy had been recommended. The committee agreed that this is an appropriate therapy with some evidence of efficacy and therefore did not make any changes to the recommendation.</p> <p>Recommendation 79 had a relatively lower level of agreement at 66.7% but only minor changes to the wording of the recommendation was required. The committee agreed to add 'blepharospasm' that 'persistent for more than 3 months' to the recommendation based on the targeted engagement exercise comments.</p> <p>All other recommendations in this section had a high level of agreement ranging 77.8–94.4% and therefore did not require any changes to the recommendations. The committee discussed some of the helpful comments that were made and used them to elaborate further on the rationales provided.</p>

5.15 Tremor in adults

5.15.1 Review question: In adults and young people who present with tremor, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological conditions?

The aim of the review was to identify signs and symptoms that if presenting with tremor would indicate a suspected neurological condition that requires referral for further specialist assessment. This would help to differentiate essential tremors, which can normally be diagnosed and initially managed in primary care, from parkinsonian tremors, which require referral for further neurological assessment.

For full details, see review protocol in appendix C.

Table 13: Characteristics of review question for tremor

Population	Adults and young people who present to a non-specialist with tremor
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Predictor variable(s) under consideration	<p>The committee identified the following predictors:</p> <ul style="list-style-type: none"> • bradykinesia • facial expressiveness • gait-disorder • head tremor • medication • progressive time-course • REM sleep disturbance • symmetrical tremor • tone • voice changes • weight loss.
Confounding factors	Any of the clinical prediction factors listed above are considered to be relevant confounders
Outcome(s)	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive values <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ cerebellar tremors ○ drug-related tremors ○ dystonic tremor (task-specific tremor) ○ essential tremor ○ neuropathic tremor ○ parkinsonism ○ physiological tremor ○ primary orthostatic tremor ○ psychogenic tremors ○ thyroid disorder.
Study design	Prospective and retrospective cohort studies

5.15.2 Clinical evidence

No relevant clinical studies were identified.

5.15.3 Economic evidence

Published literature

No relevant health economic studies were identified.

5.15.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

5.15.5 Recommendations and link to evidence

Recommendations	<p>82. Refer adults with suspected parkinsonian tremor, other asymmetric tremor, or tremor associated with stiffness, slowness, balance problems or gait disorders for neurological assessment before treatment in line with the NICE guideline on Parkinson's disease in adults.</p> <p>83. Suspect essential tremor in an adult with symmetrical postural tremor and no symptoms of parkinsonism.</p> <p>84. In adults with suspected essential tremor:</p> <ul style="list-style-type: none"> • review regular medication • check thyroid function • assess alcohol consumption using a tool such as AUDIT (Alcohol Use Disorders Identification Test), in line with the NICE guideline on alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. <p>Refer for neurological assessment only if the symptoms are disabling and first-line treatment as specified in the British national formulary is ineffective or not tolerated.</p> <p>85. Consider referring adults with troublesome tremor of the head to a movement disorder clinic.</p>
Rationale for categorising symptoms	<p>This symptom was prioritised for an evidence review for adults because the committee considered that there is a need for guidance for non-specialists on how to differentiate a parkinsonian tremor (which needs to be referred) from an essential tremor (which can be managed in primary care). It was hoped that evidence might be found to guide non-experts in the differentiation as essential tremor continues to be referred to secondary care.</p>
Relative values of different outcomes	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of tremor are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications, which can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
Quality of the clinical evidence	<p>No clinical evidence was identified. These recommendations are based on committee consensus.</p>

<p>Trade-off between benefits and harms</p>	<p>Recommendation 82 – Suspected parkinsonian tremor</p> <p>A unilateral or predominantly unilateral tremor, especially if more prominent at rest and accompanied by slowness of rapid alternating movements, is particularly suggestive of parkinsonism. People who exhibit suspected parkinsonian tremor should see a neurologist for assessment and diagnosis, as disability may be progressive, the diagnosis may have a lifelong impact, and the person may require on-going medical and social support. There are other causes of asymmetric tremor, but the committee felt that referral of these people was required in order to differentiate from Parkinson’s.</p> <p>Recommendation 83 – Symmetrical postural tremor</p> <p>Essential tremor is an action or postural tremor of limbs, and sometimes head, of variable amplitude that tends to worsen with stress and deteriorate gradually with age. It is largely bilateral and not associated with any alteration of muscle tone or slowness of movement. It is very common and poorly responsive to drug treatment. People who show signs of essential tremor but do not demonstrate signs of a parkinsonian tremor do not need to be referred to neurology. The committee stressed the need to reduce referrals to neurology for people with essential tremor, as GPs can administer or prescribe first-line treatments without input from secondary care. Exaggerated physiological tremor and essential tremor are on a continuum and can be offered the same symptomatic treatment.</p> <p>Recommendation 84 – Suspected essential tremor</p> <p>Some medicines, such as sodium valproate, and thyrotoxicosis can cause tremor. Excessive alcohol use can be associated with tremor. Essential tremor may be transiently ameliorated by alcohol and some people use alcohol to self-medicate. Clinicians require a comprehensive medication and alcohol-intake history to assess people with essential tremor. Medical treatment of tremor is generally of low efficacy, and referral should be considered only if the tremor is significantly disabling. For people with severe essential tremor, neurosurgical treatment may be an option after review by a neurologist.</p> <p>Recommendation 85 – Troublesome head tremor</p> <p>Head tremor (titubation) is a common disorder, which responds poorly to drug treatment. The condition can be socially disabling. Botulinum toxin has been shown to help control these tremors and is now widely used in the UK. People with troublesome head tremor should be referred to a neurology movement disorder clinic to be assessed for suitability for this treatment.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for the considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations do not represent a change from current best practice, and that, viewed along with the rest of this guideline, the recommendations should not increase the total number of referrals or NHS costs.</p>
<p>Other considerations</p>	<p>The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement</p>

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exercise, which only applied to recommendations where no evidence review was undertaken.

6 Information and support

6.1 Review question: What are the information, support and initial management advice needs of people who have a suspected neurological condition and their family members and carers?

The committee agreed that due to the very broad population of this guideline population which covers a large number of neurological conditions, it would be difficult to develop a focused protocol and undertake a systematic review in this area. In addition, the scope of the guideline only covers recognition and referral. It would be difficult to identify and give guidance on specific support and needs for all patients before a definitive diagnosis has been made as this may cause undue distress.

Therefore, information that might usefully be given to people presenting with neurological symptoms, or to their carers, has been included where appropriate in the recommendations relevant to each presentation. The committee also felt that the following recommendations may provide considered the need for more general advice.

6.2 Recommendations and link to evidence

<p>Recommendations</p>	<p>86. Follow the principles in the NICE guideline on patient experience in adult NHS services relating to communication, information and shared decision making.</p> <p>87. Advise adults with suspected neurological conditions to:</p> <ul style="list-style-type: none"> • check the government's information on driving with medical conditions to find out whether they might have a condition that needs to be notified to the DVLA (Driver and Vehicle Licensing Agency) • consider telling their employer, school or college if their symptoms might affect their ability to work or study.
<p>Rationale for not conducting an evidence review</p>	<p>The committee considered whether an evidence review would be helpful in this area. It was agreed that due to the broad population covered in this guideline, it would be difficult to develop a focused protocol. In addition, the scope covers assessment and referral so it would be difficult to give guidance on what information primary care physicians should provide to people without unduly worrying them before a final diagnosis is made. The committee agreed to make overarching recommendations by consensus and to cross-refer to the NICE guideline on patient experience in adult NHS services. The committee also included some recommendations on advice for people for specific symptoms where appropriate.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 86 – Support for patients, families and carers</p> <p>NICE’s guidance on patient experience provides guidance on communication with people. This includes asking the person if they would like to be accompanied at consultations. The person’s preferences about the level and type of information they want should be ascertained. Privacy must be respected and communication tailored to the needs of the person, including using pictures, symbols, large print, Braille, different languages, sign language or communications aids, or involving an interpreter, a patient advocate or family members. Communication should avoid jargon. At the end of a consultation, it is good practice to check that the person has understood the salient information.</p> <p>Copies of correspondence should be offered to the patient and any resulting queries should be answered.</p> <p>People with neurological conditions should be advised where they might find reliable high-quality information and support after consultations, from sources such as national and local support groups, networks and information services.</p> <p>Recommendation 87 – DVLA and disclosure to employer</p> <p>Doctors and other healthcare professionals should advise people about the impact of their neurological condition on safe driving and remind them of the legal requirement to notify the DVLA of any relevant neurological condition. In some circumstances, it may be appropriate for a doctor to notify the DVLA when a person will not do so themselves despite being ineligible to drive, but it remains the duty of the licence holder or applicant to notify the DVLA of any medical condition that may affect safe driving.</p> <p>People are free not to reveal health issues to their employers. The Equality Act states that employers cannot discriminate against people who are disabled, including job applicants, contract workers and existing employees. An employer has a duty to make reasonable adjustments at the workplace so as not to disadvantage disabled employees. If a person does not tell their employer about a neurological condition, they may be disadvantaged at work and may find it harder to solve a</p>

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	<p>problem, as the employer may be unaware of a significant disability and therefore not undertake reasonable adjustments.</p> <p>The Access to Medical Reports Act 1988 states that an employer cannot ask for a medical report without the person's knowledge and consent. If unhappy with the report, the person has the right to stop it being sent to their employer.</p> <p>If an occupational health assessment is part of a recruitment procedure, the employer may not be able to employ the person unless details of the neurological condition are disclosed. There are some jobs that have fundamental medical requirements – for example, pilots, train drivers, electricians and air traffic controllers require accurate colour recognition – and some jobs cannot be undertaken by a person with active epilepsy, such as those in the armed forces or which require driving on the public highway.</p>
Trade-off between net clinical effects and costs	<p>These recommendations relate to giving advice to people with suspected neurological conditions. As this would normally be given briefly as part of an existing appointment, there should be no significant impact on costs. Giving such advice is in any case a matter of safety and should already be part of clinical best practice.</p> <p>NICE's guidance on patient experience considered the cost effectiveness of giving information and made recommendations that were considered to be cost effective.</p>

7 Part 2 – Children aged under 16 – signs and symptoms and investigative tests

7.1 Attention, concentration and memory problems

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.1.1.1 Recommendations and link to evidence (consensus statement 142 to 152 in appendix S)

Recommendations	<p>88. Refer urgently children who present with discrete episodes of loss of awareness (mid-activity vacant spells) or of attention and concentration difficulties in line with the NICE guideline on epilepsies.</p> <p>89. Be aware that medicines commonly used to treat epilepsy in children can adversely affect concentration and memory.</p> <p>90. Refer children with concentration and memory difficulties that interfere with learning, school progress or behaviour to community paediatric or paediatric neurodevelopmental services for assessment.</p> <p>91. Be aware that some children with attention and concentration difficulties do not have hyperactivity.</p>
Rationale for categorising symptoms	<p>This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review was unlikely to change this.</p>
Trade-off between benefits and harms	<p>Recommendation 88 – Unrecognised epileptic absence seizures</p> <p>Concentration and memory problems are common in children who have epilepsy, both undiagnosed and diagnosed. If concentration difficulties are significant and present similarly in different settings (for example, at home and at school), the child could be having unrecognised absence seizures. If only present in 1 setting, the child is more likely to be losing concentration for other reasons.</p> <p>Absence seizures may be brief and subtle. If they occur as the children are taught or given instructions, the children will not be able to absorb and process the information. An additional clue to the onset of absence epilepsy may be that children who were previously performing as well as their peer group are now falling behind in their learning. Seizures occurring during sleep may affect a child’s ability to recall what was learnt the previous day.</p> <p>The committee agreed that if epilepsy is suspected, the child should be referred urgently for a neurological assessment.</p> <p>Recommendation 89 – Medicines commonly used to treat epilepsy</p> <p>Medicines used to prevent seizures in children may have a direct effect on concentration and memory by causing drowsiness. This is more common when higher doses are used and when children are on more than 1 drug for epilepsy. Measuring levels of some drugs in blood can be helpful in deciding if the dose needs to be adjusted. Carbamazepine slow/sustained release preparations may be</p>

	<p>preferable to standard formulations in limiting the drowsiness that usually occurs about an hour after taking a dose of carbamazepine. Parents and the child should be advised about potential adverse effects and who to contact if they are concerned.</p> <p>Recommendation 90 – Concentration and memory difficulties interfering with learning, school progress or behaviour</p> <p>Attention and concentration difficulties are a common presentation in children and could be the result of a broad range of conditions including learning difficulties, autism, attachment disorders, ADHD and hearing impairment.</p> <p>The committee noted that in current practice there is over-referral of children with concentration and memory difficulties who are much more likely to have a social, behavioural, or neurodevelopmental cause than a neurological cause. However, children with concentration and memory difficulties whose learning development is also affected should receive an assessment. A child with a primary learning disorder may have secondary difficulties with concentration and memory. A child with a primary disorder of attention may learn poorly. To understand the primary problem, the child may require assessment by educational and clinical psychology and clinicians may need to exclude other contributing factors. If there is a significant problem with learning, school progress or behaviour, the child should be referred to paediatric neurodevelopmental services, which can then direct the child on the correct pathway.</p> <p>Recommendation 91 – Attention and concentration difficulties</p> <p>The common perception of the child with attention and concentration problems is that the child is hyperactive, noisy, and destructive in home and school settings. Such children readily come to the attention of primary care, school, and paediatric neurodevelopmental services. However, there are a group of children with significant attention and concentration problems who are inattentive but not hyperactive. Girls with attention problems are more likely to have this type than boys. They do not cause a disruption in class and are therefore not promptly identified and referred as children with hyperactivity. They may present eventually as children with learning difficulties, as they are not making expected progress in school.</p>
<p>Trade-off between net clinical effects and costs</p>	<p>The committee believes that there is currently an over-referral to neurology services of children with concentration and memory difficulties whose symptoms are much more likely to have a social, behavioural, or neurodevelopmental cause than a neurological cause. Therefore, the committee agreed that referral would only be a cost-effective use of resources in those whose learning development is affected. A child with a primary learning disorder may have secondary difficulties with concentration and memory.</p> <p>The committee also noted that if children with relevant symptoms are not referred, then interference with learning development would be likely to prompt further unscheduled healthcare visits in the future, meaning that timely referral is likely to save the NHS money in the end.</p> <p>The committee therefore expects these recommendations to be cost saving for the NHS.</p>
<p>Other considerations</p>	<p>The committee noted recommendations on referral in the NICE guideline on ADHD (CG72).</p> <p>Targeted engagement exercise</p> <p>Recommendations 90 and 91 scored high levels of agreement (94.4% and 83.3% respectively) which did not warrant any changes.</p> <p>Recommendation 88 is the result of 2 recommendations that were combined subsequent to the targeted engagement exercise. Both original recommendations</p>

scored a high level of agreement (77.8% and 94.4%). However, there was some disagreement (5.6%, 1 participant) and further requests for revision regarding 'absence seizures'. The respondents did not agree with the wording and the description of such presentations. The committee discussed the comments and decided that the 2 recommendations would be clearer if they were merged. They also provided further explanation about what was meant by 'absence seizures' and cross-referred to the NICE epilepsy guideline where further details could be found.

The level of agreement with recommendation 89 was 88.9%. There was 5.6% (1 participant) disagreement. There were requests for the committee to include an evaluation of the effectiveness of the medications and their side effects, which is outside the scope of this guideline; therefore, no changes were made to this recommendation.

7.2 Blackouts and other paroxysmal events

7.2.1 Review question: In children and babies who present with paroxysmal events, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?

The aim of this review was to identify signs and symptoms that, if presenting with paroxysmal events, indicate a neurological condition requiring referral for further specialist assessment.

For full details, see review protocol in appendix C.

Table 14: Characteristics of review question

Population	Children and babies who present to a non-specialist with paroxysmal events.
Predictor variables under consideration	<ul style="list-style-type: none"> • Apnoea • Associated with mild traumatic event • Changes in the level of consciousness • Congenital or acquired cardiac disorder • Occurrence with exercise • Postural hypotension • Repetitive movements
Confounding factors	Any of the predictors listed above
Outcomes	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive values <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ behavioural (that is, temper tantrums, breath-holding attacks and emotional disorders) ○ cardiac disorders – long QT, left ventricular outflow obstruction ○ epilepsy ○ reflex anoxic seizures ○ vasovagal syncope or postural hypotension.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis

7.2.2 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

7.2.3 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

7.2.4 Recommendations and link to evidence

Recommendations	<p>92. Refer urgently children with new-onset blackouts (transient loss of consciousness) accompanied by seizure markers for neurological assessment, in line with the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s^b.</p> <p>93. Refer urgently children with mid-activity vacant spells or behavioural outbursts associated with altered consciousness or amnesia for the events to have a paediatric assessment.</p> <p>94. Refer urgently all children aged under 12 years with blackouts for paediatric assessment.</p> <p>95. Do not routinely refer children aged over 12 years with blackouts if there are clear features of vasovagal syncope, even if associated with brief jerking of the limbs. See recommendation 1.1.4.3 on uncomplicated faint in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s.</p> <p>96. For children who have blackouts, seizures or amnesia for events after a head injury, follow the recommendations pre-hospital assessment, advice and referral to hospital in the NICE guideline on head injury.</p>
Rationale for categorising symptoms	Postural hypotension and breath-holding attacks are inappropriately referred. Postural hypotension is a common presentation in teenagers. A key issue is identifying the clinical features of breath holding, reflex anoxic seizures and vasovagal syncope in children. The epilepsy guideline has a differential diagnosis

^b The committee agreed that the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ('blackouts') in over 16s is applicable to children aged under 16.

	<p>appendix. This guidance will specifically look at breath holding in children (not applicable to adults). The committee agreed that an evidence review to support their decision-making would be helpful.</p>
Relative values of different outcomes	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of paroxysmal events are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications that can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
Quality of the clinical evidence	<p>No clinical evidence was identified for inclusion in this review. The recommendations are based on committee consensus.</p>
Trade-off between clinical benefits and harms	<p>Vasovagal syncope is a common presentation in teenagers, and younger children can have breath-holding attacks. These do not require specialised neurology input but are often inappropriately referred because of concerns that they represent seizures or other significant pathology. It was hoped that a literature search might produce evidence of features that would allow non-experts to distinguish these conditions with a degree of confidence.</p> <p>Postural hypotension and breath-holding attacks may be inappropriately referred. Postural hypotension is a common presentation in teenagers. A key issue is identifying the clinical features of breath holding, reflex anoxic seizures and vasovagal syncope in children.</p> <p>Breath-holding episodes and reflex anoxic seizures are common in children under the age of 5 years. Breath holding occurs when children cry vigorously and then hold their breath in expiration. The child turns blue around the mouth, loses consciousness and then will slump to the ground if standing. The child will then start to breathe and will usually recover within a minute.</p> <p>Reflex anoxic seizures occur when a child has a sudden mild injury – often to the head – or a sudden fright. The child goes very pale, loses consciousness and then falls to the ground. The child may have some jerking movements of the limbs or face while unconscious. The child recovers within a few minutes. These episodes are triggered by excess activity of the vagus nerve triggered by the pain or fright. This causes marked slowing or cessation of heart activity.</p> <p>Neither breath-holding episodes nor reflex anoxic seizures are epileptic events. There may be a family history of children with similar episodes. Iron deficiency anaemia may be a contributing factor.</p> <p>Parents can be reassured that these events are not dangerous and the child will eventually grow out of them. They are involuntary episodes and the child cannot stop them happening. They are not a sign of a badly behaved child.</p> <p>Recommendation 92 – New-onset transient loss of consciousness</p> <p>Transient loss of consciousness in children may be caused by neurological disorders, predominantly epilepsy, by cardiac disorders or by simple syncope. Even with a clear first-hand description of the event, it is not always possible to make a confident diagnosis without specialist assessment and investigations. In the NICE guideline for TLOC in over-16s, the features of the blackout that are suggestive of epilepsy are:</p> <ul style="list-style-type: none"> • a bitten tongue

- head-turning to one side during TLOC
- No memory of abnormal behaviour that was witnessed before, during or after TLOC by someone else
- unusual posturing
- prolonged limb jerking (note that brief seizure-like activity can often occur during uncomplicated faints)
- confusion following the event, and
- prodromal *déjà vu* or *jamais vu*.

The guideline committee agreed that the recommendation for people with suspected epilepsy in the NICE guideline on transient loss of consciousness ['blackouts'] in over 16s is applicable to children aged under 16.

Children who are having blackouts where epilepsy is suspected should be referred to paediatric services to be seen within 2 weeks.

Recommendation 93 – Mid-activity vacant spells or behavioural outbursts

Vacant spells – often called absences – as a result of epilepsy in children can be difficult to distinguish from the child day-dreaming and losing concentration. Epileptic vacant spells will occur in different situations, not just at school or at home. If there are fidgety movements or lip smacking with the vacant spell, this is more suggestive of epilepsy. If the vacant spell occurs in the middle of a sentence or while the child is bringing food to the mouth, it is also suggestive of epilepsy.

Behavioural episodes – such as aggression, sudden distress, or bizarre and inappropriate behaviour – can occasionally be a symptom of epilepsy. It can be difficult to come to a diagnosis, without neurological assessment, particularly if the child has other neuro-developmental problems.

Recommendation 94 – Blackouts

The committee agreed that all children under 12 with blackouts or transient loss of consciousness (TLOC) should be referred for urgent assessment as history and examination does not always allow a diagnosis to be made confidently, the episode causes parent, carers, and school staff great anxiety, and there are a number of potentially serious causes that need to be excluded.

Recommendation 95 – Vasovagal syncope

The committee recognised that vasovagal syncope is common in childhood, particularly during adolescent years. They considered that the existing NICE guidance on recognition of vasovagal syncope contained in the Transient Loss of Consciousness in over 16s guidance (CG109) was applicable to children aged 12 to 15 years.

Features suggestive of vasovagal syncope are:

- triggered by strong emotions, pain or dehydration
- occur on standing, relieved by sitting down, and
- pallor or sweating before an episode.

Transient loss of consciousness occurring while exercising may be due to a cardiac disorder – cardiac dysrhythmia or structural disorder – and the child should be referred urgently for paediatric assessment.

Recommendation 96 – Recent head injury

Transient loss of consciousness after a head injury in children is usually immediate or within a few minutes. As in adults, there may be a lucid interval before altered conscious level occurs. Much delayed paroxysmal events after head injury in children

	– days or weeks later – is rare but warrants urgent referral for neurological assessment.
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for the considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations would not lead to additional resource use, as they are in line with current practice, as outlined in other NICE guidelines.</p>
Other considerations	<p>The committee would like to highlight that appendix A of the NICE guideline Epilepsies: diagnosis and management CG137 provides a comprehensive and detailed discussion on differential diagnosis of epilepsy in adults and children. The committee felt that it may be too detailed for a primary care physician to use when trying to make a decision about referral, but it does provide very useful information on differentiating between different types of seizures.</p> <p>The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.</p>

7.3 Confusion, acute

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.3.1.1 Recommendations and link to evidence (consensus statement 3 to 9 in appendix S)

Recommendations	<p>97. For children with unexplained acute confusion:</p> <ul style="list-style-type: none"> • arrange an emergency transfer to hospital and • measure blood glucose. <p>98. Be aware that acute confusion in children can be a symptom of meningitis, encephalitis or poisoning. If infection is suspected, follow the recommendations on identifying people with suspected sepsis and face-to-face assessment of people with suspected sepsis in the NICE guideline on sepsis.</p> <p>99. For children with acute confusion who have a non-blanching rash or other signs or symptoms suggestive of meningococcal septicaemia follow the recommendations on suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia) in the NICE</p>
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	<p style="text-align: center;">guideline on meningitis (bacterial) and meningococcal septicaemia in under 16s.</p> <p style="text-align: center;">For other signs and symptoms of meningococcal septicaemia, see bacterial meningitis and meningococcal septicaemia in children and young people – symptoms, signs and initial assessment.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change it.
Trade-off between benefits and harms	<p>Recommendation 97 – Acute confusion</p> <p>Confusion in a child may manifest as loss of normal skills, loss of speech, talking nonsense, or being less responsive. Acute confusion develops in the face of a few minutes to a few hours. It can be a symptom of a severe neurological illness such as meningitis, intracranial haemorrhage, raised intracranial pressure, and drug or alcohol poisoning. The committee decided that although there can be more benign causes such as high fever in a young child with a febrile illness, all children presenting with acute confusion should be transferred to hospital urgently, usually by ambulance. The committee recognised that in some instances, for example, in rural areas or where there is likely to be a delay in ambulance service, it may be quicker for a child to be transferred to the hospital in the carer’s car. However, it is important to weigh the benefits and harms of not waiting for an ambulance as in some cases this may delay treatment that could otherwise be started en route to the hospital.</p> <p>Hypoglycaemia can present with acute confusion and therefore blood glucose should be measured as soon as possible to avoid delays in diagnosis and treatment for the child once in hospital care. This will also save time for paramedic services. An epileptic seizure can present with rapid onset confusion and this should be considered in the differential diagnosis if a clear history of epilepsy cannot be obtained from the child or accompanying adult.</p> <p>Recommendation 98 – Presenting symptom of meningitis, encephalitis and poisoning</p> <p>Acute confusion can, on its own, be an indication of an organic brain disorder such as meningitis or encephalitis. Poisoning may also be a cause. However, body temperature should distinguish poisoning from meningitis and encephalitis. The committee considered it important to inform non-specialists of differential diagnoses, as other obvious symptoms such as a non-blanching rash, may not always be present.</p> <p>Recommendation 99 – Meningococcal septicaemia</p> <p>Acute confusion may present with associated signs and symptoms that are suggestive of meningococcal septicaemia. The committee noted the NICE guideline on meningitis and meningococcal septicaemia (CG102) and agreed to cross-refer. The committee noted that a non-blanching rash on its own is not reason enough to suspect meningococcal septicaemia; other symptoms should be considered.</p>
Trade-off between net clinical effects and costs	The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where a neurological outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.

	<p>The committee acknowledged that referral for acute confusion is considered both best practice and current practice. Therefore, there should be no change in cost impact to the NHS arising from these recommendations. Anything but immediate referral can lead to serious consequences that would have a significant impact on health outcomes and resource use through further unscheduled healthcare utilisation.</p> <p>The committee believe that measurement of blood glucose is routine practice and therefore does not represent an additional cost to the health service. More importantly, the results can avoid delays in diagnosis and treatment, and thus better health, for the child once in hospital, meaning it represents a very cost-effective use of NHS resources.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>Twenty-four participants commented on this section. 66.7% agreed with recommendation 97 on transferring children with acute confusion to hospital immediately. The remaining suggested including more detail about other possible reasons for acute confusion in children such as alcohol intoxication. The participants also requested a definition for acute confusion especially in the context of children and infants. The committee did not feel that a precise definition was possible but have included some of the features that might be seen, added to the rationale rather than the recommendation.</p> <p>There was more than 75% agreement with recommendations 98 and 99 and therefore only minor editing changes were made to these recommendations.</p>

7.4 Dizziness and vertigo in children

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.4.1 Introduction

Dizziness is a very common presentation that covers a wide range of patient symptoms and is a very common reason for referral of older children to neurology. The child is not always able to define what they mean by dizziness. It may be referred to as a feeling of light-headedness, the room spinning round (vertigo), unsteadiness on their feet, anxiety and palpitations. True vertigo is a hallucination of movement and is more suggestive of a vestibular problem but can also occur in central nervous system disease. Dizziness in children is most often due either to vestibular disturbance or reduced perfusion to the brain

7.4.2 Recommendations and link to evidence (consensus statement 42 to 48 in appendix S)

Recommendations	<p>100. Be aware that isolated dizziness in children is unlikely to be a symptom of a brain tumour if there are no accompanying symptoms or signs.</p> <p>101. Be aware that dizziness in children is often a symptom of migraine and may be the predominant feature.</p> <p>102. Be aware that in older children (usually aged over 8 years), dizziness related to change in posture is often caused by postural hypotension.</p>
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	<p>103. In children with dizziness, examine the ears for any signs of infection, inflammation or eardrum perforation.</p> <p>104. For children with recurrent episodes of dizziness:</p> <ul style="list-style-type: none"> • consider referring for cardiological assessment if there are any factors that might suggest a cardiac cause, such as blackouts (transient loss of consciousness), a family history of cardiomyopathy or unexplained sudden death, or palpitations • if there are episodes of dizziness with a fixed symptom pattern, be alert to the possibility of epilepsy as the cause and follow the recommendations in the NICE guideline on epilepsies.
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change this.
Trade-off between benefits and harms	<p>Recommendation 100 – Dizziness and brain tumours</p> <p>The committee considered that it is important to reassure clinicians that a brain tumour is a very unlikely to be caused by dizziness without any other symptoms; a tumour would usually present with accompanying symptoms such as headache, nausea and vomiting, ataxia, or drowsiness. Recommendations for referral of suspected cancer are available in the NICE guideline on suspected cancer (NG12).</p> <p>Recommendation 101 – Possible migraine</p> <p>Dizziness often presents in children as a symptom of migraine. The severity of dizziness can vary and can be profoundly disabling if it is very severe. The committee considered that clinicians should be aware that migraine might be a cause and should take a careful history to explore this possibility before deciding whether referral to paediatric neurology is appropriate. The committee noted that there will be some children who present with dizziness and migraine who will need to be referred to paediatric neurology; others may be managed in primary care. The committee agreed that clinical judgement should be used to determine the appropriate pathway and therefore could not make a more directive recommendation.</p> <p>Recommendation 102—Postural hypotension in older children</p> <p>Postural hypotension is common in children aged over 8, particularly in girls over 11 entering puberty. Postural hypotension is the most common identifiable cause of dizziness. Dizziness caused by postural hypotension does not need to be referred for neurological assessment. However, clinicians should be aware that postural hypotension may not necessarily be present at the time of examination and therefore cannot always be excluded as the cause of dizziness by checking blood pressure. The committee felt that clinicians should bear in mind the possibility of postural hypotension when assessing a patient. This will help to reduce the number of inappropriate referrals to paediatric neurology.</p> <p>Recommendation 103– Examining ears with dizziness</p> <p>Middle ear infection and middle ear effusion can be a cause of dizziness in children. The child may have fever, pain and diminished hearing, or a recent history of these. The eardrum may appear red and inflamed or bulging.</p> <p>In children where the dizziness is caused by migraine or vestibular dysfunction, examination of the ears will be normal.</p> <p>Recommendation 104—Recurrent dizziness</p>

	<p>The committee identified recurrent dizziness in children as a red flag that warrants investigation once postural hypotension has been excluded. Anaemia and dehydration may contribute to postural hypotension. Other causes of dizziness include viruses and ear infections.</p> <p>Cardiac dysrhythmias are a rare cause of dizziness and syncope in children; dizziness leading to syncope on exercise may be a helpful clue. Although rare, these are potentially serious and the committee thought that these should be considered as a potential cause in some children. The possibility of excluding cardiac disease by obtaining an ECG was discussed, but the normal ECG changes considerably during childhood, and expert interpretation is required. The committee therefore felt that if cardiac disease was considered a real possibility, on grounds of other clinical signs or symptoms, or because of family history, the child with recurrent dizziness should be referred for a cardiological assessment.</p> <p>Epilepsy may also present with recurrent episodes of dizziness or vertigo, sometimes accompanied by other symptoms evolving in a fixed pattern. If epilepsy is suspected referral, assessment and investigation should be as described in sections 1.5 and 1.6 of the NICE guideline on epilepsies (Epilepsies: diagnosis and management – CG137).</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current practice; therefore, the recommendations will not increase the number of referrals or NHS costs.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>Recommendation 100 and 101 (originally one recommendation) received 61.9 % agreement and remaining participants thought that it needed revision. In particular, participants thought that the definition of dizziness is not always clear and is often misinterpreted by both people and clinicians. Therefore, the committee has added a description to the LETR, although it is not possible to get over the fact that people will continue to use the word ‘dizziness’ to describe a range of sensations from true vertigo to mild general weakness.</p> <p>81% of participants agreed with recommendation 101 and therefore only minor editorial changes to the wording were made.</p> <p>Recommendation 104 had 66.7% agreement and revisions to the wording were suggested. The word ‘paroxysmal’ did not seem to be clear and therefore this was changed to ‘recurrent’. Further suggestions for clarifications were incorporated into the rationale.</p> <p>It was also highlighted that vestibular causes of dizziness were common causes of dizziness that should also be investigated in this group but there was no mention of them in the recommendations. Therefore, the committee added a new recommendation (recommendation 103) to highlight this.</p>

7.5 Headaches in children

7.5.1 Review question: In children under 12 who present with headache, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected neurological conditions?

The aim of this review was to identify signs and symptoms that, if presenting with headache, in children under 12, would indicate a neurological condition that requires referral for further specialist assessment. The NICE headaches guideline (CG 150) covers people 12 years and over. Therefore, this review was limited to children under 12 years.

For full details, see review protocol in appendix C.

Table 15: PICO characteristics of review question

Population	Children under 12 who present to a non-specialist with headache.
Predictors variables under consideration	<p>The committee identified the following predictors in people who present to a non-specialist with headache for inclusion in the review:</p> <ul style="list-style-type: none"> • ataxia • change in personality • failure of upward gaze • head size • nausea • nocturnal or headaches on awakening • onset of squint • progressive time course • specific learning difficulties • vomiting • weight loss.
Outcomes	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive values <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ brain tumour ○ chronic daily headaches ○ hydrocephalus ○ idiopathic intracranial hypertension ○ intracranial infection ○ migraine ○ nocturnal hypoventilation ○ raised intracranial pressure ○ sinusitis ○ venous sinus thrombosis.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis

7.5.2 Clinical evidence

No relevant clinical studies were identified. See excluded studies list in appendix L.

7.5.3 Economic evidence

Published literature

No relevant health economic studies were identified. See also the health economic study selection flow chart in appendix F.

7.5.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

7.5.5 Recommendations and link to evidence

Recommendations	<p>For recommendations on headaches or migraine in children aged over 12 years, see the NICE guideline on headaches in over 12s.</p> <p>105. Refer immediately children aged under 12 years with headache for same-day assessment, according to local pathways, if they have any one of the following:</p> <ul style="list-style-type: none">• headache that wakes them at night• headache that is present on awakening in the morning• headache that progressively worsens• headache triggered or aggravated by coughing, sneezing or bending down• headache with fever and features of meningism• headache associated with vomiting• headache associated with ataxia• headache associated with change in conscious level or pervasive lethargy• headache occurring within 5 days of a head injury• headache associated with squint or failure of upward gaze ('sunsetting'). <p>106. Refer urgently all children aged under 4 years with headache for neurological assessment.</p> <p>107. Perform or request fundoscopy for all children with recurrent headache and refer urgently for neurological assessment if there are abnormalities.</p>
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	<p>108. For all children with recurrent headache:</p> <ul style="list-style-type: none"> • be aware that hypertension might be the cause • measure the child’s blood pressure and check the measurement against blood pressure reference ranges adjusted for age and height • refer children if headaches are consistently worsened by upright posture and relieved by lying down. <p>109. Do not routinely refer children with migraine unless it is affecting their school life, social life or family activities or they have one of the features listed in recommendation 104.</p> <p>110. Be aware that emotional stress is a strong trigger of migraine and chronic, daily headache in children. Ask the child and their parent or carer about specific learning problems, bullying at school and stress in the family.</p> <p>111. Ask about analgesic use in children with recurrent headache to ensure that medicine use is not excessive and to assess the likelihood of medication overuse headache. See the NICE guideline on headaches in over 12s for more information on medication overuse headache.</p>
<p>Rationale for categorising symptoms</p>	<p>The NICE guideline on headache does not cover children under 12 years old, so there is a need for guidance regarding this population. Migraine is a common presentation but there are concerns about under-referral, delayed diagnosis, and non-recognition of refractory symptoms and worrying features of headaches. Chronic non-migraine headaches are difficult and time consuming to manage but are not referred inappropriately. There is a need for guidance for non-specialists on when to refer for example when symptoms can no longer be managed in primary care. Key issues include the following: what are the red flags for urgent referral? What are the clinical features of migraine in children under 12? What are features commonly seen with headaches that might indicate a brain tumour in children?</p> <p>The committee agreed that an evidence review to support their decision-making would be helpful.</p>
<p>Relative values of different outcomes</p>	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of headaches are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications that can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
<p>Quality of the clinical evidence</p>	<p>No evidence was identified for this review. These recommendations are based on committee consensus.</p>

Trade-off between clinical benefits and harms	<p>Recommendation 105 – Presence of red flag symptoms</p> <p>The committee recognised the listed features as those that had a high chance of indicating serious intracranial pathology including brain tumours. The committee considered that the ‘red flag’ symptoms detailed in this recommendation indicate the requirement for urgent assessment, as they could indicate significant intracranial pathology requiring immediate medical or surgical management to minimise morbidity and mortality.</p> <p>Recommendation 106 – Children under 4 years</p> <p>The committee recognised that headache under the age of 4 years is an unusual symptom and, when present, has a high chance of being associated with a significant intracranial disease. As the child is unable to articulate clearly what is wrong, parents may report excessive crying, a high-pitched cry or excessive irritability.</p> <p>Recommendation 107 – Fundoscopy</p> <p>The committee considered the examination of the retinal fundus to be an essential part of the neurological examination in children with headache to look for blurred optic disc margin or papilloedema. As not all non-specialist clinicians have the skills required, the committee recommended that this should be requested, for example, from an ophthalmologist or optician.</p> <p>Recommendation 108 – Hypertension and spontaneous intracranial hypotension</p> <p>The committee recognised that high blood pressure could cause headache in children. As normal blood pressure changes with age and body height, it was recommended that the reading be interpreted by a comparison with standardised age- and height-corrected blood pressure charts. Raised blood pressure is also a sign found in raised intracranial pressure.</p> <p>Hypertension in children is usually secondary to renal disease although there are more children recognised with primary hypertension related to obesity and salt intake.</p> <p>Spontaneous intracranial hypotension is rare and characterised by headaches worsening in the upright posture and relieved when lying down. Referral is appropriate for diagnosis and treatment, which may involve a blood patch.</p> <p>Recommendation 109 – Migraine</p> <p>The committee accepted that migraine is common in children and does not necessarily require specialist referral as it can often be managed in primary care.</p> <p>Recommendation 110 – Emotional stress</p> <p>The committee considered it appropriate to recommend that enquiry about the presence of factors responsible for emotional stress was undertaken in children presenting with headache.</p> <p>Recommendation 111 – Analgesic overuse and headache</p> <p>The committee recognised that analgesic overuse in headache may be a problem in children as well as adults.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for the considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that due to the potentially severe nature of the symptoms, when presented in the forms described in the recommendations, these</p>

	recommendations largely reflect current practice and will not lead to a significant increase in referrals to neurological services. Those recommended to be referred are at significant risk of serious harm to health, and so a rapid assessment is necessary to safeguard their future health, as well as to reduce the later costs that would occur if the symptom is not dealt with urgently. Such referrals will therefore be cost effective.
Other considerations	The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.

7.6 Head shape or size abnormalities

7.6.1 Review question: In children and babies who present with abnormal head shape or size, what is the predictive accuracy of accompanying signs and symptoms to support non-specialists in identifying neurological problems?

The objective of this review is to identify signs and symptoms that, if presenting with abnormal head shape, would indicate a neurological condition that requires referral for further specialist assessment.

For full details, see review protocol in appendix C.

Table 16: Characteristics of review question

Population	Children and babies who present to a non-specialist with abnormal head shape or size
Prognostic variable(s) under consideration	The committee identified the following predictors in children and babies who present to a non-specialist with abnormal head shape or size, for inclusion in this review: <ul style="list-style-type: none"> • acquired head injury • age • developmental delay • distance between tragus and lateral canthus of eye • facial asymmetry • fontanelle closure • history of prematurity • occipital – frontal circumference (OFC) • proptosis • ridging of cranial sutures.
Confounding factors	Any of the predictors listed above are considered to be relevant confounders
Outcome(s)	<p>Main outcomes:</p> <ul style="list-style-type: none"> • Sensitivity (%) and specificity (%) • Area under the ROC curve (AUROC) – measure of predictive accuracy • Positive and negative predictive values <p>Other outcomes:</p> <ul style="list-style-type: none"> • Adjusted odds ratios for the presence of the following conditions: <ul style="list-style-type: none"> ○ familial macrocephaly ○ growing skull fracture

	<ul style="list-style-type: none"> ○ hydrocephalus ○ microcephaly ○ multiple suture synostosis ○ positional plagiocephaly ○ single suture synostosis ○ syndromic synostosis.
Study design	Prospective and retrospective cohort studies

7.6.2 Clinical evidence

No relevant clinical studies investigating the effects of signs and symptoms accompanied by abnormal head shape or size were identified. See study selection flow chart in appendix E and the excluded studies list in appendix L.

7.6.3 Economic evidence

Published literature

No relevant health economic studies were identified. See also the health economic study selection flow chart in appendix F.

7.6.4 Evidence statements

Clinical

No relevant studies on the predictive accuracy of signs and symptoms, accompanied by abnormal head shape or size, for neurological problems were identified.

Economic

No relevant economic evaluations were identified.

7.6.5 Recommendations and link to evidence

Recommendations	
	<p>112. Refer urgently to paediatric services children with dysmorphic features and developmental delay.</p> <p>113. For all children under 4 years with suspected abnormal head shape or size:</p> <ul style="list-style-type: none">• take 3 consecutive measurements of the child's head circumference at the same appointment, using a disposable paper tape measure• plot the longest of the 3 measurements on a standardised growth chart, corrected for gestational age• if the child's head circumference is below the 2nd centile, refer for paediatric assessment. <p>Offer follow-up measurements if needed, according to clinical judgement and taking the child's age into account.</p> <p>114. For children with a head circumference measurement that differs by 2 or more centile lines from a previous measurement on a standardised growth chart (for example, an increase from the 25th to the 75th centile, or a decrease from the 50th to 9th centile):</p> <ul style="list-style-type: none">• refer to paediatric services for assessment and cranial imaging to exclude progressive hydrocephalus or microcephaly or• refer urgently to paediatric services if the child also has any of the following signs or symptoms of raised intracranial pressure:<ul style="list-style-type: none">○ tense fontanelle○ sixth nerve palsy○ failure of upward gaze ('sunsetting')○ vomiting○ unsteadiness (ataxia)○ headache. <p>115. For children with a head circumference above the 98th centile that has not changed by more than 2 centile lines from the previous measurement on a standardised growth chart, who are developing normally and who have no symptoms of raised intracranial pressure:</p> <ul style="list-style-type: none">• note the head size of the biological parents, if possible, to check for familial macrocephaly• if familial macrocephaly is likely, do not routinely refer the child in the absence of any other problem. <p>116. For babies aged under 1 year whose head is flattened on one side (plagiocephaly):</p> <ul style="list-style-type: none">• be aware that positional plagiocephaly (plagiocephaly caused by pressure outside the skull before or after birth) is the most common cause of asymmetric head shape• measure the distance between the outer canthus of the baby's eye and the tragus of their ear on each side

	<ul style="list-style-type: none"> • if the measurements differ, confirm positional plagiocephaly and do not routinely refer if the baby is developing normally • if the measurements are the same, suspect unilateral premature closure of lambdoid suture and refer to paediatric services. <p>117. Advise parents or carers of babies with positional plagiocephaly that it is usually caused by the baby sleeping in one position and can be improved by changing the baby's position when they are lying, encouraging the baby to sit up when awake, and giving the baby time on their tummy.</p>
Rationale for categorising symptoms	This symptom was prioritised for an evidence review because some children with abnormal head shape are treated unnecessarily. Treatments can involve exposure to radiation. There is a need for guidance for non-specialists on when referrals should be made, to whom, and with what urgency. Therefore, a key issue is identifying the clinical features of abnormal head shape or size that should be referred. The committee agreed that an evidence review to support their decision-making would be helpful.
Relative values of different outcomes	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of abnormal head shape or size are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications, which can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
Quality of the clinical evidence	No clinical evidence was identified for inclusion in this review. The recommendations are based on committee consensus.
Trade-off between benefits and harms	<p>Recommendation 112 – Suspected syndromic cranial synostosis</p> <p>There are a number of rare syndromes that involve premature closure of cranial sutures in association with other dysmorphic features, including disorders of facial growth and limb deformities. The investigation and management of these disorders is highly specialised and complex. Urgent referral is recommended as early surgical intervention can improve outcome for head shape and brain growth.</p> <p>Recommendation 113 – Measure head circumference</p> <p>Up until age 4, most head circumference increase is due to growth of the brain. After age 4, increase in head circumference is mainly due to growth in thickness of the skull. After the age of 4 years, disorders of brain growth or raised intracranial pressure are unlikely to present with abnormalities of head shape or size.</p> <p>The committee felt that it was important to flag the need for consistent practice for all health visitors and GPs regarding measuring the head circumference of children. Although it is current practice for health visitors to measure children's heads on their routine visits, it is not current practice for GPs to do this. Not all children attend for their routine health visitor assessments.</p> <p>The committee also discussed that the technique for measuring children's head size should become standardised for all GPs and health advisers. The committee agreed that a disposable, single use, paper tape measure should be used. This avoids problems with hygiene. In addition, a cloth tape measures can be stretched and give inaccurate measurements. It is important that the paper tape measure is not</p>

crumpled or torn prior to use. The committee recognised the potential errors in measuring head circumference in a young child who is wriggling and agreed that the longest of 3 measurements taken at that consultation should be plotted on the appropriate head circumference chart against corrected gestational age.

The tape measure should be placed above the ears, halfway between the hairline and the eyebrows and around the occiput. If the child has an asymmetric head shape, adjust the position of the tape to achieve the longest measurement.

Recommendation 114 – Exclusion of progressive hydrocephalus or microcephaly

A single head circumference measurement does not tell anything about rate of head growth. A head circumference measurement more than 2 standard deviations above or below the mean is considered abnormal. This is equivalent to above the 98th centile or below the second centile. However, a child's head may go from the 25th centile to the 75th centile over a period of a few months. This is excessive head growth and should be assumed to be hydrocephalus or raised intracranial pressure until proven otherwise. Similarly, a head circumference that drops from 50th to second centile indicates poor growth of the head and brain and should be investigated.

These signs and symptoms in their own right are suggestive of raised intracranial pressure. When seen in parallel with excessive rate of head growth, they add to the likelihood of this being a pathological process that warrants urgent referral and investigation.

The anterior fontanelle normally becomes less tense when the child sits up and more tense when the child cries. If the anterior fontanelle is tense when the child is not distressed, this is more concerning.

Sunsetting refers to the appearance of the eye with failure of upward gaze. The lower part of the pupil is covered by the lower eyelid, and the white of the sclera is seen between the iris and the upper eyelid.

Young children who have recently started walking may stop walking and revert to crawling if they have ataxia.

Recommendation 115 – Possible familial macrocephaly

Head circumference is a reflection on growth and tall-for-age children tend to have larger heads for their age. Head size is also influenced by genetic factors. 2% of children have a head circumference above the 98th centile and the majority do not have hydrocephalus or a disorder of head growth.

The head circumference charts used in the NHS gives centile lines up to age 16. The 98th centile for 16-year-old boys is 58 cm and for 16-year-old girls is 56 cm. There is a small amount of further increase in head circumference into adult life in males but not in females.

The most common causes of poor post-natal growth in head circumference is poor brain growth due to disease processes affecting the brain in later antenatal or perinatal periods or early infancy such as damage to the brain in labour or meningitis in infancy. Poor nutritional status may affect head growth. There will always be clues to these disorders in history and examination. There are rare situations where the child has a primary disorder of skull growth and the cranial sutures fuse too early. This prevents expansion of the skull vault to accommodate a growing brain. The child will eventually present with symptoms and signs of raised intracranial pressure but have a small head. Only major surgery to the skull can permit brain growth.

Recommendation 116 – Differentiating positional plagiocephaly from unilateral premature lambdoid closure

Infants frequently have a preferred lying position when asleep and awake with their head to one side. If allowed to persist in adopting this position, this eventually leads to moulding of the shape of the skull with flattening of the side of the head in contact with the lying surface. Children who are slow to sit up because of prematurity, motor developmental delay, or parental choice are more at risk of

	<p>positional plagiocephaly. Children with neurological disorders may have persistence of a primitive reflex – asymmetric tonic neck reflex – that maintains the preferred position.</p> <p>Unilateral premature closure of the lambdoid suture is much less common than positional plagiocephaly. It is often present at birth unlike positional plagiocephaly, which develops over a period of weeks as the infant adopts a preferred lying position.</p> <p>The committee discussed how measuring the distance between the tragus of the ear and the outer canthus of the eye is a useful adjunct to clinical inspection of the head shape of a child under one age and would help a clinician reassure parents that this was a benign condition. However, the committee acknowledged that this was not an absolute discriminator and that if there was uncertainty, referral for specialist assessment was appropriate.</p> <p>Recommendation 117 – Positional plagiocephaly</p> <p>Making a positive diagnosis of positional plagiocephaly allows the parents to be advised on how to change the child’s position to prevent further moulding. By identifying positional plagiocephaly early and allowing parents to reposition their child frequently, the degree of moulding will be limited. This removes the need for parents to seek expensive orthotic assessment (including radiation) and treatment for what is a benign and preventable condition.</p> <p>The aim of the advice is to give the infant more time when they are not lying in their preferred position. Parents are advised to put children to sleep on their back rather than prone to reduce the risk of SIDS. Allowing the child to lie prone when awake and playing encourages head and trunk control and relieves pressure on the back of the head. Infants who do not yet have independent sitting balance can be encouraged to sit with appropriate support or in an appropriate chair.</p> <p>Once the flat area at the back of the head is relieved of pressure with changing position, and the child is spending more time sitting, natural growth of the head will reduce the flattening. The committee does not recommend referral for investigations or management for a condition that has an excellent prognosis over time. The committee recommends referral for assessment of developmental disorders if there is concern that delay in meeting early motor milestones – rolling, sitting – is contributing to degree or maintenance of plagiocephaly. The referral would be for diagnostic assessment as well as assessing the need for therapy and provision of equipment such as adapted seating.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for the considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations represent current practice and therefore would not lead to an increase in referrals or costs to the NHS. The committee noted that these recommendations will lead to an increase in head measuring in primary care. However, this would be done quickly during the course of a routine appointment and so would not take extra time. Paper tape measures are of very low cost. By comparison, head abnormalities can have very large impacts on the health of a child, but if identified they early can be successfully treated. Thus, the advantage of early identification will outweigh any additional cost, making this recommendation cost effective or possibly cost saving.</p>
Other considerations	<p>The committee was aware that abnormal shape of the skull is important for parents and children as children grow and develop body image. Prevention of skull deformity</p>

is important even in the absence of associated neurological or developmental problems.

The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.

7.7 Hypotonia ('floppiness')

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.7.1 Recommendations and link to evidence (consensus statement 49 to 53 in appendix S)

<p>Recommendations</p>	<p>118. For babies aged under 1 year with acute-onset hypotonia (floppiness), examine the baby for signs of cardiac failure, enlargement of the liver or kidneys, pyrexia or an altered level of consciousness, and refer immediately to paediatric services.</p> <p>119. For babies under 1 year with hypotonia (floppiness) that has been present for weeks or months:</p> <ul style="list-style-type: none"> • if the baby is weak (for example, feeding and breathing difficulties), refer urgently to paediatric services or • the baby is not weak and has no signs of intercurrent illness, consider referring in line with looking for signs of cerebral palsy in the NICE guideline on cerebral palsy under 25s.
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change that.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendations 118 and 119 – Hypotonia</p> <p>Hypotonia in children may be idiopathic, or it may present as a sign of a significant organ disorder, including disorder of the brain or peripheral nervous system. If a diagnosis of a significant organ disorder or condition associated with hypotonia has already been made (for example, Down's syndrome or Alagille syndrome), this is likely to be the cause. The child does not need to be referred to paediatric neurology for diagnosis. Referral to other services should be determined depending on the underlying condition.</p> <p>The committee felt it was important to highlight potential causes of hypotonia so that those children with a possible serious disorder of cardiac, renal or liver function would be referred immediately to paediatric services.</p> <p>If an obvious cause cannot be identified, a referral to paediatric neurology is appropriate in order to exclude neurological causes. However, the committee considered that referral to paediatric services may be appropriate since local service provisions vary. If possible, arrange a referral directly to paediatric neurology.</p> <p>A child who is hypotonic may also be weak. In the older child who has already developed some motor skills, loss of these voluntary motor skills usually suggests the child is weak. In the infant who has not yet developed the ability to sit, roll over, or reach for objects, it is not always easy to decide if the child is weak and hypotonic, or only hypotonic. Weakness tends to affect the face and the limbs in young infants. In</p>

	<p>severe weakness, feeding and breathing may be affected. The child has a paucity of movement even when stimulated. The floppy child is usually able to generate some anti-gravity movement and movement against resistance when stimulated. Children who exhibit floppiness with weakness are much more likely to have an underlying progressive disorder of the nervous system. In this circumstance, an urgent referral is required to avoid a delayed diagnosis.</p> <p>An infant or child who is floppy but not weak will have good movements against gravity and resistance when stimulated or trying to perform a task. Their posture may be poor for age. The child who is weak and floppy is likely to have a paucity of spontaneous movements and limited power of movements when stimulated.</p> <p>Children with hypotonia and an altered level of consciousness are likely to have a disorder that requires immediate investigation and management; these children may need intensive care. They may deteriorate very quickly and ambulance services should be alerted to the need for support in transferring the child to hospital.</p> <p>The majority of infants who are hypotonic (floppy) in the first few weeks and months of life do not have an underlying neurological disorder or acute illness. There may be a family history of hypotonic infants. In the absence of any other signs or symptoms of neurological disorder or acute illness, decision on referral may be delayed until the child is 6 months old to see if the child is making progress with motor development.</p> <p>As there may be significant waiting time to be seen by paediatric services, an early simultaneous referral to community physiotherapy could be considered to improve strength, postural control and function.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current practice; therefore, the recommendations should not increase the number of referrals or change NHS costs.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>The first recommendation received 81% agreement during the targeted engagement exercise and the second received 61.9% with minor suggestions for rewording and clarifications around the urgency of referral.</p>

7.8 Limb or facial weakness in children

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.8.1 Recommendations and link to evidence (consensus statement 107 to 115 in appendix S)

Recommendations	<p>120. Refer immediately children with sudden-onset or rapidly progressive (hours to days) limb or facial weakness for neurological assessment.</p> <p>121. Refer urgently children with progressive limb weakness for neurological assessment.</p>
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	<p>122. Refer children with limb weakness that is part of a developmental disorder to paediatric services, in line with looking for signs of cerebral palsy in the NICE guideline on cerebral palsy under 25s.</p> <p>123. For boys with limb weakness, see recommendations 125 and 127 on motor development delay and motor development regression in boys.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for adults or children because the committee considered the referral decision to be non-contentious and an evidence review was unlikely to change this. The committee also noted relevant recommendations in existing NICE guidance covering recognition and referral.
Trade-off between benefits and harms	<p>Recommendation 120– Sudden or rapidly progressive onset of facial or limb weakness</p> <p>Sudden or rapidly progressive limb or facial weakness in a child is usually a symptom of a pathology that requires immediate neurological investigation or management. Strokes and space-occupying lesions (brain tumours or intracranial abscesses) can present with monoplegia or hemiplegia. Acute disseminated demyelination (ADEM) may present initially with weakness before the onset of altered conscious level. Children with these conditions may deteriorate rapidly.</p> <p>Onset of weakness in the legs may be a sign of Guillain–Barré syndrome or transverse myelitis (TM). It is not always possible to differentiate these conditions on clinical examination. As the weakness can progress to affect breathing and swallowing, children should be referred immediately (on the same day).</p> <p>Other pathologies of the spine and spinal cord are rare in children – for example, prolapsed discs, epidural abscess, spinal cord tumours. They may present acutely with weakness and pain, sensory disturbance as well as bladder and bowel dysfunction and should be referred immediately.</p> <p>There are less sinister causes of sudden-onset of limb weakness in children– pressure palsies affecting the common peroneal nerve, brachial plexopathy from heavy rucksacks and Todd’s paresis from prolonged seizure. The history obtained may give a clue as to the cause but referral within 24 hours would be advisable if there is any doubt about the aetiology or no sign of spontaneous improvement.</p> <p>The onset of facial weakness may be due to Bell’s palsy. The majority of children who have Bell’s palsy will make a full recovery within 12 months of being diagnosed. Although this is an essentially benign condition, the committee still felt that a child with facial weakness should be referred for an urgent paediatric opinion</p> <p>Recommendation 121 – Motor delay or progressive weakness</p> <p>Children with neuromuscular conditions may present at birth with low muscle tone, weakness, and feeding or respiratory difficulties. Less severely affected children may not present until it is apparent that the child is not making expected progress with motor skills. All children should be referred for neurological assessment and investigations. The severity and rate of progression of symptoms will determine the urgency of the referral.</p> <p>Most neuromuscular conditions presenting in infancy or early childhood are genetic in origin. As well as early diagnosis allowing the child and family access to assessment, support and information, it also allows genetic counselling and possibly antenatal diagnosis in a subsequent family pregnancy.</p> <p>Duchenne muscular dystrophy (DMD) is one of the most common and severe forms of muscular dystrophy and primarily affects boys. Motor developmental or global developmental delay may be a sign of DMD.</p> <p>Paediatric neurologists and muscle specialists are now using steroid therapy to slow down the rate of loss of mobility in boys with DMD. They aim to start treatment before the boys start to deteriorate, hence the desire to avoid delay in diagnosis.</p>

	<p>Depending on the age and type of developmental delay that is displayed, the child in question may also need support from allied health professionals, for example, physiotherapy, speech and language therapist, or occupational therapist. A referral to allied health professionals based on specific developmental needs should also be considered by the referrer.</p> <p>Recommendation 122 – Cerebral palsy</p> <p>Cerebral palsy is the most common chronic motor disorder to affect children, and it has the potential to affect children and their families' quality of life significantly. The child may require investigation, support and therapy from health services, education, and social services. Early referral and confirmation of diagnosis allows the network of care to meet the changing needs of the child and family as the child grows and develops.</p> <p>Cerebral palsy occurs in children who have none of the commonly recognised risk factors such as prematurity, twin or triplet, or poor condition at birth. Many children with cerebral palsy have comorbidities such as epilepsy, visual impairment and feeding difficulties, which may require early investigation and management.</p> <p>Other genetic and metabolic disorders present similarly to cerebral palsy. Investigations to confirm or exclude these conditions should be undertaken in a specialist setting.</p> <p>Recommendation 123 – Boys with limb weakness</p> <p>See rationale in motor developmental delay section (7.9.1.1).</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. These estimates were the committee's starting point for considering whether its recommendations caused additional referrals that would significantly affect the cost impact on the NHS.</p> <p>The committee did not believe that the recommendations for face and limb weakness would change the number of referrals and hence would not increase costs to the health service.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>The level of agreement for these sorts of recommendations ranged from 73.7% to 94.7%. The committee considered the suggestions for clarification and amended the wording and LETR accordingly.</p>

7.9 Motor development delay and unsteadiness

7.9.1 Motor development delay and unsteadiness

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.9.1.1 Recommendations and link to evidence (consensus statement 153 to 160 in appendix S)

Recommendations	<p>124. Refer immediately children with new-onset gait abnormality to acute paediatric services.</p> <p>125. Refer children to a child development service, and consider referring for physiotherapy or occupational therapy, in line with the</p>
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	<p>recommendations in the NICE guideline on cerebral palsy in under 25s, if they:</p> <ul style="list-style-type: none"> • are not sitting unsupported by 8 months (corrected for gestational age) or • are not walking independently by 15 months (girls) or 18 months (boys) (corrected for gestational age) or • show early asymmetry of hand function (hand preference) before 1 year (corrected for gestational age). <p>126. If the child is a boy, consider measuring creatinine kinase level to exclude Duchenne muscular dystrophy before the boy has had a specialist review.</p> <p>127. Refer children with motor developmental regression to a paediatric neurodevelopmental service or paediatric neurology depending on locally agreed pathways .</p> <p>128. If the child is a boy, consider measuring creatine kinase level to exclude Duchenne muscular dystrophy before the boy has had a specialist review.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change this.
Trade-off between benefits and harms	<p>Walking is typically achieved between 12 and 18 months in all children. Girls who are not walking at 15 months and boys who are not walking at 18 months are considered delayed.</p> <p>Gestational age at birth should be taken into account when assessing if a child has delay in attaining motor milestones such as sitting, crawling or walking</p> <p>Recommendation 124 – New-onset gait abnormality</p> <p>Trauma and infection should be considered as a cause of a child developing a limp. Pain may be due to abdominal problems such as appendicitis. Hip pathology such as Perthes disease and slipped femoral epiphysis may present with an abnormal gait. Pathology in the hip joint may present with a pain felt in the knee. Therefore, the committee agreed that immediate referral to acute paediatric services is justified.</p> <p>Recommendations 125 & 127 – Motor developmental delay and motor developmental regression</p> <p>Motor developmental delay can indicate muscular dystrophy, cerebral palsy, global developmental delay or other progressive neuromuscular disorders, some of which can also cause developmental regression after an initial period of normal development. The majority of children who have motor developmental delay will not have a neurological diagnosis, but may be on the lower end of the developmental spectrum. Signs of motor developmental delay can include not walking by a specified age (18 months for boys, 15 months for girls), or walking with a broad-based gait. Associated symptoms also include late sitting, early symmetry of hand function, and speech and language delay.</p> <p>The committee noted that clinicians are now strongly encouraged to consider referral for assessment of Duchenne muscular dystrophy in boys not walking at 18 months. Given the rarity of Duchenne muscular dystrophy, there will most likely be some unnecessary referrals; nevertheless, the committee considered that it is preferable to refer all children who are not walking at 18 months, so that they can be screened and reassured or diagnosed. There is no significant issue with over-</p>

	<p>referral because the assessment is relatively quick. In the majority of cases, reassurance can be provided.</p> <p>The committee suggested a referral to paediatric neurodevelopmental services or paediatric neurology depending on the local service provision.</p> <p>If the child is suspected of having cerebral palsy, then the child should be referred urgently to a child development service in line with NICE guideline of cerebral palsy in under 25s. If the child has motor developmental delay without risk factors for cerebral palsy in history and examination, referral to allied health professional depending on clinical situation – physiotherapist, occupational therapist, or speech and language therapist – for assessment and discussion on therapy could be considered.</p> <p>Recommendations 126 & 128 – Duchenne muscular dystrophy</p> <p>Creatine kinase (CK) is an inexpensive, routine test that can help identify Duchenne muscular dystrophy, which is a rare condition that in childhood is only clinically relevant in boys. The committee therefore considered that a recommendation to perform a CK test in girls is not necessary. However, if the disease is prevalent in the family and the test is used to determine if the girl is a carrier of Duchenne muscular dystrophy for future generations, then testing may be required.</p> <p>Creatine kinase levels may be mildly raised if the child’s muscles in the arm are squeezed in an attempt to get blood. Levels may also be mildly to moderately raised in other rare inflammatory or dystrophic muscle disorders. However, in DMD, it is usual to have very high levels of CK – sometimes more than 20 times the laboratory’s upper limit of normal.</p> <p>An early diagnosis of Duchenne muscular dystrophy is important so that the family can undergo genetic counselling in the event that the mother is a carrier. If the CK test is negative, DMD is highly unlikely. If non-specialists are not able to request or perform a CK test, then the committee commented that a request should be made for a CK test and the patient referred to neurodevelopmental paediatric services.</p> <p>While noting the value of CK in identifying Duchenne muscular dystrophy, the committee commented that a normal CK test could not rule out Becker muscular dystrophy. The committee pointed out that CK levels are usually very high in Duchenne muscular dystrophy; correspondingly, very high levels can occasionally be found in other genetic and acquired muscle disorders. Therefore, additional testing, such as a genetic mutation or a muscle biopsy, is required to confirm that Duchenne muscular dystrophy caused the abnormal CK level.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>CK tests are cheap routine tests, costing approximately £2.50 if ordered by a GP or £1.50 if done within a hospital (costs supplied by Salford Royal NHS Foundation Trust). A benefit of the CK test is expedited diagnosis as people will be referred directly to paediatric neuromuscular or neurology services (depending on local service provision) and the number of visits to specialists should reduce as a result. The committee estimated there would be a maximum of 10,000 CK tests carried out for this purpose per year, costing a maximum of around £20,000 (including those tests that are already conducted in current practice). Many people will be screened out before the CK test because there will be an obvious cause (for example, premature birth) or an alternative diagnosis. Given that the test is already routinely conducted in such situations and is of low cost, the committee felt it would not put additional pressures on GP surgeries and would be considered a cost-effective use</p>

	<p>of resources. The committee also noted the great impact on health and quality of life of having DMD, and the large costs involved in managing the condition in those who have it. It is advantageous to the child to diagnose DMD early, and so setting the cost of testing against this, a policy of reducing routine testing is likely to be an unwise economy as those with real needs would be diagnosed later and may incur additional expenses as a result. The committee therefore agreed that CK testing is a cost saving or cost-effective practice in this situation.</p> <p>The committee agreed that the other recommendations do not represent a change from current best practice, and that, viewed along with the rest of this guideline, the recommendations will not increase the total number of referrals or NHS costs.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>The level of agreement for this set of recommendations ranged between 68.4% and 77.8%. The respondents agreed with the recommendations but suggested minor amendments for rewording and combining recommendations. The committee agreed that the suggestions would improve the recommendations and amended them accordingly.</p>

7.9.2 Creatine kinase (CK) test

A systematic review of published evidence has been conducted for this topic.

7.9.2.1 Review question: In children and infants under 10 years of age who present with motor developmental delay, is a creatine kinase (CK) test accurate in identifying whether muscular dystrophy is present as compared to no test (and as indicated by the reference standard, diagnosis at follow-up)?

The aim of this review was to evaluate the accuracy of creatine kinase (CK) test in aiding a non-specialist in identifying muscular dystrophy in children and infants under 10 who present with motor developmental delay.

For full details, see review protocol in appendix C.

Table 17: Characteristics of review question

Population	All people who present to a non-specialist with motor developmental delay in the following stratifications: <ul style="list-style-type: none"> • children (<10 years old) • infants (<5 years old)
Target condition	Muscular dystrophy
Index test (comparator)	Creatine kinase
Reference standard(s)	<ul style="list-style-type: none"> • Diagnosis of the muscular dystrophy at follow-up • Clinical examination
Statistical measures	<p>Diagnostic accuracy of creatine kinase:</p> <ul style="list-style-type: none"> • 2x2 tables • Specificity (low false negative) • Sensitivity (high) • Positive and negative predictive values • ROC curves and area under the curve
Study design	Cohort studies, case-control studies if no other evidence is found

7.9.2.2 Clinical evidence

No relevant clinical studies were identified. See study selection flow chart in appendix E and the excluded studies list in appendix L.

7.9.2.3 Economic evidence

Published literature

No relevant health economic studies were identified. See also the health economic study selection flow chart in appendix F.

7.9.2.4 Evidence statements

Clinical

No relevant studies were identified.

Economic

No relevant economic evaluations were identified.

7.9.2.5 Recommendations and link to evidence

Recommendations	See recommendation 125 (section 7.9.1.1).
Relative values of different diagnostic measures	Measures of diagnostic accuracy including sensitivity, specificity, 2x2 tables, positive or negative predictive values and ROC curves and area under the curve were considered important outcomes. Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with muscular dystrophy would have serious implications, which may lead to deterioration of health and reduced quality of life. It can also have serious consequences on the family if they are unaware that they may be carriers of genetic conditions and have other children who may also be affected. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments and unnecessary distress to the child and the family.
Quality of the clinical evidence	No clinical evidence was identified for inclusion in this review. The recommendations are based on committee consensus.
Trade-off between clinical benefits and harms	Because muscular dystrophy is a rare condition, the committee agreed that boys suspected of having muscular dystrophy should be referred to a specialist or service with the resources to complete a CK measurement and supply counselling services when appropriate. The committee agreed that GPs, in general, do not have the time or the resources to care for children with muscular dystrophy adequately, but specialist physicians are able to provide counselling in addition to the blood test. For younger children, the referring primary care physician should consider whether to request the blood tests prior to referral if it is likely that the same blood tests would be repeated by the specialist. This is to minimise the distress caused by repeated drawing of blood from such young children. The committee felt it is important to highlight that healthcare professionals should be aware that creatine kinase levels may be mildly raised if the child's muscles in the arm are squeezed in an attempt to get blood. Levels may also be mildly-to-moderately raised in other rare inflammatory or dystrophic muscle disorders. However, in DMD, it is usual to have very high levels of CK – sometimes more than 20 times the laboratory's upper limit of normal.

	<p>The committee felt that prompt diagnosis of muscular dystrophy helps parents of children to avoid confusing internet searches and possibly damaging misinformation. The specialist will provide support and guidance for families on living and caring for a child with muscular dystrophy. A child with muscular dystrophy will also live a shorter life, and the committee felt that if the clinician can dedicate time to discuss and answer all of the questions that the family might have, the parents learning of their child's diagnosis will be better supported. This way, the family will have a full picture of their future instead of the possibly inaccurate view online research might provide. The clinician will also provide genetic counselling.</p> <p>The committee was careful to assert that this is not a screening programme. 95% of boys with motor developmental delays will not have Duchenne muscular dystrophy; however, they may have another diagnosis. If the CK test is negative, then the diagnosing clinician can rule out Duchenne muscular dystrophy and focus on other possibilities.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>CK tests are cheap routine tests, costing approximately £2.50 if ordered by a GP or £1.50 if done within a hospital (costs supplied by Salford Royal NHS Foundation Trust). A benefit of the CK test is expedited diagnosis as people will be referred directly to paediatric neuromuscular or neurology services (depending on local service provision) and the number of visits to specialists reduce as a result. The committee estimated there would be a maximum of 10,000 CK tests carried out for this purpose per year, costing a maximum of around £20,000 (including those tests that are already conducted in current practice). Many people will be screened out before the CK test because there will be an obvious cause (for example, premature birth) or an alternative diagnosis. Given that the test is already routinely conducted in such situations and is of low cost, the committee felt it would not put additional pressures on GP surgeries and would be considered a cost-effective use of resources. The committee also noted the great impact on health and quality of life of having DMD, and the large costs involved in managing the condition in those who have it. It is advantageous to the child to diagnose DMD early; therefore, setting the cost of testing against this, a policy of reducing routine testing is likely to be an unwise economy as those with real needs would be diagnosed later and may incur additional expenses as a result. The committee therefore agreed that CK testing is a cost saving or cost-effective practice in this situation.</p>
Other considerations	<p>The committee was aware that there is concern that the diagnosis of Duchenne muscular dystrophy (DMD) is delayed in some boys. The consensus on the ideal time to start steroid therapy in boys is by the age of 4 years or before they start to plateau in their motor development and lose motor skills. New treatments to reverse the genetic defects in DMD are offered to boys with specific gene mutations early in the disease process. Therefore, the committee was keen to develop recommendations that would encourage clinicians in primary care to consider DMD as part of the differential diagnosis for a boy with developmental problems and ensure timely referral for investigations.</p> <p>However, the committee was aware that families find the diagnosis of DMD distressing, and they should have ready access to clinical and genetic counselling. Making the diagnosis early allows other family members to receive genetic counselling to assist them in deciding if they wish genetic testing to look for carrier</p>

status for mutations in the dystrophin gene. This would allow antenatal diagnosis of second or subsequent affected offspring in the family.

The committee made this recommendation by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, this recommendation was only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.

7.10 Posture distortion in children

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.10.1 Recommendations and link to evidence (consensus statement 33 to 41 in appendix S)

<p>Recommendations</p>	<p>129. Refer immediately children with abnormal neck posture and a recent head or neck trauma to an emergency department for assessment, and follow recommendations 1.2.9 and 1.2.10 on cervical immobilisation in the NICE guideline on head injury and recommendation 1.1.4 on spinal immobilisation in the NICE guideline on spinal injury.</p> <p>130. In children with abnormal neck posture, check whether painful cervical lymphadenopathy is the cause.</p> <p>131. Refer children who develop abnormal limb posture that has no musculoskeletal cause for neurological assessment.</p> <p>132. Be aware that abnormal head tilt in children can be a symptom of posterior fossa tumour.</p>
<p>Rationale for categorising symptoms</p>	<p>This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be uncontentious and an evidence review is unlikely to change the decision.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 129– Recent history of head or neck trauma</p> <p>This may indicate instability of cervical spine through bony or ligamentous injury. The child should be referred immediately to a centre with imaging and paediatric neurosurgical services. Ensure that a potentially unstable neck is protected for the journey. Excess movement of the unstable cervical spine can cause irreversible and severe damage to the spinal cord with ensuing paralysis. Therefore, if there is uncertainty about how to stabilise the neck for transfer to hospital, the child should not be moved until emergency services are in attendance.</p> <p>Recommendation 130- Painful cervical lymphadenopathy</p> <p>This is a relatively common presentation in primary care and acute paediatrics services. The child adopts a favoured head position to reduce the discomfort from the enlarged lymph nodes. Children with severe throat infections such as epiglottitis and retropharyngeal abscess may also present with head tilt. These conditions usually have more obvious localised symptoms as well as lymphadenopathy. Management of the primary condition is necessary.</p> <p>Recommendation 131 – Onset of abnormal limb posture</p> <p>Children may adopt an abnormal posture of the head, neck, trunk or limbs because of pain or injury to the affected part. This is the most common cause. Refer to</p>

	<p>paediatric specialist for assessment. Less common causes of abnormal posture include abnormalities of tone, such as dystonia, or weakness. These may be transient and intermittent.</p> <p>Children with an onset of abnormal posture but without a history of an associated acute event or an obvious musculoskeletal cause should be referred within 2 weeks for paediatric neurological assessment. There are benign causes of abnormal posture; however, it is a priority to exclude progressive causes requiring treatment.</p> <p>Children with primary dystonia may be incorrectly diagnosed with a functional movement disorder. Primary dystonia in children is rare. The child may initially present with focal dystonia, which is intermittent. It may be triggered by stress or exercise.</p> <p>Secondary dystonia is more common than primary dystonia in children. The most common secondary dystonia presents in children with cerebral palsy. In secondary dystonia, there is usually a history of neurological and developmental problems.</p> <p>Recommendation 132 – Abnormal head tilt</p> <p>Abnormal head tilt may present before other typical symptoms of posterior fossa tumours, such as ataxia, vomiting and headaches. This finding is sometimes dismissed leading to delay in diagnosis, and the committee therefore considered it useful to draw attention to the possibility. This should prompt further examination of the child - a detailed neurological examination will usually be abnormal.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for consideration of whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>All recommended referrals are in line with current practice; therefore, the number of referrals is not expected to increase, and there will be no change in costs to the NHS.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>Recommendations 130 and 132 received a high level of agreement (82.6 % and 100 % respectively); thus, the committee did not discuss or change them. However, comments provided by the participants were taken into consideration to elaborate on the rationales for these recommendations.</p> <p>Of the 23 participants who commented on these recommendations, Only 1 participant disagreed with recommendation 129 although the reason for disagreement was not clear from the comment. 65.2% agreed with this recommendation. Comments were on the need to stabilise the neck in a child being transferred with suspected instability of the spine following a recent head or neck trauma. This has been added to the LETR.</p> <p>56.3% agreed with recommendation 131, abnormal posture of the limb, and the remaining thought it needed revisions. The committee considered the comments provided and added further justifications to the LETRs accordingly.</p>

7.11 Sensory symptoms such as tingling or numbness in children

An evidence review was carried out in this area for both adults and children. Please see section 5.10.

7.11.1 Recommendations and link to evidence

<p>Recommendations</p>	<p>133. Refer urgently children who have tingling accompanied by other peripheral nervous system symptoms such as weakness, bladder dysfunction or bowel dysfunction for neurological assessment.</p> <p>134. Be aware that tingling in children may be the first symptom of an acute polyneuropathy (Guillain–Barré syndrome) or other neuro-inflammatory conditions. If the child has features suggesting motor impairment, refer urgently for neurological assessment.</p> <p>135. Refer children with isolated tingling, altered sensation or paraesthesia for neurological assessment if the symptoms are episodic and are not associated with compression of a nerve. For more information see the recommendations on diagnosis and investigations in the NICE guideline on epilepsies.</p> <p>136. Do not routinely refer children for neurological assessment of temporary tingling or numbness if there is a clear history of the symptom being triggered by activities known to cause nerve compression, such as carrying a heavy backpack or sitting with crossed legs.</p> <p>137. Be aware that in children hyperventilation is a common cause of transient tingling in the limbs.</p>
<p>Rationale for categorising symptoms</p>	<p>The committee felt that an evidence review for this symptom would be helpful because tingling or altered body sensation in children is an unusual presentation and it is not always clear what the causes are. Functional neurological disorders do occur, usually in teenagers but tend to present with loss of function. There are many causes of limb pain in children; most are not neurological.</p>
<p>Relative values of different outcomes</p>	<p>Measures of diagnostic accuracy including sensitivity, specificity, positive predictive value, negative predictive value, ROC, AUC as well as adjusted odds ratios were all considered important outcomes to determine whether the signs and symptoms in the presence of sensory symptoms are indicative of a neurological condition that requires referral for a specialist assessment.</p> <p>Sensitivity and specificity were considered to be of equal importance. Sensitivity was important because the consequences of missing a patient with a neurological condition would have serious implications, which can lead to rapid deterioration of health or even death. Specificity was important because incorrectly diagnosing an individual may result in inappropriate administration of medications or treatments. Only adjusted odds ratios from studies that had conducted a multivariate analysis including the predictors of interest were considered.</p>
<p>Quality of the clinical evidence</p>	<p>No evidence was identified for this review. These recommendations are based on committee consensus.</p>
<p>Trade-off between clinical benefits and harms</p>	<p>Recommendation 133 – Tingling and other peripheral nervous system symptoms</p> <p>These symptoms and signs may indicate pathology affecting the spinal cord. This can be acquired lesions such as tumour or haematoma, or a congenital lesion, such as tethered spinal cord. It is not easy to make the diagnosis on clinical examination and all children should be referred urgently to a centre where imaging of the spinal cord can be done.</p> <p>Recommendation 134 – Guillain–Barré syndrome</p>

	<p>Guillain–Barré syndrome is a relatively rare polyneuropathy that is usually self-limiting but can have serious consequences before it remits, chiefly by affecting respiratory function. Although this danger relates to motor function, the first complaint may be of tingling in the extremities. If this symptom is progressive the presence of motor signs or symptoms should be sought. If Guillain–Barré syndrome is suspected, the child should be referred urgently.</p> <p>Recommendation 135 – Transient altered sensation</p> <p>When not associated with nerve compression, transient positive or negative sensory symptoms may be related to epilepsy and require neurological assessment. If epilepsy is suspected, refer urgently in line with NICE guideline on Epilepsies: diagnosis and management – CG137 (sections 1.5 and 1.6)</p> <p>Recommendation 136 – Transient compression neuropathies</p> <p>These are common in children related to posture or carrying heavy objects and do not require referral for neurological assessment.</p> <p>Recommendation 137 – Hyperventilation</p> <p>Transient tingling in the limbs may be caused by over-breathing, which may be an emotional reaction. This symptom does not need neurological assessment.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations would not lead to additional resource use, as they largely reflect current practice. Reassurance that some children do not need referral for neurological assessment may lead to a slight decrease in unnecessary referrals, leading to a cost saving.</p>
Other considerations	<p>The committee made these recommendations by consensus following an evidence review that did not yield any relevant clinical or economic evidence. Therefore, in line with NICE standard methods, these recommendations were only subject to the main stakeholder consultation and not to the additional targeted engagement exercise, which only applied to recommendations where no evidence review was undertaken.</p>

7.12 Sleep disorders in children

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.12.1 Recommendations and link to evidence (consensus statement 175 to 194 in appendix S)

Recommendations	<p>138. Refer urgently children with neuromuscular disorders who have early morning headaches or new-onset sleep disturbance for a respiratory assessment.</p> <p>139. Refer urgently children who have symptoms suggestive of new-onset epileptic seizures in sleep for neurological assessment.</p>
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	<p>140. Refer children with symptoms suggestive of narcolepsy, with or without cataplexy, for neurological assessment or a sleep clinic assessment according to local pathways.</p> <p>141. Refer children with symptoms of sleep apnoea to ear, nose and throat or paediatric respiratory services, as appropriate, and offer advice on weight loss if the child is obese.</p> <p>142. Refer children aged over 5 years with new-onset night terrors and children with night terrors that persist after age 12.</p> <p>143. Reassure parents or carers of children aged under 5 years who have night terrors, repetitive movements, sleep talking or sleep walking that these are common in healthy children and rarely indicate a neurological condition.</p> <p>144. Offer advice on sleep hygiene to parents or carers of children with insomnia, and consider referring to a health visitor if the child is aged under 5 years.</p> <p>145. Consider referring children with sleep disorders associated with neurodevelopmental disorders or learning disabilities to community paediatric services.</p> <p>146. Be aware that sleep disorders in children may be a symptom of gastro-oesophageal reflux or constipation. See the recommendations on diagnosing and investigating gastro-oesophageal reflux disease in the NICE guideline on gastro-oesophageal reflux disease in children and young people, and the NICE guideline on constipation in children and young people.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review was unlikely change that. The committee recognised that sleep disorders in children are a common presentation and considered that there is a need for guidance for non-specialists on where to refer.
Trade-off between benefits and harms	<p>Recommendation 138 – Early-morning headaches</p> <p>Children with neuromuscular disorders, particularly boys with Duchenne muscular dystrophy, may present with headaches on awakening. This can be an early sign of respiratory failure due to hypoventilation during sleep. For boys with DMD, this may occur later in the first decade or into the second decade of life. The headaches may affect quality of life due to daytime drowsiness. The child should be referred urgently to paediatric respiratory services for assessment, including sleep study and consideration of non-invasive ventilation at night.</p> <p>Children who present with headaches that wake them from sleep may be developing raised intracranial pressure. One of the common causes of raised intracranial pressure in children is a brain tumour. This possibility is covered separately within this guideline (see recommendation 104).</p> <p>Recommendation 139 – Nocturnal epilepsy</p> <p>Episodes of abnormal behaviour from sleep are common in childhood and include night terrors, nocturnal seizures and sleep apnoea with arousal. Parents will often</p>

video the episode and this can be very helpful in identifying the cause. Night terrors occur in children mainly under the age of 5. The child wakes up an hour or so after going to sleep, distressed and inconsolable. The episode may last up to 20 minutes, and then the child rolls over and goes back to sleep again.

Red flags for nocturnal seizures are:

- a stereotyped pattern of behaviour during the episode
- starting as a focal seizure and then becoming generalised
- difficulty rousing the child following the event.

Seizures at night may affect the child's concentration the next day and the child may have excessive daytime drowsiness. Unless the event is witnessed, it can be difficult to decide if the child has had a seizure or an alternative event. It is important to decide what is causing the sleep disturbance as starting or increasing anti-epileptic drugs may not be appropriate. In accordance with NICE epilepsy guidelines, the child should be referred to a specialist in the management of the epilepsies as soon as possible where investigations may include EEG, sleep EEG and video-telemetry. Depending on the local provision, the referral pathway may include a paediatric neurologist or a paediatrician with expertise in epilepsy.

The committee recognised that like adults, children with epilepsy are of significantly increased risk of death compared to the general population. Nocturnal seizures are a known risk factor for Sudden Unexpected Death in Epilepsy (SUDEP). Early referral for investigation is warranted.

Recommendation 140 – Narcolepsy with or without cataplexy

Narcolepsy is a condition that is easily missed in children. It can present as daytime drowsiness, falling asleep in unusual circumstances or as poor school performance and poor concentration. Diagnosis, assessment, and management are best achieved by a service with experience of this condition, and the child should be referred to neurological services.

Recommendation 141 – Sleep apnoea

Sleep apnoea is not uncommon in infants and young children and may be due to gastro-oesophageal reflux or intercurrent infection. Sleep apnoea is more common in children who have been born prematurely and have not yet developed a mature control of breathing.

In older children, recurrent sleep apnoea may be due to narrow upper airways due to enlarged tonsils and adenoids. Children suspected of this should be referred to ENT.

The committee also wished to highlight that children who have neuromuscular disorders, such as Duchenne muscular dystrophy, are more susceptible to hypotonia. Hypotonia in the muscles of the airways can cause sleep apnoea and other breathing disorders

Sleep apnoea secondary to obesity does occur in children. The child should be referred to paediatric services for dietary advice and consideration of sleep study.

Sleep apnoea in children causes parents a lot of anxiety. Children who have had a significant apnoeic event in sleep should be referred to paediatric services for investigation of possible causes and advice to parents on avoiding risk factors.

Recommendation 142 – New-onset night terrors

Epileptic seizures can occasionally be difficult to distinguish from night terrors, and both night terrors and epilepsy can occur many times in a night. Since night terrors are uncommon in children over the age of 5, children in whom night terrors commence after the age of 5 and those in whom night terrors of onset below the age of 5 persist after the 12th birthday are at high risk of misdiagnosis of epilepsy. In such circumstances, referral for diagnostic review is appropriate as epilepsy carries with it a risk of adverse outcome.

	<p>Recommendation 143 – Sleep disturbances</p> <p>The committee recognised that clinicians would already be aware that sleep disturbance is common in childhood. However, reassuring parents that it is a normal part of development may help to reduce the pressure for an unnecessary referral. Sleep disturbances such as night terrors, sleep walking, or repetitive movements do not require a referral to neurology. In many cases, sleep disturbances will resolve as a child gets older.</p> <p>Recommendation 144 – Sleep disturbances in under 5s</p> <p>The committee also wanted to highlight advice and support (for example, from health visitors) that is available outside of hospital settings as this may also lead to a reduced burden on secondary care. Sleep disturbances are often caused by not achieving effective bedtime routines. Once an appropriate sleeping pattern is identified, sleep disturbances will often resolve unaided.</p> <p>The health visitor can provide very useful parenting advice from their experience with other families and knowledge of this child since early infancy. The health visitor is also able to do home visits and advise the parents on environment and sleeping arrangements in the house.</p> <p>Recommendation 145 – Neurodevelopmental disorders or learning disabilities</p> <p>Children with neurodevelopmental disorders often have poor sleeping patterns, have sleep disorders and experience sleep disturbances. This group is often referred to paediatric services for sleep-related issues. The committee felt that this group should be considered separately, as a referral to paediatric services may or may not be appropriate given the prevalence of sleep issues in this population. Clinical judgement should be used to assess individual cases.</p> <p>Children with significant visual impairment are at higher risk of sleep disturbance than children with normal sight.</p> <p>Sleep disturbances are also more likely to occur in children with intellectual disabilities or autism. Many children will be referred anyway, but in some cases, referral will be because of a suspected intellectual disability or autistic spectrum disorder rather than a sleep disorder. The committee considered that the appropriate pathway should be to community paediatric services, as within this team there is the expertise to assess the child and advise parents.</p> <p>Recommendation 146 – Gastro-oesophageal reflux or constipation</p> <p>Gastro-oesophageal reflux and constipation in children are associated with neurodevelopmental rather than neurological causes and commonly present with sleep disorders. The committee considered it important to highlight these conditions to non-specialists as potential causes. Taking a history should identify these causes.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit costs £175 and a paediatric outpatient visit costs £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considerations concerning its recommendations causing additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that these recommendations do not represent a change from current best practice, and that, viewed along with the rest of this guideline, the recommendations should not increase the total number of referrals or NHS costs.</p>
Other considerations	<p>The committee noted the wider impact that lack of sleep can have on families, even leading to a family breakdown.</p>

Targeted engagement exercise

This set of recommendations reached a very high level of agreement ranging from 77.8% to 100%. Therefore, the recommendations remained mostly unchanged except for minor refinement of the wording to make them clearer.

7.13 Speech problems in children

Recommendations from this section are based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.13.1 Recommendations and link to evidence (consensus statement 209 to 217 in appendix S)

<p>Recommendations</p>	<p>147. Refer urgently children with new-onset slurred or disrupted speech that is not attributable to prescribed medicines, recreational drugs or alcohol for neurological assessment.</p> <p>148. Consider referring children aged over 2 years with abnormal speech development to speech and language services.</p> <p>149. Be aware that delay or regression in speech and language in children can be a symptom of autism. Follow the recommendations on recognising children and young people with possible autism and referring children and young people to the autism team in the NICE guideline on recognition, referral and diagnosis of autism spectrum disorder in under 19s.</p>
<p>Rationale for categorising symptoms</p>	<p>There are well established pathways into speech therapy already in place for speech developmental delay. Therefore, an evidence review in this area is not required. However, the committee felt that it would be helpful to provide guidance for non-specialists to help differentiate acute onset from speech developmental delay.</p>
<p>Trade-off between benefits and harms</p>	<p>Recommendation 147 – New-onset slurred or disrupted speech</p> <p>New-onset slurred or disrupted speech, whether as an isolated problem or accompanied by loss of other developmental skills, can indicate the presence of an acute or progressive neurological disorder or epilepsy, which requires urgent neurological assessment.</p> <p>Stuttering and stammering in children is unlikely to be a symptom of an underlying progressive neurological disorder. It is a form of dysfluent speech. It occurs commonly in children during a period of rapid speech development. Referral to child development services or speech therapy would only be warranted if it were having a significant impact on child's ability to communicate.</p> <p>Recommendation 148 – Abnormalities of speech development</p> <p>Abnormal speech development is a very common presentation in children. Children who experience abnormal speech development (such as delayed speech or stuttering) may require support from speech and language services. In some localities, a referral to speech and language therapy must be accessed through community paediatric services. The committee discussed the appropriate age for referral and noted that there is a wide range within which development can be considered normal. It was therefore agreed that referrals should not be made before the age of 2. Until that age, development may be within normal limits, and</p>

	<p>speech difficulties may resolve unaided. Referral between 2 and 3 years is ideal so that treatment can be undertaken before the child starts school.</p> <p>The committee noted guidance from the College of Speech and Language Therapists that suggests work with families is undertaken before the age of 3, with 1-to-1 support through speech and language therapists undertaken as a second-line option.</p> <p>Recommendation 149 – Delay or regression in speech and language and suspected autism</p> <p>Autism can present with speech and language delay or regression in communication skills, delayed speech being more likely than loss of previously acquired speech. Children with autism will likely present with additional signs alongside speech difficulties, such as problems with socialisation and an interest in a limited range of activities.</p> <p>The committee noted the NICE guideline on recognition, referral and diagnosis of autism spectrum disorder in under 19s (CG128) and agreed to cross-refer. Once on the autism pathway, a differential diagnosis can be made by the specialist teams.</p> <p>The committee noted that the current waiting list for autism assessment could be 2–3 years. If a child presents with the loss of speech and language accompanied by the loss of other developmental skills, the diagnosis is less likely to be autism, and the child should be referred urgently for neurological assessment.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, the first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current practice; therefore, the recommendations should not increase the number of referrals or costs to the NHS.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>There was a high level of agreement with this set of recommendations ranging from 72.2–94.4%. Therefore, the recommendations remained mostly unchanged except for minor refinement of the wording to make them clearer.</p>

7.14 Squint

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.14.1 Recommendations and link to evidence (consensus statement 218 to 224 in appendix S)

Recommendations	<p>150. Refer immediately children with new-onset squint that occurs together with loss of red reflex in one or both eyes to ophthalmology services.</p>
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	<p>151. Refer immediately children with new-onset squint that occurs together ataxia, vomiting or headache to acute paediatric services.</p> <p>152. Refer urgently children with paralytic squint for neurological assessment, even in the absence of other signs and symptoms of raised intracranial pressure.</p> <p>153. Refer children with non-paralytic squint to ophthalmology services.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be non-contentious and an evidence review is unlikely to change this.
Trade-off between benefits and harms	<p>Recommendation 150 – Squint with loss of red reflex in 1 or both eyes Loss of red reflex can indicate a retinoblastoma or other progressive pathology of the globe. Because of the risk of retinoblastoma spreading to the other eye, the committee agreed that referral should be immediate (same day). Children presenting with the onset of squint and loss of red reflex in one or both eyes should be diagnosed, scanned and operated on as soon as possible to decrease the impact on the patient’s vision. The committee recognised that the local service provision may vary, but ophthalmological services will be aware of the local pathway.</p> <p>Recommendation 151 – Squint with ataxia, vomiting or headache Squint presenting with accompanying symptoms such as ataxia, vomiting or headache may indicate raised intracranial pressure. The committee agreed that children presenting with squint and any of these symptoms should be referred immediately (same day). A paralytic squint, where the child loses the ability to move the eye fully in a particular direction is a sign of cranial nerve palsy. The most common is a sixth nerve palsy (abducens nerve) causing the eye to point inwards; the child is unable to move the eye to look outwards. Paralytic squints should be assumed to be caused by pressure on one of the cranial nerves involved in eye movements and the child should be referred same day.</p> <p>Recommendation 152 – Onset of paralytic squint Damage to the brainstem by tumour or inflammation can present with loss of movement of one or both eyes. This symptom should trigger urgent referral for diagnosis.</p> <p>Recommendation 153 – Non-paralytic squint In most children, an asymmetrical alignment of the eyes causes squint. In a non-paralytic squint, the child retains the ability to move the eye fully in all directions. The committee agreed that in the absence of any other signs or symptoms such as loss of red reflexes, ataxia, vomiting or headaches this would only require a routine referral to ophthalmology.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs showing that an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considering whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current practice (in the case of the third recommendation, this is already</p>

	recommended by NICE); therefore, the recommendations should not increase the number of referrals or costs to the NHS.
Other considerations	Targeted engagement exercise As expected, this topic was not contentious and there was a very high level of agreement with the recommendations ranging from 94.4% to 100%. Therefore, no changes were made to the recommendations.

7.15 Tics and involuntary movements in children

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.15.1 Recommendations and link to evidence (consensus statement 67 to 83 in appendix S)

Recommendations	<p>154. Refer immediately children who have sudden-onset chorea, ataxia or dystonia for neurological assessment.</p> <p>155. Do not routinely refer children with simple motor tics that are not troublesome to the child.</p> <p>156. Advise parents or carers of children with a tic disorder to discuss the disorder with the child’s school, emphasising that the tic is an involuntary movement and the child should not be reprimanded for it.</p> <p>157. Do not offer medicine for motor tics in children without specialist referral and advice (see recommendation 159).</p> <p>158. Be aware that tics and stereotypies (repetitive or ritualistic movements such as body rocking) are more common in children with autism or a learning (intellectual) disability.</p> <p>159. For children with a tic disorder that has a significant impact on their quality of life, consider referring according to local pathways, as follows:</p> <ul style="list-style-type: none"> • referral to mental health services if the tic disorder is associated with symptoms of anxiety or obsessive compulsive behaviour • referral to the neurodevelopmental team if the tic disorder is associated with symptoms suggestive of autism or attention deficit hyperactivity disorder • referral for neurological assessment if the tic disorder is severe.
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be uncontroversial and an evidence review is unlikely to change the decision.
Trade-off between benefits and harms	Recommendation 154 – Sudden-onset chorea, ataxia, dystonia or other involuntary movements

A sudden onset of 1 of these movement disorders can be a symptom of a progressive neurological disease such as a space-occupying lesion, metabolic disturbance, a degenerative condition, a para-infectious condition such as rheumatic fever or be drug-induced. Children with sudden-onset involuntary movements are at risk of developing further neurological signs and symptoms. All children should be referred immediately (on the same day) for a neurological assessment, ideally to a centre where specialist investigations such as an MRI of brain and lumbar punctures can be performed.

Recommendation 155 – Simple motor tic disorder

Tics are brief repetitive movements, usually of no purpose, which the child feels the urge to do but can suppress for short periods of time. They are a common symptom in children, particularly in boys. About 20% of boys will have tics at some time during childhood. Tics can take the form of vocalisations – grunting, snorting or whistling. They are usually simple motor tics and are more likely to occur when the child is anxious or excited. The child has a particular tic for some weeks and then it disappears to be replaced by a different tic some time later.

The vast majority of simple tic disorders resolve on their own within 2 to 3 years. Typically, the presence and strength of the tic varies. In the instances where the simple tic disorder lasts until the teenage years, it typically resolves by the age of early adulthood. With a clear history of intermittent simple motor tics in the absence of neurodevelopmental problems, a referral for further neurological assessment is not warranted.

Recommendation 156 – Advice to parents and carers

The committee noted that tics are more often of concern to parents and carers rather than to the child. Parents and carers may find tics irritating or be concerned that their child will be teased at school. Children can become anxious about their tics if they think they may be punished or told to stop the movement.

Parents and carers should be given a clear explanation that these movements are involuntary, that they are not part of a progressive brain disorder and that drawing attention to the movements may aggravate the condition. This will help parents and carers understand the nature of the condition. Parents and carers should be advised to pass this information onto schools and other carers with whom their children interact.

Recommendation 157 – Offering medication

Non-pharmacological interventions are the first line of treatment. Habit reversal therapy may be useful when the tics are causing the child distress in school or at home.

Drug treatment for a tic disorder is reserved for cases where the tics are functionally disabling and non-pharmacological treatments have been ineffective.

Typical neuroleptic drugs used to suppress tics are clonidine and neuroleptic drugs – pimozide, haloperidol and sulpiride. However, the side effects of such medications can be severe and irreversible. Only a specialist who is experienced in the use of neuroleptic drugs in children should offer them. The specialist can advise parents and children of the benefits and risks of neuroleptic drugs.

Recommendation 158 – Autism or intellectual (learning) disorders

Children with autism have a higher risk of developing involuntary movements such as tics and stereotypies. Stereotypies are simple movements such as body rocking, hand flapping or flickering fingers in front of the eyes. The child may be able to stop them voluntarily. The movements of a stereotypy may persist for minutes or hours unlike tics, which are very brief.

Epilepsy is more common in children with autism. The differentiation between involuntary movements and epilepsy can be difficult in a child with communication and intellectual (learning) problems; therefore, a referral may be appropriate for investigation and management of the neurodevelopmental disorders, as well as

	<p>confirming the nature of the involuntary movements if the clinician cannot confidently exclude epilepsy.</p> <p>Recommendation 159 – Tic disorder accompanied by symptoms of other neurodevelopmental disorders</p> <p>Referral may be considered for management of tics that cause significant impairment of activities or quality of life, as drug treatment or habit reversal therapy can be considered to manage the situation.</p> <p>Children who have tics in association with a neurodevelopmental disorder are likely to have multiple needs from different teams, including neurology, psychology and occupational therapy. As such, these children should be assessed and managed in a multidisciplinary setting.</p> <p>Obsessive and compulsive behaviours presenting in association with tics are likely to be a symptom of Tourette’s Syndrome. These behaviours may have a significant impact on daily life and the child’s ability to participate in usual, daily activities. The management of obsessive and compulsive behaviours in children requires a multidisciplinary assessment and referral to the local service with appropriate skills.</p> <p>Children with simple motor tics may develop an anxiety disorder if they are afraid that they will be punished, teased, or told to stop the movements. This can manifest in different ways including physical symptoms such as tremor, headaches and sweating, or emotional symptoms such as poor behaviour or refusal to attend school. The child and family will benefit from a discussion with someone who understands the problem and therefore they should be referred to secondary care if the tic and associated symptoms are sufficiently severe. This may not necessarily be to a psychologist in the first instance but could be a paediatric neurologist or developmental paediatrician.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and their cost to the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs where an outpatient visit cost £175 and a paediatric outpatient visit cost £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. The committee used these estimates as a starting point for considerations of whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee believes that the recommendations would reduce overall referrals to neurology and likewise would ensure that only those who stand to benefit from further interventions are referred. This would reduce costs to the NHS without compromising treatment for those that could benefit from it.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>There was a high level of agreement with recommendations 154–158, ranging between 89–94.7% and only minor edits to the wording were needed.</p> <p>Recommendation 159 was originally 3 recommendations that received varying levels of agreement, ranging from 68.4–75%. Participants felt that these recommendations would be better combined. There was 5% disagreement (3 participants) with the original recommendation regarding referral of children with tic disorder and anxiety. It was not clear what the exact reason for disagreement was but some comments suggested that this recommendation may result in excessive numbers of referrals to psychology services and the recommendation was modified accordingly.</p>

7.16 Tremor in children

Recommendations from this section are based on the committee’s knowledge and expertise with further validation by external experts through a targeted engagement exercise.

7.16.1 Recommendations and link to evidence (consensus statement 225 to 233 in appendix S)

Recommendations	<p>160. Refer urgently children presenting with tremor for neurological assessment if:</p> <ul style="list-style-type: none"> • they have additional neurological signs and symptoms such as unsteadiness or • the onset of the tremor was sudden. <p>161. Be aware that isolated postural tremor in children may be a side effect of sodium valproate or a beta-adrenergic agonist.</p> <p>162. Consider thyroid function tests for children with postural tremor and other symptoms or signs suggestive of thyroid overactivity.</p> <p>163. Refer children with postural tremor for occupational therapy only if the tremor is affecting activities of daily living such as writing, eating or dressing.</p>
Rationale for categorising symptoms	This symptom was not prioritised for an evidence review for children because the committee considered the referral decision to be uncontentious and an evidence review is unlikely to change the decision.
Trade-off between benefits and harms	<p>Recommendation 160 – Tremor with additional neurological signs and symptoms or sudden onset</p> <p>Progressive neurological disorders present with additional symptoms and signs alongside a tremor. Dystonic tremors are extremely rare in children. When they do occur, the child has usually had a long, pre-existing history of dystonia.</p> <p>Tremor can occasionally be the initial symptom of a space-occupying lesion in children. Other signs of space-occupying lesions are usually present on examination, in particular progressive weakness. The tremor may be of sudden onset but a careful informant history is required to confirm that this is genuinely the case. Occasionally, children may present with a sudden onset of tremor related to a specific task. These children should be referred to exclude progressive disorders.</p> <p>Recommendation 161 – Isolated tremor - iatrogenic causes</p> <p>Isolated tremor is a dose-related side effect of sodium valproate and beta-agonists (for example, salbutamol). These drugs should be excluded as a potential cause before a referral is made. If they are thought likely to be the cause of the tremors, the prescriber should consider the potential benefits and harms of reducing the dose, withdrawing, temporarily stopping these drugs or changing to an alternative drug for the underlying condition.</p> <p>Recommendation 162 – Thyroid function tests</p> <p>Hyperthyroidism can be a cause of isolated postural tremor in children and should be excluded before referring. Thyroid function tests (in particular Thyroid Stimulating Hormone [TSH] and free thyroxine [FT4]) are available to non-specialists and should be requested if a postural tremor presents alongside other symptoms suggestive of hyperthyroidism to exclude it as a cause. If hyperthyroidism is confirmed, a referral to paediatric endocrinology is a more appropriate referral pathway than paediatric neurology.</p> <p>For younger children, the referring primary care physician should consider whether to request the blood tests prior to referral if it is likely that the same blood tests</p>

	<p>would be repeated by the specialist. This is to minimise the distress caused by repeated drawing of blood from such young children.</p> <p>Recommendation 163 – Tremor affecting daily living</p> <p>As a tremor is rarely caused by a progressive neurological condition, effective management of the tremor should be the priority. An occupational therapist has the skills to assess how the tremor affects both home and school life. Children’s therapists will monitor the child and refer to paediatric neurology if necessary.</p> <p>A tremor that has not changed over time and is seen in isolation with no other neurological signs and symptoms does not require neurological investigation, but it may need to be monitored. Parents may be anxious, so it is important to reassure them after taking a history and assessing that no further investigation is required.</p>
Trade-off between net clinical effects and costs	<p>The committee was provided with estimates of the number of referrals to neurologists from 2015/16 and how much this cost the NHS. During 2015/16, there were 517,806 first-time neurological outpatient attendances. Using NHS reference costs of an outpatient visit costing £175 and a paediatric outpatient visit costing £285, first-time referrals to neurologists cost approximately £93 million in total, or £87 million for adults and £6 million for children. These estimates were a starting point for the committee to consider whether its recommendations caused additional referrals that would have a significant cost impact on the NHS.</p> <p>The committee agreed that the recommendations did not represent a change from current best practice, and that, viewed along with the rest of this guideline the recommendations should not increase the total number of referrals or referral costs should not increase. The committee agreed that thyroid function tests were either part of routine practice or would be conducted at some point within the patient pathway; therefore, the only change in practice would be to move the test to an earlier point in the pathway. This would not affect total costs to the health service, which should remain unchanged.</p>
Other considerations	<p>Targeted engagement exercise</p> <p>There was a very high level of agreement with this set of recommendations ranging from 82.4% to 100%. Therefore, the recommendations were unchanged except for minor rewording to make them clearer.</p>

8 Reference list

1. Chen L, Lee W, Chambers BR, Dewey HM. Diagnostic accuracy of acute vestibular syndrome at the bedside in a stroke unit. *Journal of Neurology*. 2011; 258(5):855-861
2. Department for Education. Special educational needs in England: January 2016. London. Department for Education, 2016. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/539158/SF_R29_2016_Main_Text.pdf
3. Department of Health. The UK strategy for rare diseases. London. Department of Health, 2013. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/260562/UK_Strategy_for_Rare_Diseases.pdf
4. Diamond IR, Grant RC, Feldman BM, Pencharz PB, Ling SC, Moore AM et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *Journal of Clinical Epidemiology*. 2014; 67(4):401-409
5. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of Internal Medicine*. 2013; 158(4):280-286
6. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification. A study of 153 cases. *Journal of Neurology, Neurosurgery and Psychiatry*. 1990; 53(10):834-843
7. House of Commons Committee of Public Accounts. Services for people with neurological conditions: Seventy-second report of session 2010-12. London. The Stationary Office Limited, 2012. Available from: <https://www.publications.parliament.uk/pa/cm201012/cmselect/cmpubacc/1759/1759.pdf>
8. Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE. HINTS to diagnose stroke in the acute vestibular syndrome: Three-step bedside oculomotor examination more sensitive than early MRI diffusion-weighted imaging. *Stroke*. 2009; 40(11):3504-3510
9. Kerber KA, Meurer WJ, Brown DL, Burke JF, Hofer TP, Tsodikov A et al. Stroke risk stratification in acute dizziness presentations: A prospective imaging-based study. *Neurology*. 2015; 85(21):1869-1878
10. National Audit Office. Services for people with neurological conditions: A progress review London. National Audit Office, 2015. Available from: <https://www.nao.org.uk/wp-content/uploads/2015/07/Services-for-people-with-neurological-conditions-progress-review.pdf>
11. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: <http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview>
12. National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. London. National Institute for Health and Clinical Excellence, 2008. Available from: <https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf>
13. Navi BB, Kamel H, Shah MP, Grossman AW, Wong C, Poisson SN et al. Rate and predictors of serious neurologic causes of dizziness in the emergency department. *Mayo Clinic Proceedings*. 2012; 87(11):1080-1088

14. Newman-Toker DE, Kerber KA, Hsieh YH, Pula JH, Omron R, Saber Tehrani AS et al. HINTS outperforms ABCD2 to screen for stroke in acute continuous vertigo and dizziness. *Academic Emergency Medicine*. 2013; 20(10):987-996
15. Newman-Toker DE, Tehrani ASS, Mantokoudis G, Pula JH, Guede CI, Kerber KA et al. Quantitative video-oculography to help diagnose stroke in acute vertigo and dizziness: Toward an ECG for the eyes. *Stroke*. 2013; 44(4):1158-1161
16. Novielli N, Cooper NJ, Abrams KR, Sutton AJ. How is evidence on test performance synthesized for economic decision models of diagnostic tests? A systematic appraisal of Health Technology Assessments in the UK since 1997. *Value in Health*. 2010; 13(8):952-957
17. Public Health England. Defining adult neurological conditions: National Neurology Intelligence Network technical briefing. PHE Publications gateway number: 2104781, 2015.
18. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology*. 2005; 58(10):982-990
19. Reuber M, Mitchell AJ, Howlett SJ, Crimlisk HL, Grunewald RA. Functional symptoms in neurology: questions and answers. *Journal of Neurology, Neurosurgery and Psychiatry*. 2005; 76(3):307-314
20. Review Manager (RevMan) [Computer program]. Version 5. Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration, 2015. Available from: <http://tech.cochrane.org/Revman>
21. Royal College of Physicians. Local adult neurology services for the next decade. Report of a working party. London. RCP, 2011. Available from: <https://www.mstrust.org.uk/sites/default/files/files/Local%20adult%20neurology%20services%20for%20the%20next%20decade.pdf>
22. The Neurological Alliance. The invisible patients: revealing the state of neurology services. London. The Neurological Alliance, 2015. Available from: http://www.neural.org.uk/store/assets/files/495/original/Invisible_patients_-_revealing_the_state_of_neurology_services_final_14_January_2015_.pdf
23. Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in Medicine*. 2002; 21(4):589-624
24. Van Houwelingen HC, Zwinderman KH, Stijnen T. A bivariate approach to meta-analysis. *Statistics in Medicine*. 1993; 12(24):2273-2284
25. WinBUGS [Computer programme] version 1.4. Cambridge. MRC Biostatistics Unit University of Cambridge, 2015. Available from: <http://www.mrc-bsu.cam.ac.uk/software/bugs/the-bugs-project-winbugs/>
26. World Health Organization. Atlas : country resources for neurological disorders 2004. Geneva. World Health Organization, 2004. Available from: http://www.who.int/mental_health/neurology/neurogy_atlas_lr.pdf

9 Acronyms and abbreviations

Acronym or abbreviation	Description
ADEM	Acute disseminated demyelination
ADHD	Attention deficit hyperactivity disorder
AVS	Acute vestibular syndrome
BBPV	Benign paroxysmal positional vertigo
bHIT	Bedside head-impulse test
CAD	Coronary artery disease
CEA	Cost-effectiveness analysis
CFS	Chronic fatigue syndrome
CHF	Chronic heart failure
CI	Confidence interval
CK	Creatine kinase
CNS	Central nervous system
CUA	Cost-utility analysis
DMD	Duchenne muscular dystrophy
DWI	Diffusion-weighted imaging
ECG	Electrocardiogram
ED	Emergency department
EEG	Electroencephalogram
ESR	Erythrocyte sedimentation rate
GBS	Guillain–Barré syndrome
GCA	Giant-cell arteritis
GRADE	Grading of recommendations assessment, development and evaluation
h-HIT	Head-impulse test
HINTS	Head-Impulse—Nystagmus—Test-of-Skew
ICER	Incremental cost-effectiveness ratio
ME	Myalgic encephalopathy or myalgic encephalomyelitis
MVA	Multivariate analysis
NGC	National Guideline Centre
NICE	National Institute of Health Care and Excellence
NPH	Normal pressure hydrocephalus
NPV	Negative predictive value
OECD	Organisation for Economic Co-operation and Development
PPV	Positive predictive value
QALY	Quality adjusted life year
RR	Relative risk
SD	Skew deviation
SP	Smooth pursuit
TIA	Transient ischemic attack
TM	Transverse myelitis
TMJ	Temporomandibular joint disorders
vHIT	Video head-impulse test

Acronym or abbreviation	Description
VN	Vestibular neuritis
vSP	Vertical smooth pursuit

10 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

10.1 Guideline-specific terms

Term	Definition
Abducens nerve palsy	See sixth nerve palsy.
Acute confusion	Sudden onset of decrease in consciousness or cognition that develops over hours or days.
Anosmia	Loss of the sense of smell.
Apraxic gait	Loss of normal sequencing required for walking, without and loss of muscle power, abnormal sensation or incoordination. This can manifest as a short stride length, instability on the feet, difficulty turning, tendency to festinate, or gait initiation failure.
Ataxia	Loss of coordination of either limbs, gait or trunk. Ataxia is often used synonymously with unsteadiness of gait; however, the 2 terms are different. For clarity, see unsteadiness of gait.
Ataxic gait	A wide-based gait and uncoordinated movements.
Bell's palsy	Unilateral lower motor neurone pattern facial weakness. It affects all parts of the face including eyebrows and eye closure.
Beta-adrenergic agonist	Medicine that relaxes the airway smooth muscle.
Brief	Less than 2 hours.
Canthus	The outer or inner corner of the eye, where the eyelids meet.
Cataplexy	Cataplexy occurs when a strong emotion or laughter causes a person to suffer sudden muscle weakness. Consciousness usually remains intact.
Cauda equina syndrome	A serious neurological condition where damage to the cauda equina causes loss of function of the lumbar plexus of the spinal canal below the termination of the spinal cord. It usually presents with lower limb weakness, urinary retention, perianal numbness and loss of anal tone.
Cervical radiculopathy	This occurs when a nerve in the neck is compressed or irritated where it branches away from the spinal cord. It is also known as a pinched nerve. This can cause pain to radiate into the shoulder, down the arm and into the hand as well as cause muscle weakness.
Chorea	Involuntary fidgety movement.
Clumsiness	Poor coordination.
Cranial arteritis	See giant-cell arteritis.
Craniosynostosis or cranial synostosis	A rare condition in which a baby is born with an abnormally shaped skull.
Creatine Kinase test	A test to measure the level of creatine kinase in the brain, skeletal muscles and heart. An elevated level of creatine kinase can be seen in conditions that produce damage to the skeletal muscles or brain.
Dense amnesia	An episode of an inability to form new memories and recall the recent past.
Dizziness	A subjective sensation of spinning (vertigo) or a more vague sensation of unsteadiness and sometimes a feeling of light-headedness or pre-syncope.
Duchenne muscular dystrophy	A genetic disorder characterized by progressive muscle degeneration and weakness, beginning around the age of 4 in boys.

Term	Definition
Dysgeusia	A condition in which a foul, salty, rancid, or metallic taste sensation persists in the mouth.
Dysphonia	Distortion of quality of speech for example a hoarse voice, wobbly voice, or a soft talker.
Dyspraxia	Coordination difficulties. Differentiation between developmental delay and motor planning. Inability to plan and carry out motor functions despite no loss of power, sensation or cerebellar incoordination.
Dystonia	A movement disorder where a person's muscles contract uncontrollably. Dystonia can affect 1 muscle, a muscle group, or the entire body.
Epley manoeuvre	A manoeuvre used to treat benign paroxysmal positional vertigo of the posterior or anterior canals. The Epley manoeuvre is also referred to as the repositioning manoeuvre.
Epworth sleepiness score	This is a subjective measure of a person's sleepiness.
Fibromyalgia	A condition characterised by chronic, widespread musculoskeletal pain, fatigue and a heightened pain response to pressure.
Functional neurological disorder	A condition in which patients experience neurological symptoms in the absence of any identifiable causative physical or structural abnormality.
Functional symptoms	A subjective manifestation of illness in the absence of any identifiable causative physical or structural abnormality.
Fundoscopy	See ophthalmoscopy.
Giant-cell arteritis	Inflammatory disease of blood vessels most commonly involving large and medium arteries of the head, predominantly the branches of the external carotid artery.
Guillain–Barré syndrome	Rapid-onset muscle weakness and sensory symptoms caused by the immune system damaging the peripheral nervous system.
Hallpike manoeuvre	The Dix–Hallpike test, or Nysten–Barany test, is a diagnostic manoeuvre used to identify benign paroxysmal positional vertigo.
HINTS test	A 3-part exam including the horizontal head impulse test, the nystagmus test, and the test of skew deviation.
Horton disease	See giant-cell arteritis.
Hypotonia	Floppiness or low or reduced muscle tone or strength.
Immediate referral	As soon as possible; within a few hours; the same day.
Labyrinthitis	Inflammation of the inner ear. It can result in vertigo, possible hearing loss or ringing in the ears.
Laryngeal dystonia	The involuntary contractions of the vocal chords. Laryngeal dystonia affects the vocal chords permanently although its strength can vary. It presents as a hoarse, husky, whispery or wobbly voice.
Lumbar canal stenosis	Narrowing of the intraspinal lumbar canal, causing nerve root injury. This commonly presents with neurogenic claudication (pain that is exacerbated by walking or standing, and relieved by sitting or lying down).
Lymphadenopathy	Abnormal lymph nodes size, number or consistency. Also called adenopathy.
Macrocephaly	A child's head circumference that measures greater than the 98 th percentile.
Meningism	This 3-symptom syndrome comprises neck stiffness, intolerance of bright light and headache.

Term	Definition
Motor development delay	The lack of development of skills that require muscle involvement, such as crawling, running and jumping, within an expected age range.
Narcolepsy	A long-term brain disorder that causes sleep attacks – falling asleep suddenly and without warning.
Non-epileptic paroxysmal events	Intermittent, sudden-onset non-epileptic seizures that mimic an epileptic seizure but do not involve abnormal, rhythmic discharges of cortical neurons. These are often behavioural rather than neurological. Some differential diagnoses include temper tantrums and breath-holding.
Nystagmus	A regular rhythmic movement of the eyes, which can either consist of an alternating slow drift followed by a fast jerk or continuous slow oscillations.
Ophthalmoscopy	A test to see inside the fundus and other structures of the eye using an ophthalmoscope (or fundoscope).
Plagiocephaly	Flat head syndrome (babies).
Posterior fossa tumour	A swelling or abnormal growth in the posterior fossa, a small space in the skull found near the bottom of the skull by the brainstem and cerebellum.
Postural tremor	Tremor on maintained posture.
Rapidly progressive	Hours to days.
Referral	Routine referral unless otherwise specified.
Repositioning manoeuvre	See Epley manoeuvre.
Saddle anaesthesia	The loss of sensation restricted to the area of the buttocks, perineum and inner surfaces of the thighs. It is frequently associated with cauda equina syndrome. See cauda equina syndrome.
Sensory symptoms	Sensory symptoms are abnormal sensations that can include positive and negative symptoms. Positive symptoms include tingling, pain or pins and needles, and negative symptoms can include numbness.
Simple motor tic	A single, repetitive, involuntary and transient movement. It is not associated with anxiety or compulsive behaviours.
Sixth nerve palsy	Dysfunction of the cranial nerve VI (the abducens nerve) responsible for contracting the lateral rectus muscle to abduct the eye. See abducens nerve palsy.
Slowly progressive	Weeks to months.
Sodium valproate	Medication primarily used to treat epilepsy and bipolar disorder and as a mood stabiliser.
Squint head	Asymmetrical head shape.
Standardised growth chart	A measurement used by paediatricians and other healthcare providers to follow a child's growth over time.
Stereotyped	The same each time.
'Stocking' or 'glove and stocking' persistent altered sensation	A pattern of peripheral nerve disease characterised by a sharp demarcated and length dependent loss of pain, touch, temperature, joint position and vibration sensation, accompanied by weakness, muscular atrophy and loss of tendon reflexes. For example, the 'stocking' pattern of distal diabetic polyneuropathy characterised by waxing and waning paraesthesias that worsen at night.
Strabismus	Squint.
Temporal arteritis	See giant-cell arteritis.
Test of skew	A test to determine skew deviation (vertical ocular misalignment, vertical strabismus, vertical heterotopia, or vertical squint).

Term	Definition
Tragus	A prominence on the inner side of the external ear, in front of and partly closing the passage to the organs of hearing.
Tummy time	While awake, babies lie prone on their tummies for a supervised period.
Unsteadiness of gait	An abnormality in walking that can be caused by disease of or damage to the legs and feet (including the bones, joints, blood vessels, muscles, and other soft tissues) or to the nervous system that controls the movements necessary for walking. Unsteadiness of gait is often used synonymously with ataxia; however, the 2 terms are different. For clarity, see ataxia.
Urgent referral	Within 2 weeks.
Vasovagal syncope	A loss of consciousness mediated by the vagus nerve. It is usually characterised by a self-limited period of hypotension with bradycardia or peripheral vasodilation. Vasovagal syncope is the most common type of fainting, and can occur in response to heat, stress or standing for a long period of time.
Vestibular neuritis	See labyrinthitis.

10.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base-case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples, see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.

Term	Definition
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case-control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the

Term	Definition
	<p>‘true’ population blood pressure is not higher than 150 and not lower than 110”. In such a case, the 95% CI would be 110 to 150.</p> <p>A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).</p>
Confounding factor	<p>Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with.</p> <p>For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore, age is a confounding factor.</p>
Consensus methods	<p>Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.</p>
Control group	<p>A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called ‘usual care’) or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences.</p> <p>Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.</p>
Cost–benefit analysis (CBA)	<p>Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.</p>
Cost–consequences analysis (CCA)	<p>Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.</p>
Cost-effectiveness analysis (CEA)	<p>Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).</p>
Cost-effectiveness model	<p>An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.</p>
Cost–utility analysis (CUA)	<p>Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.</p>
Decision analysis	<p>An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.</p>

Term	Definition
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.

Term	Definition
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as (£20,000 × QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).

Term	Definition
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with negative test results who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: $TN/(TN+FN)$
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as $(£20,000 \times \text{mean QALYs}) - \text{mean cost}$. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group.

Term	Definition
	Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the ‘reference category’, and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public’s health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people’s health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone’s health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with positive test results who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: $TP/(TP+FP)$
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Prevalence	See Pre-test probability.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is

Term	Definition
	associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested; the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months

Term	Definition
	<p>pregnant, but would probably also include those who are 5 and 7 months pregnant.</p> <p>If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative').</p> <p>Breast screening is a 'real-life' example. The number of women who are recalled for a second breast-screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.</p>
Sensitivity analysis	<p>A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.</p> <p>One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.</p> <p>Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated.</p> <p>Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified.</p> <p>Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).</p>
Significance (statistical)	<p>A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$).</p>
Specificity	<p>The proportion of true negatives that are correctly identified as such. For example, in diagnostic testing, the specificity is the proportion of non-cases correctly diagnosed as non-cases.</p> <p>See related term 'Sensitivity'.</p> <p>In terms of literature searching, a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.</p>
Stakeholder	<p>An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:</p> <ul style="list-style-type: none"> • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	<p>See Markov model</p>
Systematic review	<p>A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.</p>
Time horizon	<p>The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.</p>

Term	Definition
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis that separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYES).