

Suspected neurological conditions

Suspected neurological conditions: recognition and referral

NICE guideline 127

Appendices A–R

May 2019

Final version

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#), [Scottish Government](#), and [Northern Ireland Executive](#). All NICE guidance is subject to regular review and may be updated or withdrawn.

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Appendices

Appendix A: Scope

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Guideline scope

Suspected neurological conditions: recognition and referral

Topic

The Department of Health in England has asked NICE to develop a clinical guideline on the recognition and referral of suspected neurological conditions.

For more information about why this guideline is being developed, and how the guideline will fit into current practice, see the [context](#) section.

Who the guideline is for

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

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the [Welsh Government](#), [Scottish Government](#), and [Northern Ireland Executive](#).

Equality considerations

NICE has carried out [an equality impact assessment](#) during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to disabilities, communication difficulties, functional symptoms and psychiatric disorders.

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1 What the guideline is about

1.1 *Who is the focus?*

Groups that will be covered

- 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.

Groups that will not be covered

- Neonates (infants aged 28 days and under)

1.2 *Settings*

- Primary and secondary care.

1.3 *Activities, services or aspects of care*

Key areas that will be covered

- 1 Indications for referral to specialist care, including referral for people with existing neurological conditions in the event of a change in symptoms.
- 2 Examinations, assessment tools and investigative tests that non-specialists could use to help them decide whether a person with symptoms suggestive of a neurological condition should undergo further investigation or be referred to a specialist.
- 3 Information, support and initial management advice for people with a suspected neurological condition and their family members and carers.

Areas that will not be covered

- 1 Assessment, diagnosis and management of suspected neurological problems after referral to specialist neurological services.
- 2 Neurological conditions for which recognition and referral by non-specialists is already adequately covered by NICE guidance that is published or in development. If recognition and/or referral are already covered in existing NICE guidance, then this guideline will cross-refer.

1.4 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and personal social services (PSS) perspective, as appropriate.

1.5 Key issues and questions

While writing this scope, we have identified the following key issues, and key questions related to them:

- 1 Indications for referral to specialist care.
 - 1.1 Which criteria (symptoms, signs, risk factors and red flags) indicate the need for referral for further neurological assessment?
 - 1.2 Which criteria (symptoms, signs and risk factors) indicate there is no need for referral for further neurological assessment?
- 2 Examinations, assessment tools and investigative tests that non-specialists could use to help them decide whether a person with symptoms suggestive of a neurological condition should have further investigation or be referred to a specialist.
 - 2.1 What examinations should non-specialists carry out when a person presents with symptoms suggestive of a neurological condition?
 - 2.2 What assessment tools, such as algorithms, could non-specialists use when a person presents with symptoms suggestive of a neurological condition?
 - 2.3 What investigative tests should non-specialists use when a person presents with symptoms suggestive of a neurological condition?
- 3 Information, support and initial management advice for people with a suspected neurological condition and their family members and carers.
 - 3.1 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 key questions may be used to develop more detailed review questions, which guide the systematic review of the literature.

1.6 Main outcomes

The main outcomes that will be considered when searching for and assessing the evidence are:

- 1 Time to referral.
- 2 Time to diagnosis.
- 3 Number of referrals.
- 4 Positive predictive value of symptoms.
- 5 Diagnostic accuracy of tests.
- 6 Patient satisfaction.
- 7 Carer satisfaction.
- 8 Quality of life.

2 Links with other NICE guidance, NICE quality standards, and NICE Pathways

2.1 NICE guidance

NICE guidance about the experience of people using NHS services

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to neurological conditions:

- [Patient experience in adult NHS services](#) (2012) NICE guideline CG138

NICE guidance in development that is closely related to this guideline

NICE is currently developing the following guidance that is closely related to this guideline:

- [Motor Neurone Disease: assessment and management](#). NICE guideline. Publication expected February 2016.

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- [Cerebral palsy: diagnosis and management](#). NICE guideline. Publication expected January 2017.
- [Parkinson's disease: diagnosis and management in primary and secondary care](#). NICE guideline. Publication expected April 2017.
- [Dementia: assessment, management and support for people living with dementia and their carers](#). NICE guideline. Publication expected September 2017.
- [Primary brain tumours and cerebral metastases](#). NICE guideline. Publication expected July 2018.

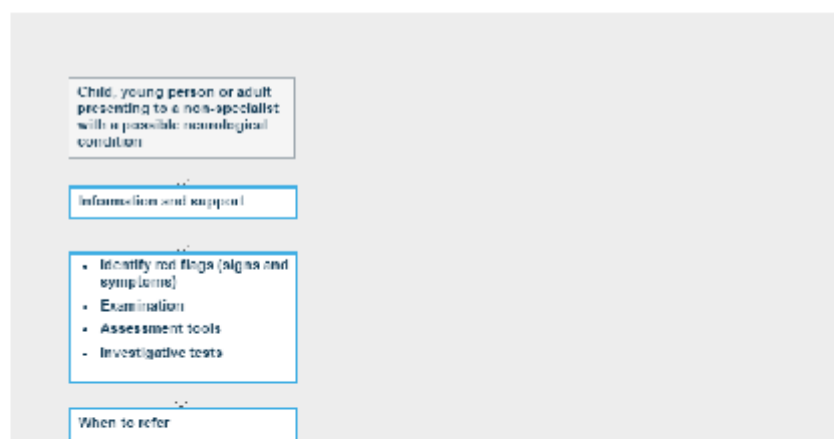
2.2 NICE Pathways

[NICE Pathways](#) bring together all related NICE guidance and associated products on a topic in an interactive topic-based flow chart.

When this guideline is published, the recommendations will be incorporated into the existing pathway on [neurological conditions](#).

An outline of the new pathway, based on the scope, is included below. It will be adapted and more detail added as the recommendations are written during guideline development.

Neurological conditions: recognition and referral overview



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3 Context

3.1 Key facts and figures

Neurological conditions account for about 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 ([Local adult neurology services for the next decade: report of a working party](#), Royal College of Physicians). It is estimated that 2–3% of children will have special needs or some level of disability, with most disabilities 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 as adults. Some conditions can be recovered from completely, but others can cause rapid deterioration or have a slower, more sustained disease course. Some conditions are fairly common, such as migraine (which affects 1 in 5 women or 1 in 15 men) and others are rare, such as Guillain–Barre syndrome (which affects about 1200 people in the UK per year). Most neurological disorders have an impact on quality of life, and some cause serious disability and have a substantial impact on the person and their family members and carers.

People often present with symptoms that are difficult to diagnose (functional symptoms) and can make diagnosing neurological conditions hard. Up to one-fifth of new neurology outpatients have functional symptoms.

3.2 Current practice

People with suspected neurological conditions often need referral to a specialist to be diagnosed. However, some referrals are unnecessary. On the other hand, some people with neurological conditions are initially misdiagnosed or have a delayed referral to a specialist. These issues with referral come from a lack of support and knowledge among non-specialists about neurological conditions. A report from the Neurological Alliance ([The invisible patients: revealing the state of neurology services](#)) found that nearly

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one-third of people with a neurological condition had to see their GP 5 or more times before being referred to a specialist.

People suspected of having neurological conditions may have additional information needs because of the type of investigations that need to be done; as well needing information on the possibility of living with a neurological condition.

3.3 Policy, legislation, regulation and commissioning

Legislation, regulation and guidance

Many specialist professional and charitable bodies have produced guidance for specific neurological conditions, but there is a lack of guidance available for neurological conditions in general. This lack of support, particularly for uncommon neurological conditions, was highlighted by the National Audit Office in the report on [Services for people with neurological conditions](#). It made the recommendation that 'the Department [of Health] should instruct NICE to develop a generic quality standard covering other neurological conditions'.

The [UK Strategy for Rare Diseases](#) (Department of Health) highlights issues with delays to diagnosis and aims to improve the overall patient journey from first contact with the NHS.

4 Further information

This is the final scope, incorporating comments from registered stakeholders during consultation.

The guideline is expected to be published in January 2018.

You can follow progress of the [guideline](#).

Our website has information about how [NICE guidelines](#) are developed.

1 Appendix B: Declarations of interest

2 The September 2014 version of the NICE code of practice for declaring and dealing with conflicts of
3 interest policy was applied to this guideline.

4 Richard Grunewald (Chair)

GC meeting	Declaration of interest	Classification	Action taken
Upon application	Received an honorarium from a pharmaceutical sponsor (UCB) in the last 2 years to provide masterclasses and to lecture on psychogenic non-epileptic seizures and has been offered an honorarium by the same company to provide a lecture in October on the use of clozapine in Parkinson's disease.	Personal financial non-specific	Declare and participate
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
27/03/2017			
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Anna Botsie**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	Sent apologies.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	Sent apologies.	N/A	N/A
Eighth GC meeting 12/12/2016	Sent apologies.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	Sent apologies	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Katherine Carpenter**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	Chair of The British Psychological Society Division of Neuropsychology's Policy Unit (2012–2015); Chair of The British Psychological Society's Division of Neuropsychology Executive Committee (2015 – present); Research (to end March 2016) with The University of Oxford on predicting cognitive outcomes resulting from chronic brain lesions and their surgical treatment. Funding from the Oxford University Hospitals NHS Foundation Trust Biomedical Research Centre; a grant from the BMA held by Dr Jane Adcock, Consultant Neurologist, and Dr Natalie Voets, University of Oxford MRC Research Fellow, FMRIB Centre; and the Cairns Charitable Trust Fund.	Personal non-financial non-specific Personal non-financial non-specific Personal non-financial non-specific	Declare and participate Declare and participate Declare and participate
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	Sent apologies.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	I have been asked by the Neurosciences Directorate to carry out a review of the Clinical Neuropsychological service at the National Hospital for Neurology and Neurosurgery, Queen Square. I expect to receive an NHS capped daily rate in remuneration (£3,000–4,000 approximately)	Personal, financial, non-specific	Declare and participate
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Paul Eunson**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	Trustee of the Castang Foundation, a charity that funds research and education into prevention and management of disability in children. No payment was received for this work other than travelling expenses to attend committee meetings.	Personal non-financial non-specific	Declare and participate
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	Update of paper published 3 years ago on aetiology of cerebral palsy accepted for publication again.	Personal non-financial non-specific	Declare and participate
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	Sent apologies.	N/A	N/A
Twelfth GC meeting 28/03/2017	Sent apologies.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Susanne Friess**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	Sent apologies.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	Sent apologies.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	Sent apologies.	N/A	N/A

1 **Carole Gavin**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
20/04/2016			
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	Sent apologies.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	Sent apologies.	N/A	N/A
Eighth GC meeting 12/12/2016	Sent apologies.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	Sent apologies.	N/A	N/A
Thirteenth GC meeting 10/05/2017	Sent apologies.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Paul Hepple**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Nassif Mansour**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	Clinical lead for Neurology – Kingston CCG. Member of the London Neurosciences Leadership group – NHS England. Chair of the Primary Care Neurology Society	Personal non-financial non-specific Personal non-financial non-specific Personal non-financial non-specific	Declare and participate Declare and participate Declare and participate
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	Sent apologies.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Guy Parckar**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	Chief Executive of the Dystonia Society. The Dystonia Society has in the past received funding from health or pharmaceutical companies (Medtronic, Ipsen, Merz) for specific projects, and funding from the Department of	Non-personal financial non-specific	Declare and participate

GC meeting	Declaration of interest	Classification	Action taken
	<p>Health, although this funding pre-dates GP's appointment and was not received in the last 12 months.</p> <p>Trustee – Neurological Alliance (unpaid voluntary role). The Neurological Alliance receives financial support from health or pharmaceutical companies in the form of corporate membership fees. The industry group comprises:</p> <ul style="list-style-type: none"> - AbbVie - Biogen - Coloplast - Genzyme - Merck Serono - Novartis - UCB 	Non-personal financial non-specific	Declare and participate
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	Trustee of Neurological Alliance – In August, the Alliance produced a report about GP recognition of neurological conditions, which is relevant to the work of the Committee. No direct involvement in the production of the report at all.	Non-personal non-financial specific	Declare and participate
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
13/12/2016			
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	Sent apologies.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Wojteck Rakowicz**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	Association of British Neurologists: Council Member (2013–16): ending May 2016 Unpaid. Association of British Neurologists: ABN advisory group (AAG) for Neuromuscular Disease (2016–19) Unpaid.	Personal non-financial non-specific	Declare and participate
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	MHRA Expert Advisory Panel on Orthopaedic implants	Personal non-financial non-specific	Declare and participate
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	The Muscular Dystrophy Campaign have asked me about the guideline and asked me to make a presentation to their Service Development committee when it has been approved.	Personal non-financial specific	Declare and participate

1 **Sandra Scrivens**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	Sent apologies.	N/A	N/A
Third GC meeting 24/05/2016	Sent apologies.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **Tony Wootton**

GC meeting	Declaration of interest	Classification	Action taken
Upon application	No declarations.	N/A	N/A
First GC meeting 08/03/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting	No change to existing declarations.	N/A	N/A

Suspected neurological conditions
Declarations of interest

GC meeting	Declaration of interest	Classification	Action taken
02/11/2016			
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

1 **NGC team**

GC meeting	Declaration of interest	Classification	Action taken
First GC meeting 08/03/2016	In receipt of NICE commissions	N/A	N/A
Second GC meeting 20/04/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 24/05/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 13/07/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 12/09/2016	No change to existing declarations.	N/A	N/A
Sixth GC meeting 13/09/2016	No change to existing declarations.	N/A	N/A
Seventh GC meeting 02/11/2016	No change to existing declarations.	N/A	N/A
Eighth GC meeting 12/12/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Ninth GC meeting 13/12/2016	No change to existing declarations.	N/A	N/A
Tenth GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eleventh GC meeting 27/03/2017	No change to existing declarations.	N/A	N/A
Twelfth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Thirteenth GC meeting 10/05/2017	No change to existing declarations.	N/A	N/A
Fourteenth GC meeting 10/10/2017	No change to existing declarations.	N/A	N/A

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1 Appendix C: Clinical review protocols

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

C.1.1 Dizziness and vertigo including the HINTS test in adults

C.1.151 Dizziness and vertigo

Component	Description
Review question	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?
Objectives	To identify signs and symptoms that, if presenting with dizziness or vertigo, would indicate a neurological condition that requires referral for further specialist assessment.
Population	Adults and young people who present to a non-specialist with dizziness.
Presence or absence of predictor	The committee identified the following predictors in adults and young people who present with dizziness, for inclusion in the review: <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 exam • intermittency • limb weakness • nystagmus • postural dizziness • skew deviation • tinnitus • vomiting.
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"> ○ 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

Component	Description
	<ul style="list-style-type: none"> o vertebrobasilar insufficiency.
Study design	Prospective or retrospective cohort studies with multivariate analysis
Exclusions	<ul style="list-style-type: none"> • Neonates (infants aged 28 days and under) • Studies unadjusted for any of the identified predictors listed above • Studies with univariate analysis only
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • ataxia • cranial nerve disorder (the committee specified the 8th nerve) • epilepsy • functional Disorders • headaches and migraine • multiple sclerosis and inflammatory disorders • tumours of the nervous system • catch-all group – rare and other neurological diseases. <p>The following neurological condition groups will not be included in the search strategy:</p> <ul style="list-style-type: none"> • central nervous system infections • development disorders • neuromuscular diseases • peripheral nerve disorders • sleep disorders • traumatic brain and spine injury. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016</i></p>
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Statistical outputs may include sensitivity, specificity, adjusted odds ratios and AUC. • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings that the committee evaluated to be generalisable to a non-specialist setting will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with dizziness or vertigo.

C.1.112 HINTS test

Component	Description
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?
Objectives	To evaluate the diagnostic accuracy of HINTS test in diagnosing a central nervous system cause for 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.

Study design	Possible designs include cross sectional, cohort studies (including both retrospective and prospective analyses). Case-control studies will only be included if there is no other evidence as they are biased.
Population	All people with new onset vertigo or dizziness suspected (or under investigation for) stroke or MS
Setting	Secondary care settings for example, emergency departments
Index test	HINTS
Reference standard	MRI
Statistical measures	The following diagnostic accuracy measures of the HINTS test if available: <ul style="list-style-type: none"> • 2x2 tables • Specificity • Sensitivity • Positive or negative predictive value • ROC curves and area under the curve
Other exclusions	None identified
Review strategy	Stratification – groups that cannot be combined: <ul style="list-style-type: none"> • none identified <p>Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity:</p> <ul style="list-style-type: none"> • none identified <p>Appraisal of methodological quality:</p> <ul style="list-style-type: none"> • The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). • The overall quality of the evidence will be assessed using an adapted version of GRADE. <p>Synthesis of data:</p> <ul style="list-style-type: none"> • diagnostic meta-analysis will be conducted where appropriate outcome data is available and can be pooled.

C.1.12 Facial pain, atraumatic

Component	Description
Review question	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?
Objectives	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.
Population	Adults who present to a non-specialist with atraumatic facial pain.
Presence or absence of predictor	The committee identified the following predictors in people who present to a non-specialist with atraumatic facial pain for inclusion in the review: <ul style="list-style-type: none"> • double vision • electric shock – elicited by stimulating face • fatigue and malaise

Component	Description
	<ul style="list-style-type: none"> • fever • history of polymyalgia rheumatic • 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 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"> ○ carotid and vertebral artery dissection ○ cluster headache ○ dental pain ○ max sinusitis ○ migraine facial pain ○ occipital neuralgia ○ temporal arteritis ○ tension headache ○ TMJ dysfunction ○ trigeminal neuralgia.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis
Exclusions	<ul style="list-style-type: none"> • Neonates (babies aged 28 days and under) • Children • Studies unadjusted for any of the identified predictors listed above • Studies with univariate analysis only
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • cranial nerve disorder • functional disorders • multiple sclerosis and inflammatory disorders • catch-all group – rare and other neurological diseases. <p>The committee proposed the following additional specific neurological conditions for inclusion in the search strategy:</p> <ul style="list-style-type: none"> • cluster headache • migraine presenting with facial pain. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016</i></p>
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Statistical outputs may include sensitivity, specificity, adjusted odds ratios and AUC. • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings, which the committee evaluated to be generalisable to a non-specialist setting, will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies.

Component	Description
	<ul style="list-style-type: none"> The overall quality of the evidence will be assessed using an adapted version of GRADE. The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with atraumatic facial pain.

C.1.13 Memory failure in adults (Memory tests)

Component	Description
Review question	In people 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?
Objectives	To evaluate the negative predictive value of neuropsychological assessment in ruling out organic memory failure in young patients suspected of early onset dementia
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.
Population	All people having a memory assessment including those with suspected (or under investigation for) memory failure, anxiety and depression, chronic fatigue syndrome, fibromyalgia and pain syndromes
Setting	Primary care
Index tests	<ul style="list-style-type: none"> 6CIT test 7-minute screen ACE-3 questionnaire GP-COG Mini COG Mini-mental exam
Reference standards	<ul style="list-style-type: none"> Clinical examination Specialist diagnosis of dementia
Statistical measures	<p>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 would also be interested in any of the following diagnostic accuracy measures:</p> <ul style="list-style-type: none"> 2x2 tables repeatability (intra-tester reliability) ROC curves and area under the curve Specificity. <p>If the data is available, the committee will be interested the difference in diagnostic accuracy of shorter tests compared to longer ones.</p>
Other exclusions	None
Review strategy	<p>As it is unlikely that papers will have an exact age cut-off of 50 years, papers with an age cut-off close to 50 may be considered after assessment of the directness of the population.</p> <p>Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity:</p> <ul style="list-style-type: none"> language (where tests are administered to non-native language speakers) learning disability <p>Appraisal of methodological quality:</p>

	<ul style="list-style-type: none"> • The risk of bias of each study will be assessed using the QUADAS-2 checklist (per target condition). • The overall quality of the evidence will be assessed using an adapted version of GRADE. <p>Synthesis of data:</p> <ul style="list-style-type: none"> • diagnostic meta-analysis will be conducted where appropriate outcome data is available and can be pooled.
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C.14 Sensory symptoms such as tingling or numbness in adults and children

Component	Description
Review question	In people 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?
Objectives	To identify signs and symptoms that, if presenting with tingling or altered sensation in the body, would indicate a neurological condition requiring referral for further specialist assessment.
Population	People presenting to a non-specialist with tingling or altered sensation in the body stratified into the following 2 groups: <ul style="list-style-type: none"> • Adults, young people and children (>5 years) • Children (<5 years old) and babies
Presence or absence of predictor	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: <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 paresthetica) ○ demyelination ○ drug toxicity – chemotherapy, alcohol, platinum-based drugs ○ functional (hyperventilation) ○ mononeuropathy multiplex ○ peripheral neuropathy ○ radiculopathy ○ seizures ○ small fibre neuropathy ○ TIAs

Component	Description
	<ul style="list-style-type: none"> ○ tethering of the spinal cord.
Study design	Prospective or retrospective cohort studies and case-control studies with multivariate analysis.
Exclusions	<ul style="list-style-type: none"> • Neonates (infants aged 28 days and under) • Studies that are unadjusted for any of the identified predictors listed above • Studies with univariate analysis only
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • epilepsy • functional disorders • multiple sclerosis and inflammatory disorders • peripheral nerve disorders • spondylotic myelopathy and radiculopathy • tumours of the nervous system • catch-all group – rare and other neurological diseases. <p>The following neurological condition groups will not be included in the search strategy:</p> <ul style="list-style-type: none"> • ataxia • central nervous system infections • cranial nerve disorder • development disorders • headaches and migraine • neuromuscular diseases • sleep disorders • traumatic brain and spine injury. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016</i></p>
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Statistical outputs may include sensitivity, specificity, adjusted odds ratios and AUC • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings, which the committee evaluated as generalisable to a non-specialist setting, will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance which has identified early signs and symptoms for neurological conditions which present with tingling or altered sensation in body.

C.15 Tremor in adults

Component	Description
Review question	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?
Objectives	To identify signs and symptoms that if presenting with tremor would indicate a suspected neurological condition that requires referral for further specialist assessment

Component	Description
Population	Adults, young people, and children (>5 years old) who present to a non-specialist with tremor
Presence or absence of clinical predictor	The committee Identified the following predictors: <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.
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"> ○ 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 or retrospective cohort studies and case-control studies with multivariate analysis
Exclusions	<ul style="list-style-type: none"> • Neonates (infants aged 28 days and under) • Infants (<5 years old) as this age group would get referred or have basic investigations done • Studies unadjusted for any of the identified predictors listed above • Studies with univariate analysis only
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • ataxia • development disorders • inflammatory disorders • neuromuscular diseases • parkinsonism and other extrapyramidal disorders or tic disorder • rare and other neurological diseases • tumours of the nervous system. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016</i></p>

Component	Description
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings, which the committee evaluate to be generalizable to a non-specialist setting, will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with tremor.

C.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

C.2.1 Blackouts and other paroxysmal events

Component	Description
Review question	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?
Objectives	To identify signs and symptoms that, if presenting with paroxysmal events, indicate a neurological condition requiring referral for further specialist assessment.
Population	Children and babies who present to a non-specialist with paroxysmal events.
Presence or absence of predictors	<p>The committee identified the following predictors in people who present with paroxysmal events (for example, absences, epileptic seizures, blank spells, involuntary movements) for inclusion in the review:</p> <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.
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
Exclusions	<ul style="list-style-type: none"> • Young people and adults

Component	Description
	<ul style="list-style-type: none"> • Neonates (babies aged 28 days and under) • Studies unadjusted for any of the identified predictors listed above • Studies with univariate analysis
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • ataxia • central nervous system infections • cranial nerve disorder • development disorders • epilepsy • functional disorders • headache and migraine • multiple sclerosis and inflammatory disorders • neuromuscular diseases • Parkinson's disease and other extrapyramidal disorders or tic disorder • peripheral nerve disorders • sleep disorders • traumatic brain and spine injury • tumours of the nervous system • catch-all group – rare and other neurological diseases. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016</i></p>
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings, which the committee evaluated to be generalisable to a non-specialist setting, will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with non-epileptic paroxysmal events.

C.2.12 Headache

Component	Description
Review question	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?
Objectives	To identify signs and symptoms that, if presenting with headache, would indicate a suspected neurological condition that requires referral for further specialist assessment.
Population	Children under 12 who present to a non-specialist with headache.
Presence or absence of predictors	<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

Component	Description
	<ul style="list-style-type: none"> • head size • nausea • nocturnal or headaches on awakening • onset of strabismus • 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
Exclusions	<ul style="list-style-type: none"> • Neonates (infants aged 28 days and under) • Adults and young people aged 12 or over, as these would be covered by CG150 (Headaches in over 12s: diagnosis and management) • Studies unadjusted for any of the identified predictors listed above • Studies with univariate analysis
How the information will be searched	<p>The following neurological condition groups* will form the basis of the search strategy:</p> <ul style="list-style-type: none"> • central nervous system infections • development disorders • functional Disorders • headaches and migraine • tumours of the nervous system • catch-all group – rare and other neurological diseases. <p><i>*Condition groups taken from Defining Adult Neurological Conditions, National Neurology Intelligence Network, April 2016.</i></p>
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Statistical outputs may include sensitivity, specificity, adjusted odds ratios and AUC. • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings that the committee evaluate to be generalisable to a non-specialist setting will be included in the review.

Component	Description
	<ul style="list-style-type: none"> • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with headache.

C.2.13 Head shape or size abnormalities

Component	Description
Review question	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?
Objectives	To identify signs and symptoms which if presenting with abnormal head shape or size would indicate a neurological condition that requires referral for further specialist assessment
Population	Children and babies who present to a non-specialist with abnormal head shape or size
Presence or absence of predictor	<p>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:</p> <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.
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"> ○ familial macrocephaly ○ growing skull fracture ○ hydrocephalus ○ microcephaly ○ multiple suture synostosis ○ positional plagiocephaly ○ single suture synostosis ○ syndromic synostosis.
Study design	Prospective or retrospective cohorts
Exclusions	<ul style="list-style-type: none"> • Neonates (infants aged 28 days and under) • Studies unadjusted for any of the identified predictors listed above <ul style="list-style-type: none"> ○ studies with univariate analysis only

Component	Description
How the information will be searched	The following condition groups will form the basis of the search strategy: <ul style="list-style-type: none"> • central nervous system infections • cranial nerve disorder • development disorders • epilepsy • headaches and migraine • motor neurone disease and spinal muscular atrophy • neuromuscular diseases • peripheral nerve disorders • sleep disorders • traumatic brain and spine injury • tumours of the nervous system • catch-all group – rare and other neurological diseases.
Key confounders	Any of the predictors listed above
The review strategy	<ul style="list-style-type: none"> • Meta-analysis where appropriate will be conducted. • Evidence from indirect settings, which the committee evaluate to be generalisable to a non-specialist setting, will be included in the review. • The risk of bias of each study will be assessed using the QUADAS-2 checklist for diagnostic studies or the NGC checklist for prognostic studies. • The overall quality of the evidence will be assessed using an adapted version of GRADE. • The review may cross-refer to existing NICE guidance, which has identified early signs and symptoms for neurological conditions that present with abnormal head shape or size.

C.2.14 Motor developmental delay and unsteadiness (creatine kinase tests)

Component	Description
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)?
Objectives	To evaluate the accuracy of creatine kinase test in aiding a non-specialist in identifying muscular dystrophy in children and infants under 10 who present with motor developmental delay
Study design	Cohort studies, case control if no other evidence identified
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).
Setting	Non-specialist setting (for example, primary care)
Index test	Creatine kinase
Reference standard (could be more than one)	<ul style="list-style-type: none"> • Diagnosis of the muscular dystrophy at follow-up • Clinical examination
Statistical measures	Diagnostic accuracy of creatine kinase: <ul style="list-style-type: none"> • 2x2 tables • Specificity (low false negative)

	<ul style="list-style-type: none"> • Sensitivity (high) • Positive and negative predictive values • ROC curves and area under the curve.
Other exclusions	Neonates (infants aged 28 days and under)
Review Strategy	<p>Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity:</p> <ul style="list-style-type: none"> • age • muscle injury. <p>Where possible, results for different types of muscular dystrophies will be analysed separately.</p> <p>Appraisal of methodological quality:</p> <ul style="list-style-type: none"> • The risk of bias each study will be assessed using the QUADAS-II checklist (per target condition). • The overall quality of the evidence will be assessed using an adapted version of GRADE. <p>Synthesis of data:</p> <ul style="list-style-type: none"> • diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

1 Appendix D: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocols in appendix D above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix G.
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2000, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).³⁴¹</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.

- If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.
- If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded health economic studies in appendix M.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2000 or later but that depend on unit costs and resource data entirely or predominantly from before 2000 will be rated as 'Not applicable'.
- Studies published before 2000 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

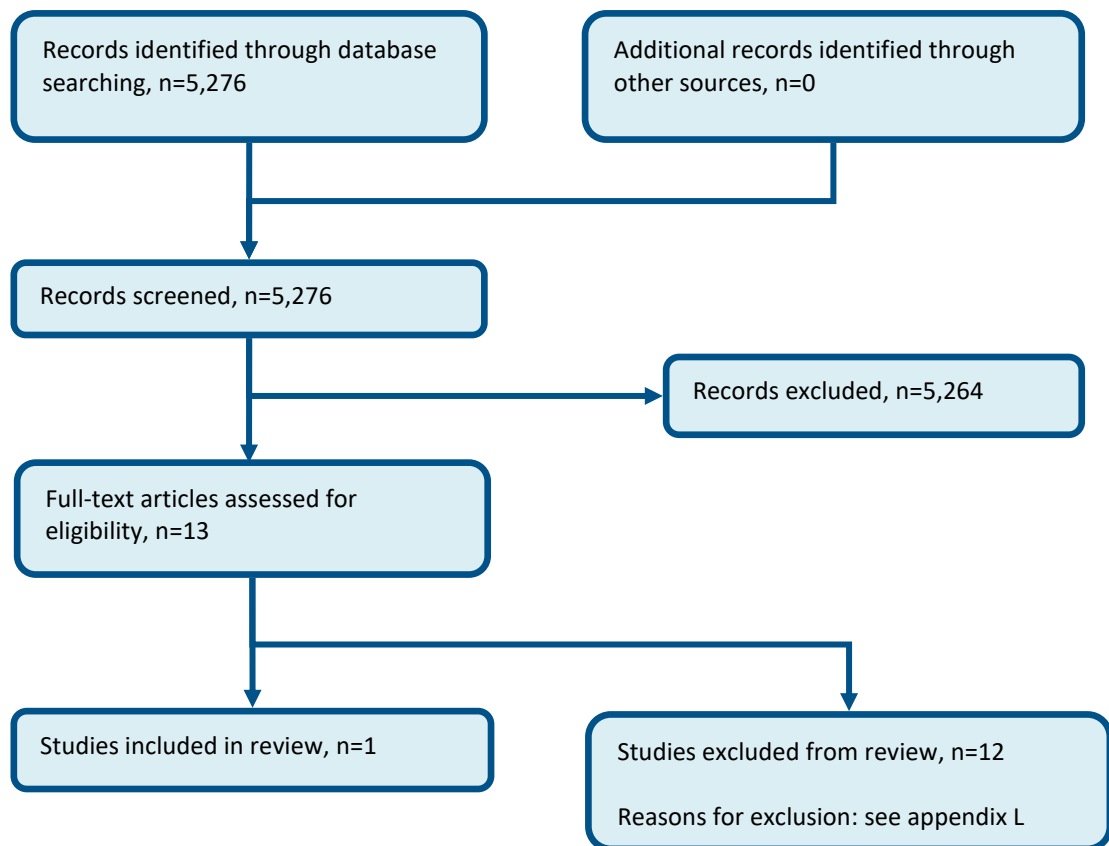
1 Appendix E: Clinical study selection

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

E.1.1 Dizziness and vertigo including the HINTS test in adults

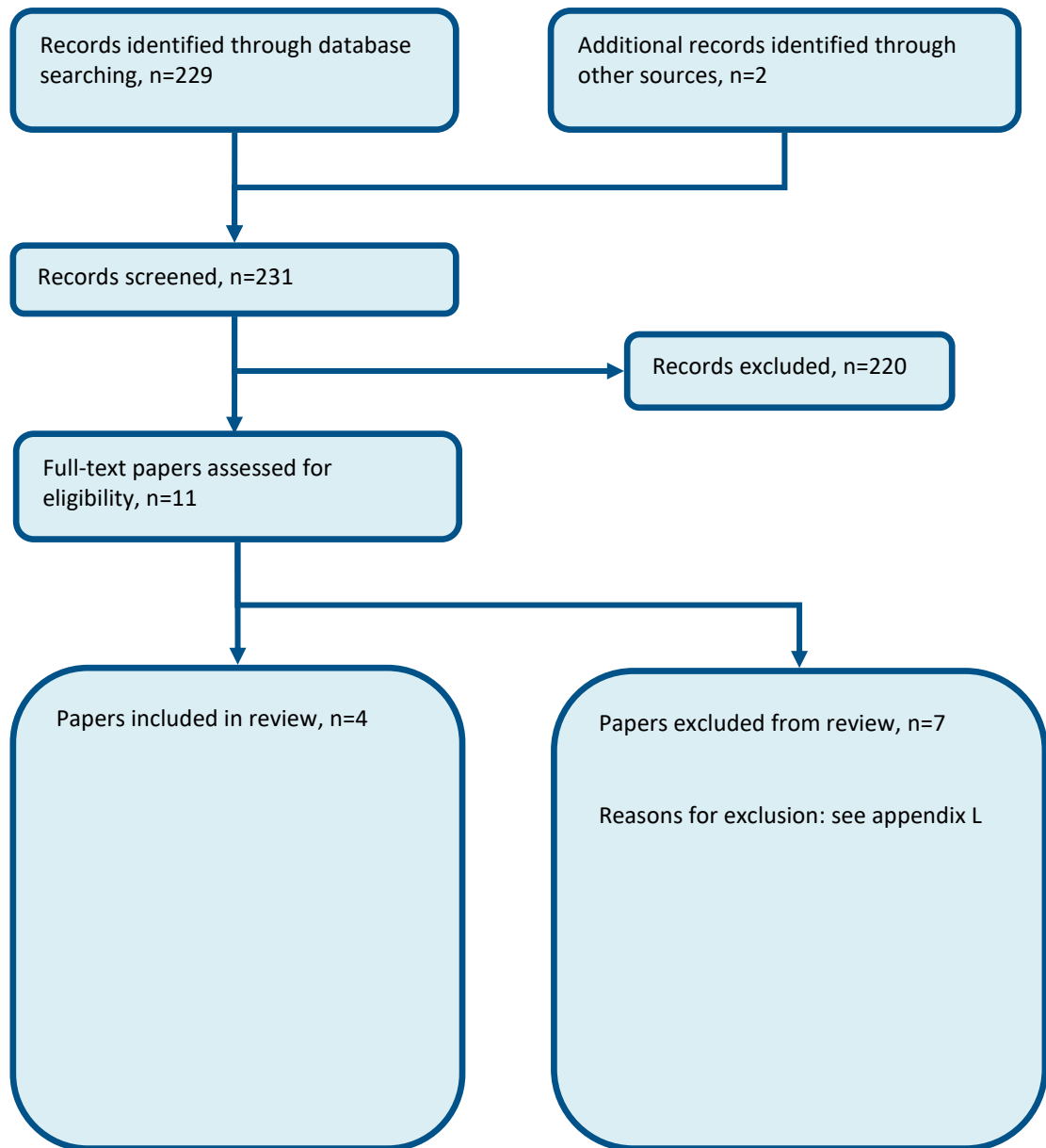
E.1.151 Dizziness and vertigo

Figure 1: Flow diagram of article selection for dizziness review



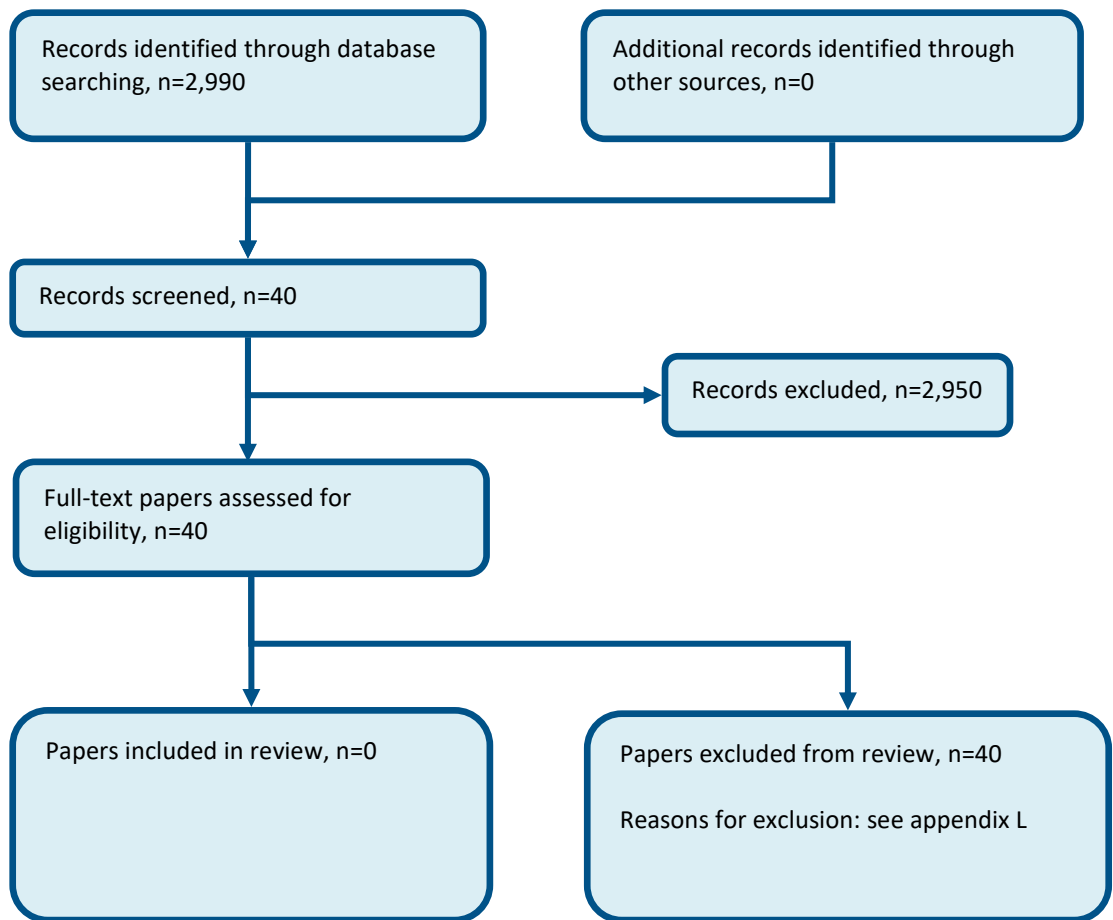
E.1.112 HINTS test

Figure 2: Flow chart of clinical study selection for the review of HINTS



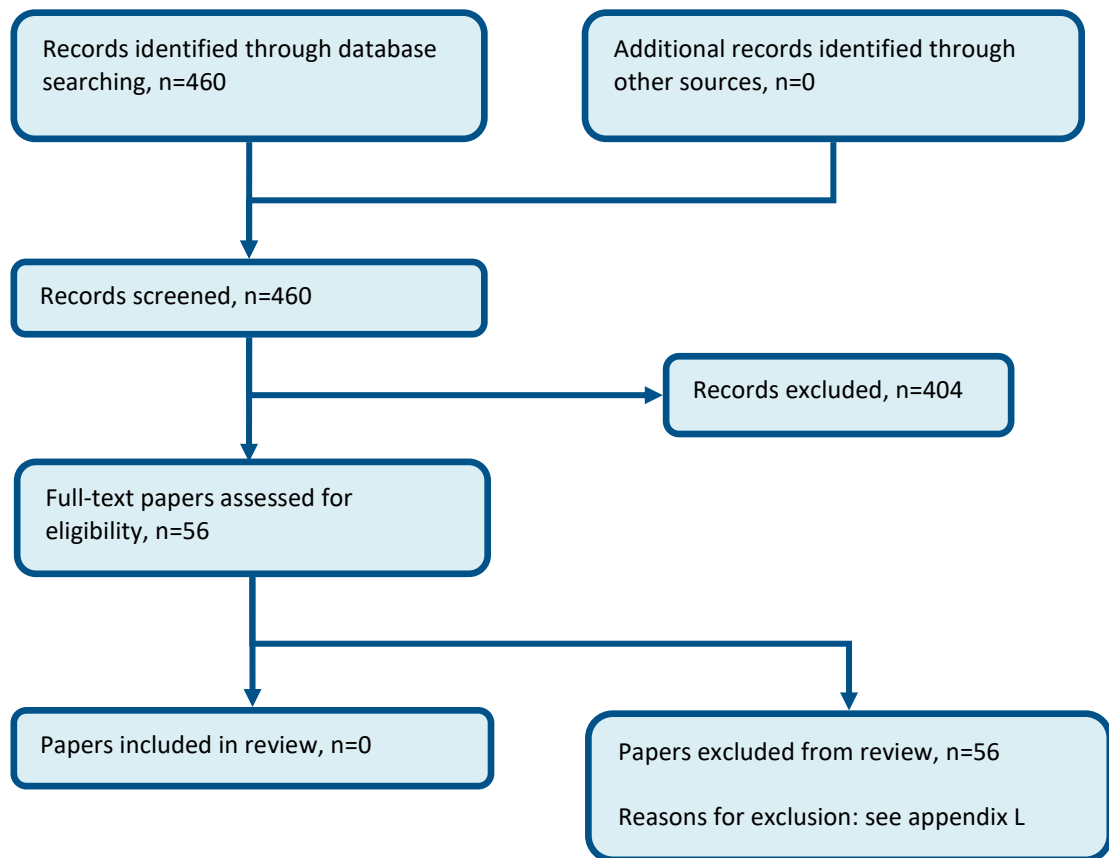
E.1.12 Facial pain, atraumatic

Figure 3: Flow chart of clinical study selection for the review of headaches in children



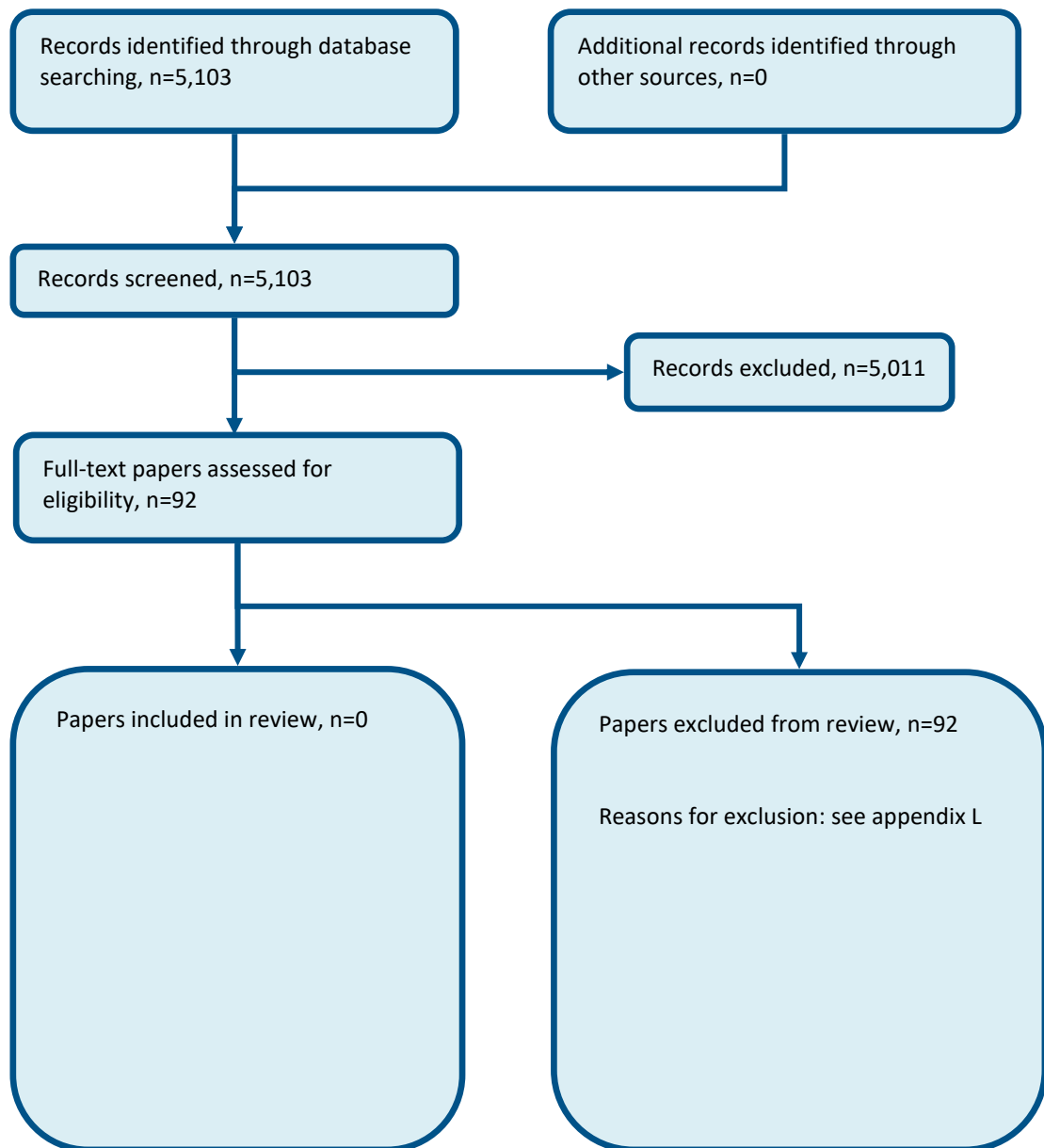
E.1.13 Memory failure in adults (Memory tests)

Figure 4: Flow chart of clinical study selection for the review of memory tests



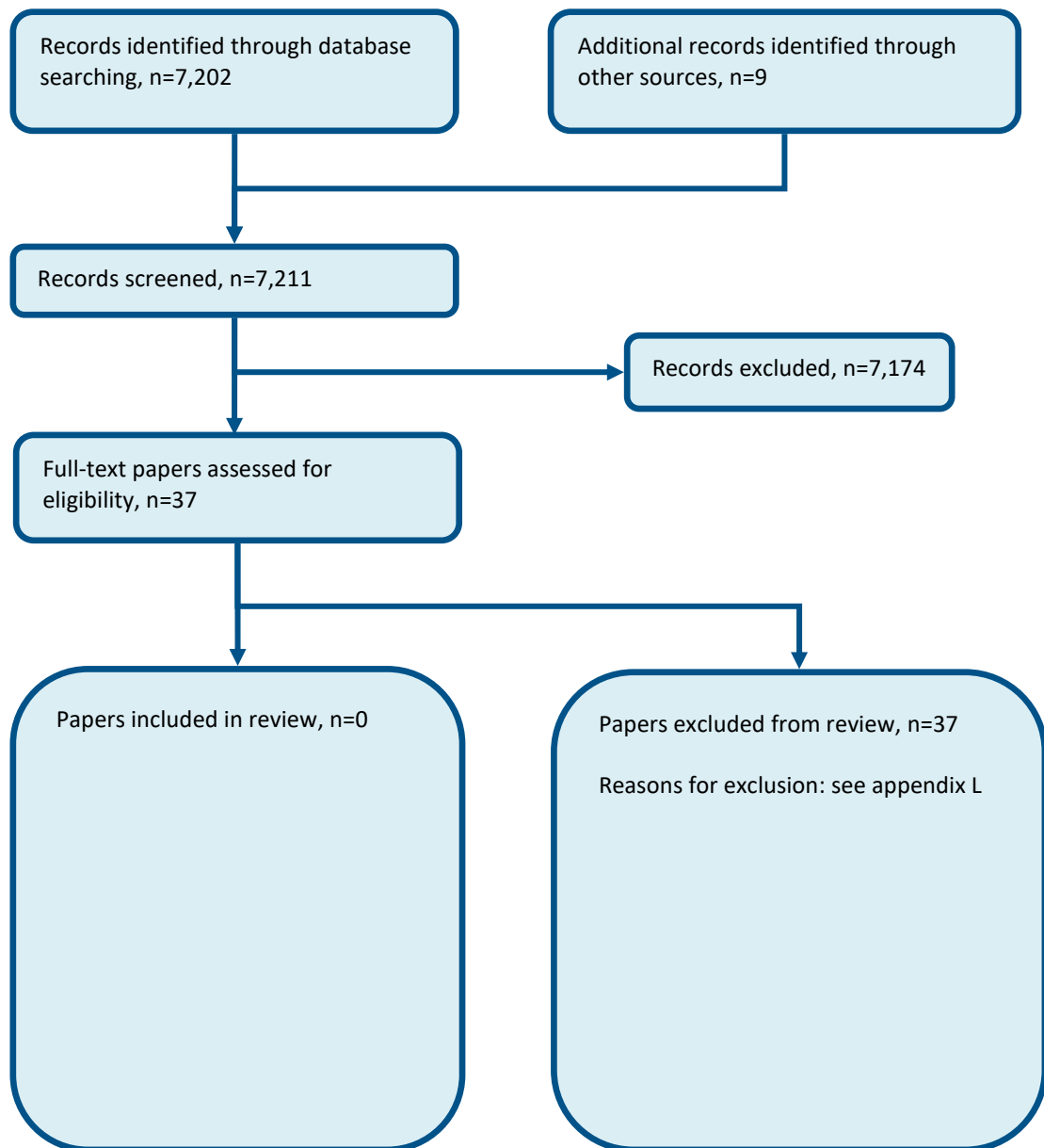
E.14 Sensory symptoms such as tingling or numbness in adults

Figure 5: Flow chart of clinical study selection for the review of tingling



E.1.15 Tremor in adults

Figure 6: Flow chart of clinical study selection for the review of tremor

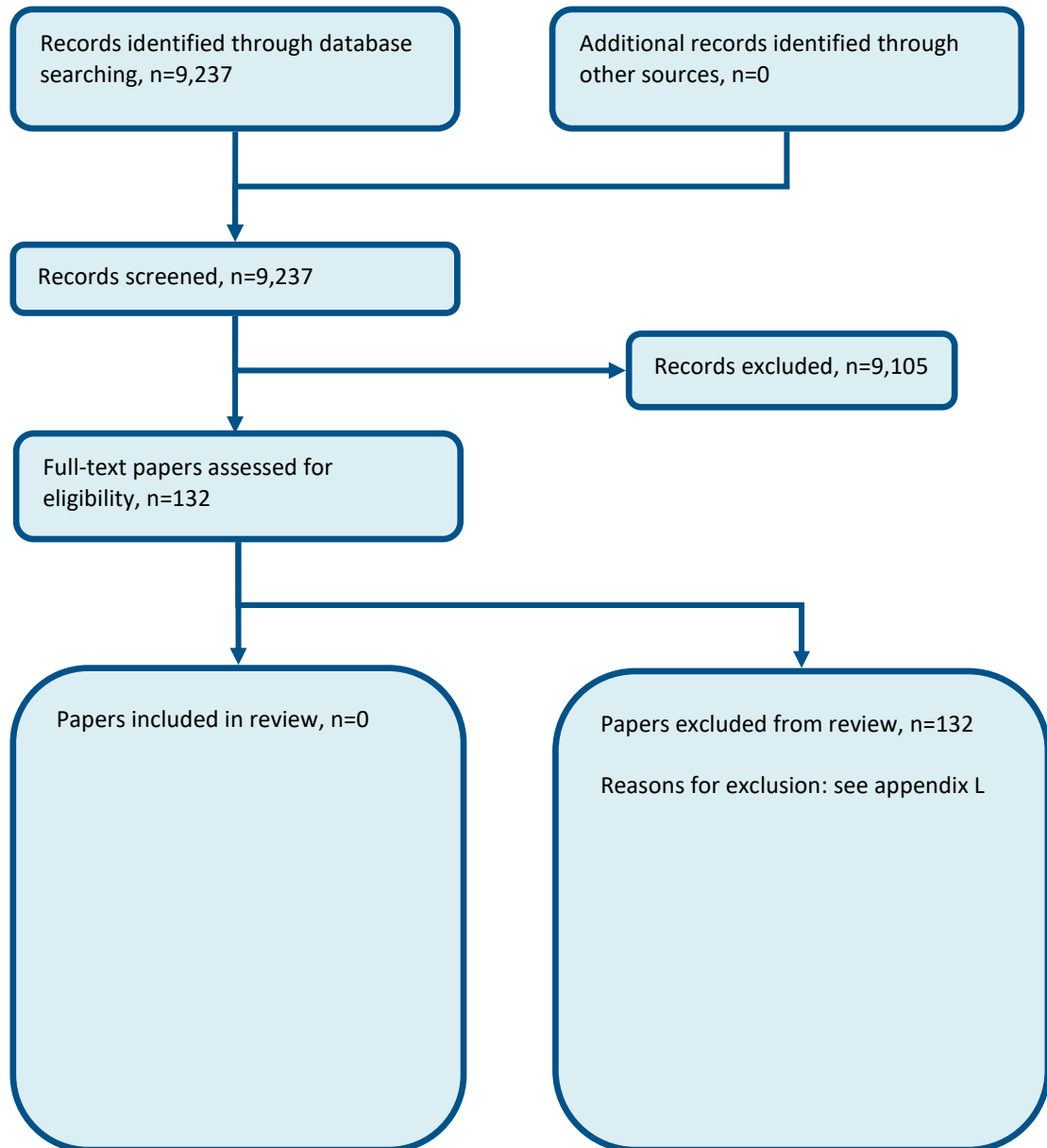


E.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

2

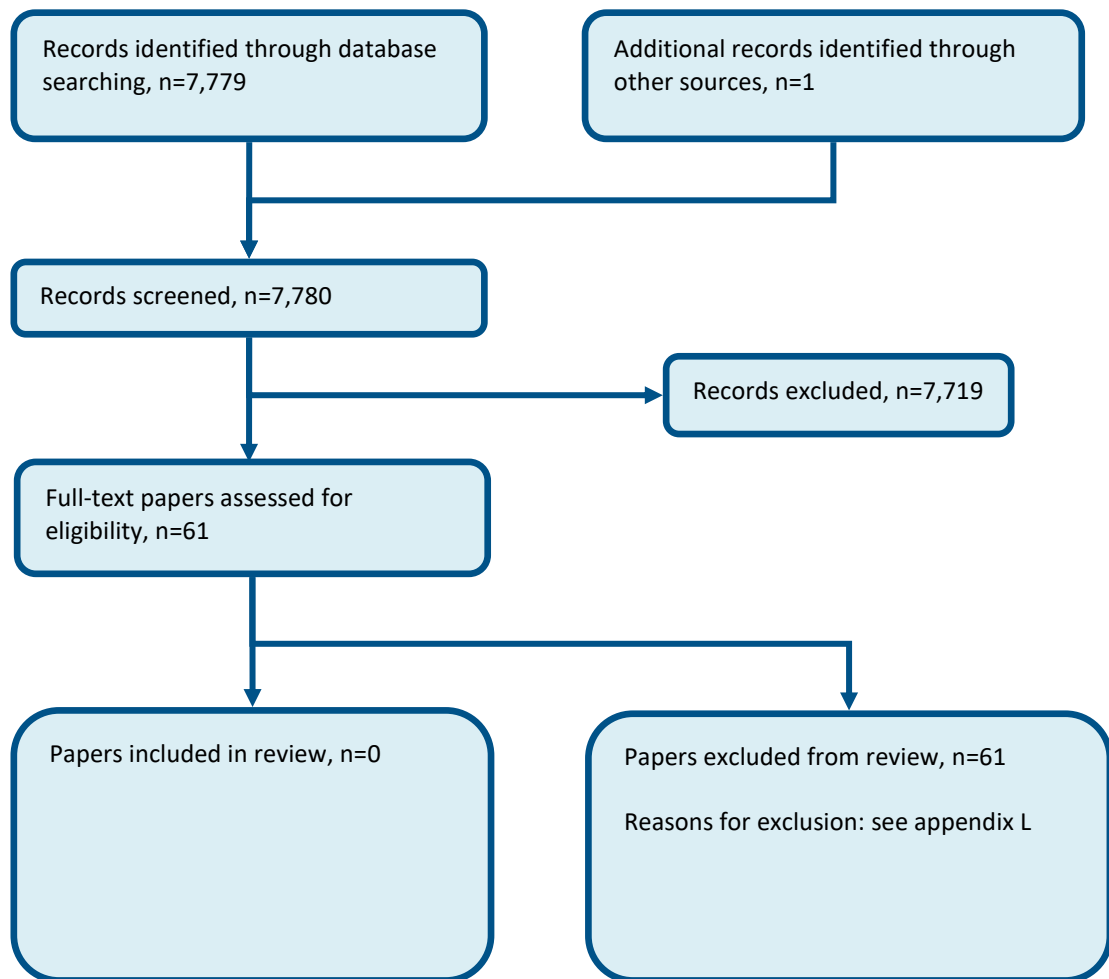
E.2.3 Blackouts and other paroxysmal events

Figure 7: Flow chart of clinical study selection for the review of paroxysmal events



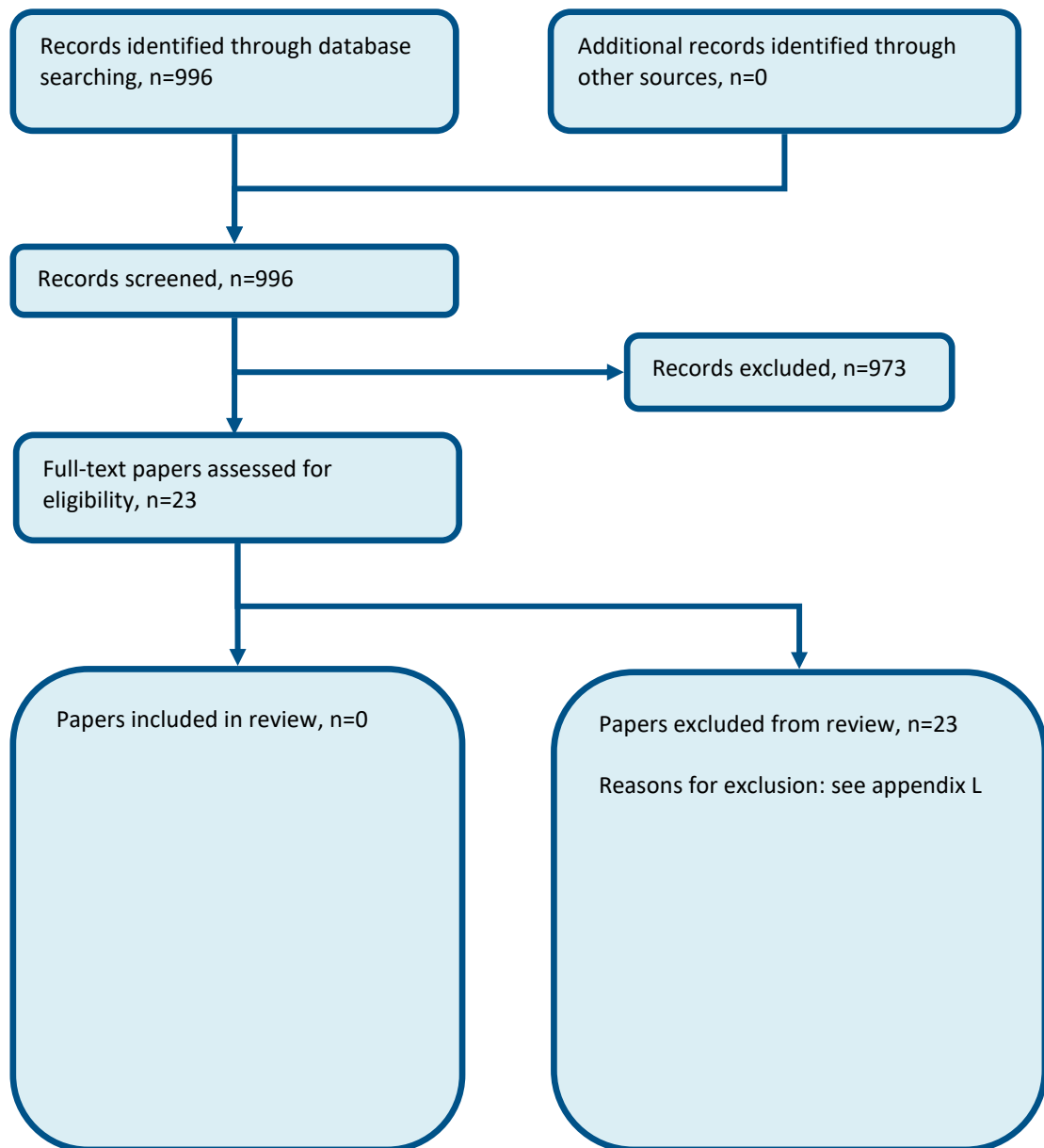
E.2.12 Headache

Figure 8: Flow chart of clinical study selection for the review of headaches in children



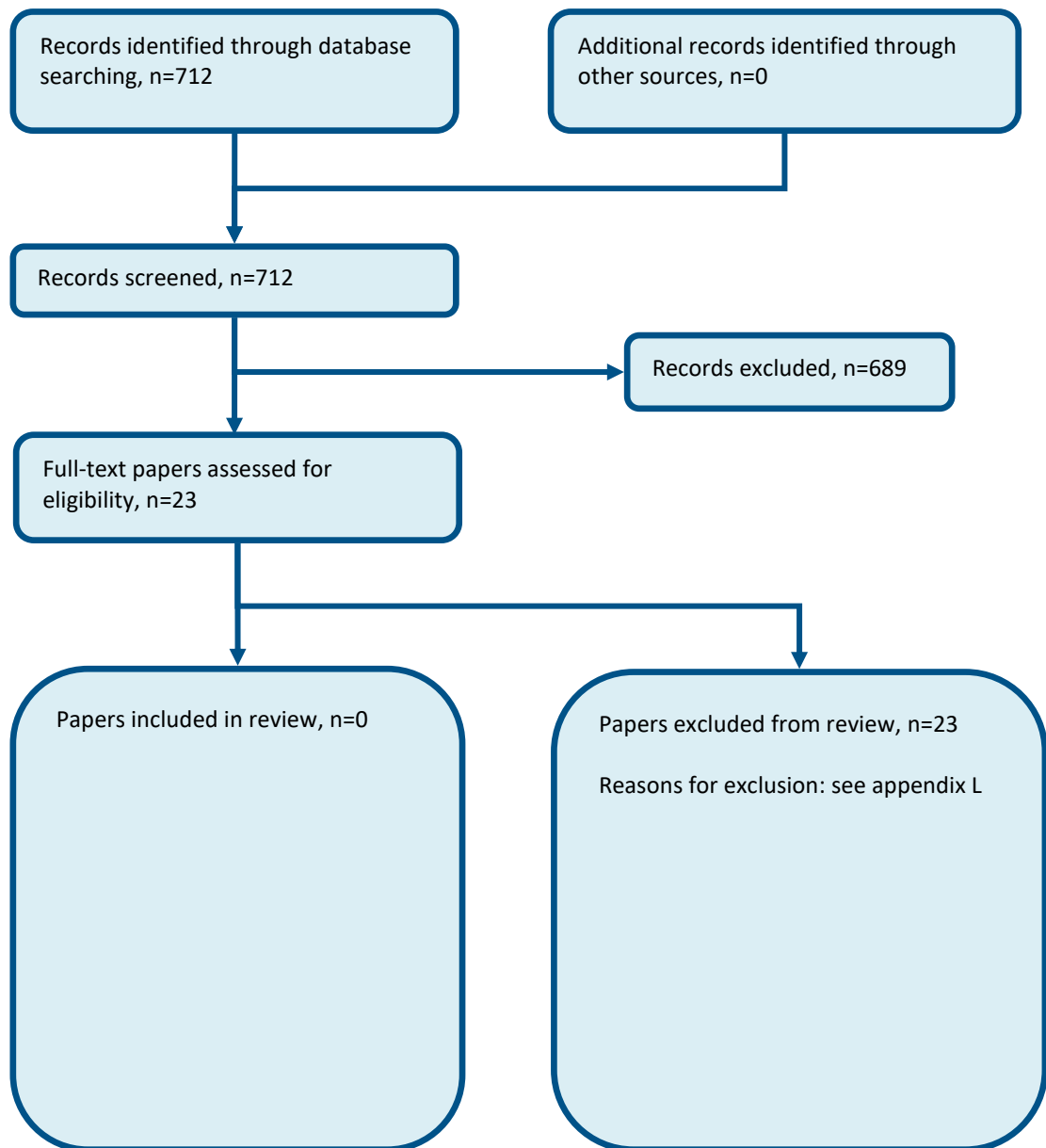
E.2.13 Head shape or size abnormalities

Figure 9: Flow chart of clinical study selection for the review of abnormal head shape or size



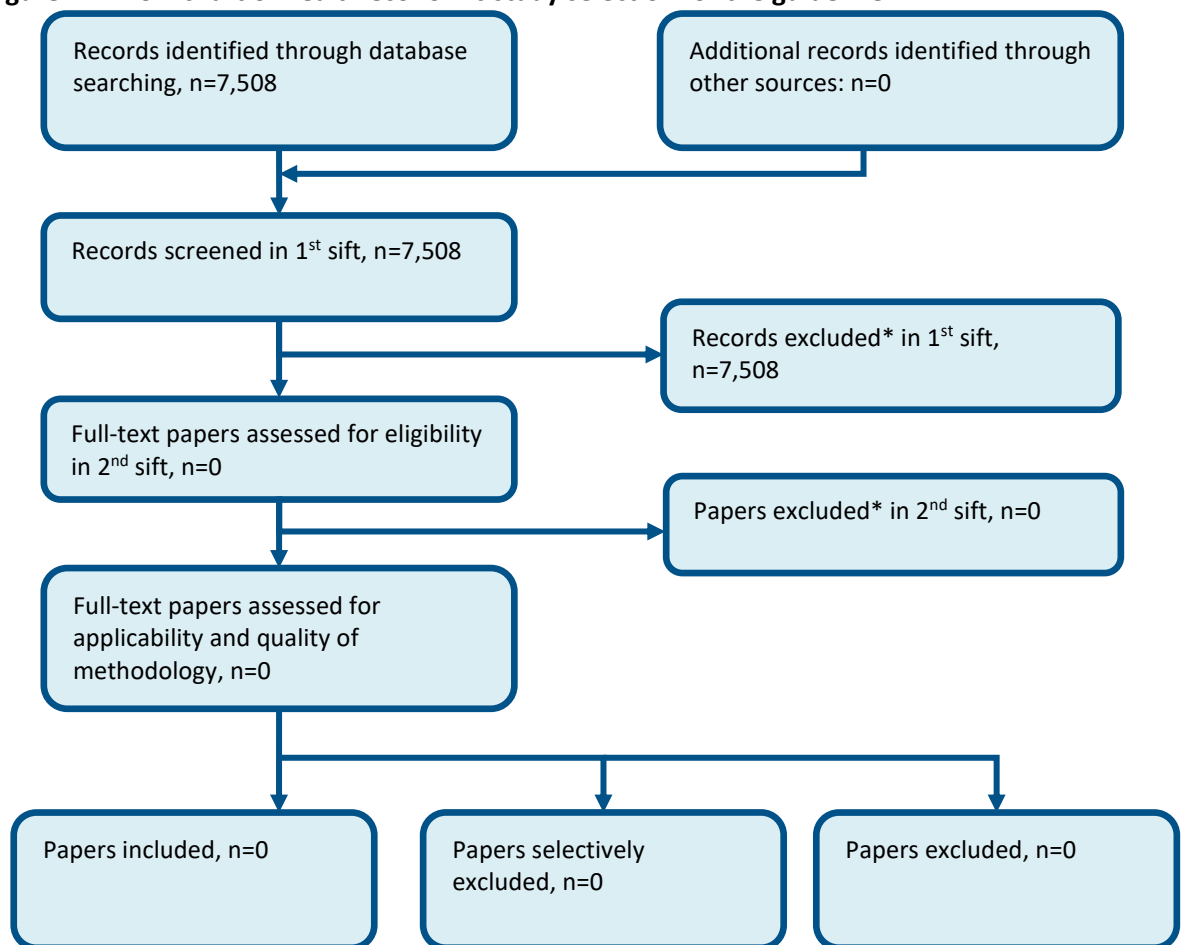
E.2.14 Motor developmental delay and unsteadiness (creatine kinase tests)

Figure 10: Flow chart of clinical study selection for the review of motor developmental delay (CK test)



1 Appendix F: Health economic study selection

Figure 11: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

2

1 **Appendix G: Literature search strategies**

G.1 Contents

Introduction	Search methodology
Section G.2	Population search
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Section G.2.2	Study design and other filters search terms
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G.3.2	Health economic studies [HE]
G.3.3	Observational studies [OBS]
G.3.4	Prognostic and prediction rule studies [PROG]
G.3.5	Signs and symptoms [SIGNS]
Section G.3.5	Searches for specific questions with interventions and relevant populations
G.4.1	Abnormal head shape
G.4.2	Atraumatic facial pain
G.4.3	Dizziness
G.4.4	Headaches in children
G.4.5	HINTS test
G.4.6	Memory tests
G.4.7	Motor developmental delay (CK test)
G.4.8	Paroxysmal events in children
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Section G.4.4	Health economics search terms
G.5.1	Health economic reviews

2 Search strategies used for the Suspected neurological conditions guideline are outlined below and
 3 were run in accordance with the methodology in the NICE guidelines manual 2014, available from
 4 <https://www.nice.org.uk/article/pmg20/>. Searches were run between **3rd June and 9th March 2017**
 5 (see individual questions for exact date). Any studies added to the databases after this date (even
 6 those published prior to this date) were not included unless specifically stated in the text. Where
 7 possible searches were limited to retrieve material published in English.

8 All searches for the **clinical reviews** were run in Medline (OVID) and Embase (OVID). Additionally the
 9 Cochrane Library (Wiley) was searched for certain questions relating to predictive tests, see Table 1.

10 Searches for **clinical prediction studies** were usually constructed combining population terms with
 11 clinical predictor terms and sometimes outcomes. Search filters were added to the search where
 12 appropriate. A search filter for signs and symptoms was also used in questions G.4.2, G.4.3, G.4.4,
 13 G.4.8, G.4.9 and G.4.10.

14 **Table 1: Databases used**

Question	Question number	Databases
Abnormal head shape	G.4.1	Medline and Embase
Atraumatic facial pain	G.4.2	Medline and Embase
Dizziness	G.4.3	Medline and Embase
Headaches in children	G.4.4	Medline and Embase
HINTS test	G.4.5	Medline, Embase and Cochrane

Question	Question number	Databases
Memory tests	G.4.6	Medline, Embase and Cochrane
Motor developmental delay (CK test)	G.4.7	Medline, Embase and Cochrane
Paroxysmal events in children	G.4.8	Medline and Embase
Tingling	G.4.9	Medline and Embase
Tremor	G.4.10	Medline and Embase

1 Searches for the health economic reviews were run in Medline, Embase, the NHS Economic
2 Evaluations Database (NHS EED) and the Health Technology Assessment (HTA) database. NHS EED
3 and HTA databases are hosted by the Centre for Research and Dissemination (CRD). The NHS EED
4 database has not been updated since 2015.

5 For Medline and Embase an economic filter (instead of a study type filter) was added to the same
6 clinical search strategy. Searches in CRD and HEED were constructed using population terms only.

G.2 Population search strategies

8 There is no standard population for this guideline. The guideline covers a range of signs and
9 symptoms each potentially indicating one of several underlying neurological conditions. The
10 underlying conditions varied depending on the sign or symptom being investigated. Consequently,
11 search strategies were created for 18 identified core conditions. For each search sign and symptom,
12 terms were combined with the relevant core conditions. More information about each review
13 question is provided in the review protocols in appendix C and appendix D.

G.2.1 Age groups

15 Searches G.4.1, G.4.4, G.4.7 and G.4.8 only applied to children and infants so a specific filter was
16 applied.

G.2.1.1 Children and babies

18 Medline search terms

1.	exp child/
2.	exp pediatrics/
3.	(child* or toddler* or infant* or baby or babies*).ti,ab.
4.	(pediatric*1 or paediatric*1).ti,ab.
5.	exp infant/
6.	or/1-5

19 Embase search terms

1.	exp child/
2.	exp pediatrics/
3.	(child* or toddler* or infant* or baby or babies*).ti,ab.
4.	(pediatric*1 or paediatric*1).ti,ab.
5.	or/1-4

20 Cochrane search terms

#1.	MeSH descriptor: [child] explode all trees
#2.	MeSH descriptor: [pediatrics] explode all trees
#3.	(child* or toddler* or infant* or baby or babies*).ti,ab

#4.	(pediatric*1 or paediatric*1):ti,ab
#5.	MeSH descriptor: [infant] explode all trees
#6.	(or #1-#5)

G.2.12 Conditions

G.2.221 Ataxia

3 Medline search terms

1.	exp ataxia/ or exp spinocerebellar degenerations/ or exp spinocerebellar ataxias/
2.	(ataxia* or spastic paraplegia*).ti,ab.
3.	(spinocerebellar adj3 (degeneration* or disease)).ti,ab.
4.	or/1-3

4 Embase search terms

1.	exp ataxia/
2.	(ataxia* or spastic paraplegia*).ti,ab.
3.	(spinocerebellar adj3 (degeneration* or disease)).ti,ab.
4.	or/1-3

5 CRD search terms

#1.	MeSH descriptor ataxia explode all trees
#2.	MeSH descriptor spinocerebellar degenerations explode all trees
#3.	MeSH descriptor spinocerebellar ataxias explode all trees
#4.	((ataxia* or spastic paraplegia*)
#5.	((spinocerebellar adj3 (degeneration* or disease)))
#6.	#1 or #2 or #3 or #4 or #5

G.2.262 Brain spinal injury

7 Medline search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((head or brain or spinal or spine) adj3 (injur* or trauma)).ti,ab.
3.	((skull or spinal or spine) adj3 fracture*).ti,ab.
4.	exp spinal injuries/ or spinal cord injuries/ or exp neck injuries/
5.	(whiplash or coma* or concussion*).ti,ab.
6.	(injur* adj3 (intracranial or nerve* or plexus or cervical or thoracic or lumbar or peripheral or cauda equina or cord or lumbosacral or neck or brain or spinal or spine)).ti,ab.
7.	(traumatic adj3 (brain or spine or spinal or oedema* or edema* or haemorrhag* or hemorrhag*).ti,ab.
8.	or/1-7

8 Embase search terms

1.	exp brain injury/ or head injury/ or traumatic brain injury/
2.	((head or brain or spinal or spine) adj3 (injur* or trauma)).ti,ab.
3.	((skull or spinal or spine) adj3 fracture*).ti,ab.

4.	spine injury/ or cervical spine injury/ or spinal cord injury/ or cervical spinal cord injury/ or neck injury/ or whiplash injury/
5.	(whiplash or coma or concussion).ti,ab.
6.	(injur* adj3 (intracranial or nerve* or plexus or cervical or thoracic or lumbar or peripheral or cauda equina or cord or lumbosacral or neck or brain or spinal or spine)).ti,ab.
7.	(traumatic adj3 (brain or spine or spinal or oedema* or haemorrhag*)).ti,ab.
8.	or/1-7

G.2.213 Cranial nerve diseases

2 Medline search terms

1.	cranial nerve diseases/ or exp abducens/ or nerve diseases/ or exp accessory nerve diseases/ or exp glossopharyngeal nerve diseases/ or exp hypoglossal nerve diseases/ or exp olfactory nerve diseases/ or exp optic nerve diseases/ or exp trochlear nerve diseases/ or exp vagus nerve diseases/ or exp vestibulocochlear nerve diseases/
2.	exp facial nerve diseases/
3.	((abducens or nerve or accessory or glossopharyngeal or hypoglossal or olfactory or optic or visual cortex or trochlear or vagus or vestibulocochlear or cochlear) adj3 (disease* or disorder*)).ti,ab.
4.	((cranial or facial or hemifacial or hemi-facial) adj3 (disease* or palsy or palsies* or neuralgia or neuropath* or spasm*)).ti,ab.
5.	(melkersson-rosenthal syndrome or bell's palsy or bells palsy or trigeminal neuralgia or trigeminus neuralgia or postzoster neuralgia or melkersson syndrome or facial myokymia or geniculate ganglionitis).ti,ab.
6.	or/1-5

3 Embase search terms

1.	cranial neuropathy/ or abducens nerve disease/ or accessory nerve disease/ or glossopharyngeal nerve disease/ or hypoglossal nerve disease/ or olfactory nerve disease/ or optic nerve disease/ or vagus nerve disease/ or trochlear nerve disease/ or vestibulocochlear nerve disease/
2.	((abducens or nerve or accessory or glossopharyngeal or hypoglossal or olfactory or optic or visual cortex or trochlear or vagus or vestibulocochlear or cochlear) adj3 (disease* or disorder*)).ti,ab.
3.	((cranial or facial or hemifacial or hemi-facial) adj3 (disease* or palsy or palsies* or neuralgia or neuropath* or spasm*)).ti,ab.
4.	(melkersson-rosenthal syndrome or bell's palsy or bells palsy or trigeminal neuralgia or trigeminus neuralgia or postzoster neuralgia or melkersson syndrome or facial myokymia or geniculate ganglionitis).ti,ab.
5.	bell palsy/
6.	melkersson rosenthal syndrome/
7.	hemifacial spasm/
8.	facial nerve disease/ or hemifacial atrophy/ or face pain/ or herpes zoster oticus/ or moebius syndrome/
9.	trigeminus neuralgia/
10.	or/1-9

4 CRD search terms

#1.	MeSH descriptor cranial nerve diseases
#2.	MeSH descriptor accessory nerve diseases explode all trees
#3.	MeSH descriptor glossopharyngeal nerve diseases explode all trees

#4.	MeSH descriptor olfactory nerve diseases explode all trees
#5.	MeSH descriptor optic nerve diseases
#6.	MeSH descriptor trochlear nerve diseases explode all trees
#7.	MeSH descriptor vagus nerve diseases explode all trees
#8.	MeSH descriptor vestibulocochlear nerve diseases explode all trees
#9.	MeSH descriptor facial nerve diseases explode all trees
#10.	((abducens or nerve or accessory or glossopharyngeal or hypoglossal or olfactory or optic or visual cortex or trochlear or vagus or vestibulocochlear or cochlear) adj3 (disease* or disorder*)))
#11.	((cranial or facial or hemifacial or hemi-facial) adj3 (disease* or palsy or palsies* or neuralgia or neuropath* or spasm*)))
#12.	((melkersson-rosenthal syndrome or bell's palsy or bells palsy or trigeminal neuralgia or trigeminus neuralgia or postzoster neuralgia or melkersson syndrome or facial myokymia or geniculate ganglionitis))
#13.	MeSH descriptor abducens nerve diseases explode all trees
#14.	MeSH descriptor hypoglossal nerve diseases explode all trees
#15.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

G.2.214 Central nervous system diseases

2 Medline search terms

1.	exp central nervous system infections/
2.	exp central nervous system viral diseases/
3.	rabies/
4.	((amoebic or phaeomycotic or anoxic) adj3 (brain abscess* or brain disease*)),ti,ab.
5.	(meningeal tuberculoma or tuberculous meningitis).ti,ab.
6.	rabies.ti,ab.
7.	poliomyelitis.ti,ab.
8.	((post-polio or post polio or postpolio) adj1 syndrome).ti,ab.
9.	(creutzfeldt-jakob disease or panencephalitis or multifocal leukoencephalopath*).ti,ab.
10.	((intracranial or intraspinal or intra-cranial or intra-spinal or intra cranial or intra spinal) adj4 (phlebitis or thrombophlebitis)).ti,ab.
11.	((intracranial or intra-cranial or intraspinal or intra-spinal or extradural or subdural or sub-dural or extra-dural or intraspinal or intra-spinal) adj4 (abscess* or granuloma)).ti,ab.
12.	vertigo.ti,ab.
13.	((central nervous system or cns) adj3 (virus* or infection* or attack* or cysticercosis)).ti,ab.
14.	(meningitis or choriomeningitis or meningococcal).ti,ab.
15.	(encephalitis or meningoencephalitis or meningomyelitis or myelitis or cerebral cryptococcosis or rhinocerebral mucormycosis).ti,ab.
16.	((chagas' disease or tubercularosis) adj3 nervous system).ti,ab.
17.	or/1-16

3 Embase search terms

1.	central nervous system infection/ or brain infection/ or central nervous system tuberculosis/ or exp meningitis/ or exp poliomyelitis/ or exp postpoliomyelitis syndrome/ or rabies/
2.	((amoebic or phaeomycotic or anoxic) adj3 (brain abscess* or brain disease*)),ti,ab.
3.	(meningeal tuberculoma or tuberculous meningitis).ti,ab.
4.	rabies.ti,ab.

5.	poliomyelitis.ti,ab.
6.	((post-polio or post polio or postpolio) adj1 syndrome).ti,ab.
7.	(creutzfeldt-jakob disease or panencephalitis or multifocal leukoencephalopath*).ti,ab.
8.	((intracranial or intraspinal or intra-cranial or intra-spinal or intra cranial or intra spinal) adj4 (phlebitis or thrombophlebitis)).ti,ab.
9.	((intracranial or intra-cranial or intraspinal or intra-spinal or extradural or subdural or sub-dural or extra-dural or intraspinal or intra-spinal) adj4 (abscess* or granuloma)).ti,ab.
10.	vertigo.ti,ab.
11.	((central nervous system or cns) adj3 (virus* or infection* or attack* or cysticercosis)).ti,ab.
12.	(meningitis or choriomeningitis or meningococcal).ti,ab.
13.	(encephalitis or meningoencephalitis or meningomyelitis or myelitis or cerebral cryptococcosis or rhinocerebral mucormycosis).ti,ab.
14.	((chagas' disease or tuberculosis) adj3 nervous system).ti,ab.
15.	or/1-14

1 CRD search terms

#1.	MeSH descriptor central nervous system infections explode all trees
#2.	MeSH descriptor central nervous system viral diseases explode all trees
#3.	MeSH descriptor rabies
#4.	((amoebic or phaeomycotic or anoxic) adj3 (brain abscess* or brain disease*))
#5.	((meningeal tuberculoma or tuberculous meningitis))
#6.	(rabies)
#7.	(poliomyelitis)
#8.	((post-polio or post polio or postpolio) adj1 syndrome))
#9.	((creutzfeldt-jakob disease or panencephalitis or multifocal leukoencephalopath*)
#10.	((intracranial or intraspinal or intra-cranial or intra-spinal or intra cranial or intra spinal) adj4 (phlebitis or thrombophlebitis)))
#11.	((intracranial or intra-cranial or intraspinal or intra-spinal or extradural or subdural or sub-dural or extra-dural or intraspinal or intra-spinal) adj4 (abscess* or granuloma))
#12.	(vertigo)
#13.	((central nervous system or cns) adj3 (virus* or infection* or attack* or cysticercosis)))
#14.	((meningitis or choriomeningitis or meningococcal))
#15.	((encephalitis or meningoencephalitis or meningomyelitis or myelitis or cerebral cryptococcosis or rhinocerebral mucormycosis))
#16.	((chagas' disease or tuberculosis) adj3 nervous system))
#17.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

G.2.25 Developmental disorders

3 Medline search terms

1.	hydrocephalus/
2.	neurocutaneous syndromes/
3.	Neurofibromatosis/
4.	(hydrocephalus or neurofibromatos* or phakomatos* or neurocutaneous syndrome*).ti,ab.
5.	spina bifida.ti,ab.
6.	or/1-5

1 **Embase search terms**

1.	(hydrocephalus or neurofibromatos* or phakomatos* or neurocutaneous syndrome* or macrocephal* or microcephal* or subdural haemorrhag* or subdural hemorrhag*).ti,ab.
2.	hydrocephalus/
3.	phakomatosis/
4.	neurofibromatosis/
5.	spina bifida.ti,ab.
6.	or/1-5

2 **CRD search terms**

#1.	MeSH descriptor hydrocephalus
#2.	MeSH descriptor neurocutaneous syndromes
#3.	MeSH descriptor neurofibromatosis
#4.	((hydrocephalus or neurofibromatos* or phakomatos* or neurocutaneous syndrome*))
#5.	(spina bifida)
#6.	#1 or #2 or #3 or #4 or #5

G.2.236 Epilepsy

4 **Medline and Embase search terms**

1.	exp epilepsy/
2.	(epileps* or seizure* or blackout* or status epilepticus or convulsion*).ti,ab.
3.	(staring adj1 (episode* or spell* or fit*)).ti,ab.
4.	(continuous spike wave of slow sleep or landau-kleffner syndrome or lennox-gastaut syndrome or infant\$ spasm*).ti,ab.
5.	or/1-4

5 **CRD search terms**

#1.	MeSH descriptor epilepsy explode all trees
#2.	((epileps* or seizure* or blackout* or status epilepticus or convulsion*))
#3.	((staring adj1 (episode* or spell* or fit*)))
#4.	((continuous spike wave of slow sleep or landau-kleffner syndrome or lennox-gastaut syndrome or infant\$ spasm\$))
#5.	#1 or #2 or #3 or #4

G.2.257 Extrapyramidal diseases

7 **Medline search terms**

1.	exp parkinson disease/
2.	huntington disease/
3.	basal ganglia diseases/
4.	tourette syndrome/
5.	exp tics/ or tremor/ or chorea/
6.	exp dystonia/
7.	exp multiple system atrophy/
8.	(huntington or parkinson*).ti,ab.
9.	tourette* syndrome.ti,ab.
10.	(dystonia* or torticollis or chorea or extrapyramidal disorder* or myoclonus).ti,ab.

11.	(multiple system atroph* or shy-drager syndrome or segawas syndrome).ti,ab.
12.	parkinsonian disorders/
13.	myoclonus/
14.	(tic or tics or tremor*).ti,ab.
15.	blepharospasm/
16.	blepharospasm.ti,ab.
17.	pantothenate kinase-associated neurodegeneration/
18.	((hallervorden-spatz or basal ganglia) adj2 disease).ti,ab.
19.	neuroleptic malignant syndrome/
20.	(malignant neuroleptic syndrome or neuroleptic malignant syndrome or supranuclear ophthalmoplegia or striatonigral degeneration).ti,ab.
21.	or/1-20

1 Embase search terms

1.	exp parkinson disease/
2.	exp huntington chorea/
3.	extrapyramidal syndrome/
4.	gilles de la tourette syndrome/
5.	tic/
6.	exp tremor/
7.	extrapyramidal symptom/ or chorea/ or dystonia/ or torticollis/
8.	shy drager syndrome/
9.	(huntington or parkinson*).ti,ab.
10.	tourette* syndrome.ti,ab.
11.	(dystonia* or torticollis or chorea or extrapyramidal disorder* or myoclonus).ti,ab.
12.	(multiple system atroph* or shy-drager syndrome or segawas syndrome).ti,ab.
13.	(tic or tics or tremor*).ti,ab.
14.	blepharospasm.ti,ab.
15.	((hallervorden-spatz or basal ganglia) adj2 disease*).ti,ab.
16.	(malignant neuroleptic syndrome or neuroleptic malignant syndrome or supranuclear ophthalmoplegia or striatonigral degeneration).ti,ab.
17.	parkinsonism/
18.	myoclonus/
19.	blepharospasm/
20.	neurodegeneration with brain iron accumulation/
21.	neuroleptic malignant syndrome/
22.	or/1-21

2 CRD search terms

#1.	MeSH descriptor parkinson disease explode all trees
#2.	MeSH descriptor huntington disease
#3.	MeSH descriptor basal ganglia diseases
#4.	MeSH descriptor tourette syndrome
#5.	MeSH descriptor tics explode all trees
#6.	MeSH descriptor tremor
#7.	MeSH descriptor chorea

#8.	MeSH descriptor dystonia explode all trees
#9.	MeSH descriptor multiple system atrophy explode all trees
#10.	((huntington or parkinson*))
#11.	(tourette* syndrome)
#12.	((dystonia* or torticollis or chorea or extrapyramidal disorder* or myoclonus))
#13.	((multiple system atroph* or shy-drager syndrome))
#14.	MeSH descriptor parkinsonian disorders
#15.	MeSH descriptor myoclonus
#16.	((tic or tics or tremor*))
#17.	MeSH descriptor blepharospasm
#18.	(blepharospasm)
#19.	MeSH descriptor pantothenate kinase-associated neurodegeneration
#20.	((hallervorden-spatz or basal ganglia) adj2 disease))
#21.	MeSH descriptor neuroleptic malignant syndrome explode all trees
#22.	((malignant neuroleptic syndrome or neuroleptic malignant syndrome or supranuclear ophthalmoplegia or striatonigral degeneration))
#23.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

G.2.218 Functional diseases

2 Medline search terms

1.	dissociative disorders/
2.	((dissociative or functional or somatoform or hypochondriacal) adj (disorder* or dysfunction*)).ti,ab.
3.	(dissociative adj3 (amnesia or fugue* or stupor* or trance* or convulsion* or sensory loss* or an?esthesia or motor)).ti,ab.
4.	or/1-3

3 Embase search terms

1.	dissociative disorder/
2.	((dissociative or functional or somatoform or hypochondriacal) adj (disorder* or dysfunction*)).ti,ab.
3.	(dissociative adj3 (amnesia or fugue* or stupor* or trance* or convulsion* or sensory loss* or an?esthesia or motor)).ti,ab.
4.	or/1-3

4 CRD search terms

#1.	MeSH descriptor dissociative disorders
#2.	((((dissociative or functional or somatoform or hypochondriacal) adj (disorder* or dysfunction*)))
#3.	((dissociative adj3 (amnesia or fugue* or stupor* or trance* or convulsion* or sensory loss* or an?esthesia or motor)))
#4.	#1 or #2 or #3

G.2.259 Headache

6 Medline search terms

1.	exp headache/ or exp headache disorders/
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2.	(migraine* or headache*).ti,ab.
3.	or/1-2

1 **Embase search terms**

1.	exp "headache and facial pain"/
2.	(migraine* or headache*).ti,ab.
3.	or/1-2

2 **CRD search terms**

#1.	MeSH descriptor headache explode all trees
#2.	MeSH descriptor headache disorders explode all trees
#3.	((migraine* or headache*))
#4.	#1 or #2 or #3

G.2.2.80 Motor neurone disease

4 **Medline and Embase search terms**

1.	exp motor neuron disease/
2.	(motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*).ti,ab.
3.	((primary or amyotrophic) adj lateral scleros*).ti,ab.
4.	(progressive adj (muscular atroph* or bulbar pals*).ti,ab.
5.	(pseudopolyneur* or pseudo-polyneur* or psuedo polyneur*).ti,ab.
6.	((pseudobulbar or pseudo-bulbar or pseudo bulbar) adj pals*).ti,ab.
7.	((bulbar or respirat* or limb) adj onset*).ti,ab.
8.	(lou gehrig* or lou-gehrig* or gehrig*).ti,ab.
9.	monomelic amyotroph*.ti,ab.
10.	((anterior or ventral) adj (horn or column) adj3 (disease* or disorder*)).ti,ab.
11.	(flail* adj (arm* or leg*) adj (syndrome* or disorder*)).ti,ab.
12.	((frontotemporal or fronto temporal or fronto-temporal) adj dement*).ti,ab.
13.	or/1-12

5 **CRD search terms**

#1.	MeSH descriptor motor neuron disease explode all trees
#2.	((motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*))
#3.	((primary or amyotrophic) adj lateral scleros*))
#4.	((progressive adj (muscular atroph* or bulbar pals*)))
#5.	((pseudopolyneur* or pseudo-polyneur* or psuedo polyneur*))
#6.	((pseudobulbar or pseudo-bulbar or pseudo bulbar) adj pals*))
#7.	((bulbar or respirat* or limb) adj onset*))
#8.	((lou gehrig* or lou-gehrig* or gehrig*))
#9.	(monomelic amyotroph*)
#10.	((anterior or ventral) adj (horn or column) adj3 (disease* or disorder*))
#11.	((flail* adj (arm* or leg*) adj (syndrome* or disorder*)))
#12.	((frontotemporal or fronto temporal or fronto-temporal) adj dement*))
#13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

G.2.2.11 Multiple sclerosis and inflammatory disorders

2 Medline search terms

1.	exp multiple sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	myelitis, transverse/
5.	ms.ti.
6.	(transverse myelitis or positional plagiocephal* or encephalomyelitis).ti,ab.
7.	demyelinating diseases/ or exp demyelinating autoimmune diseases, cns/ or exp hereditary central nervous system demyelinating diseases/ or leukoencephalopathy, progressive multifocal/ or marchiafava-bignami disease/ or myelinolysis, central pontine/
8.	((demyelinat* or marchiafava-bignami or central pontine or acute transverse or subacute or optic* or devics or leukoencepha*) adj3 (myelitis or myelinolysis or neuromyelitis or disease* or disorder*)).ti,ab.
9.	or/1-8

3 Embase search terms

1.	multiple sclerosis/
2.	((multiple or disseminated) adj2 scleros*).ti,ab.
3.	encephalomyelitis disseminata.ti,ab.
4.	myelitis, transverse/
5.	ms.ti.
6.	(transverse myelitis or positional plagiocephal* or encephalomyelitis).ti,ab.
7.	((demyelinat* or marchiafava-bignami or central pontine or acute transverse or subacute or optic* or devics or leukoencepha*) adj3 (myelitis or myelinolysis or neuromyelitis or disease* or disorder*)).ti,ab.
8.	demyelinating disease/ or acute disseminated encephalomyelitis/ or acute inflammatory demyelinating polyneuropathy/ or alpers disease/ or chronic inflammatory demyelinating polyneuropathy/ or demyelination/ or leukodystrophy/ or marchiafava bignami disease/ or progressive multifocal leukoencephalopathy/ or schilder disease/ or subacute combined degeneration/ or subacute sclerosing panencephalitis/
9.	or/1-8

4 CRD search terms

#1.	MeSH descriptor multiple sclerosis explode all trees
#2.	((multiple or disseminated) adj2 scleros*))
#3.	(encephalomyelitis disseminata)
#4.	MeSH descriptor myelitis, transverse
#5.	(ms)
#6.	((demyelinat* or marchiafava-bignami or central pontine or acute transverse or subacute or optic* or devics or leukoencepha*) adj3 (myelitis or myelinolysis or neuromyelitis or disease* or disorder*)))
#7.	MeSH descriptor demyelinating diseases
#8.	MeSH descriptor demyelinating autoimmune diseases, cns explode all trees
#9.	MeSH descriptor hereditary central nervous system demyelinating diseases explode all trees
#10.	MeSH descriptor leukoencephalopathy, progressive multifocal
#11.	MeSH descriptor marchiafava-bignami disease
#12.	MeSH descriptor myelinolysis, central pontine

#13.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
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G.2.2.12 Myelopathies and radiculopathies

2 Medline search terms

1.	exp spondylosis/
2.	(spondylosis or spinal stenosis or radiculopath* or myelopath* or leukoencephalopath*).ti,ab.
3.	radiculopathy/
4.	vertebral canal stenosis/
5.	or/1-4

3 Embase search terms

1.	exp spondylosis/
2.	(spondylosis or spinal stenosis or radiculopath* or myelopath* or leukoencephalopath*).ti,ab.
3.	radiculopathy/
4.	vertebral canal stenosis/
5.	or/1-4

4 CRD search terms

#1.	MeSH descriptor spondylosis explode all trees
#2.	MeSH descriptor radiculopathy
#3.	((spondylosis or spinal stenosis or radiculopath* or myelopath* or leukoencephalopath*)
#4.	MeSH descriptor spinal stenosis
#5.	#1 or #2 or #3 or #4

G.2.2.13 Neuromuscular disease

6 Medline search terms

1.	neuromuscular diseases/
2.	myasthenia gravis/
3.	exp myositis/
4.	myositis.ti,ab.
5.	exp muscular dystrophies/
6.	((neuromuscular or immobility) adj3 (disorder* or disease*)).ti,ab.
7.	(ischaemic infarction* adj3 muscle*).ti,ab.
8.	(muscular dystroph* or muscular atroph* or myositis or myastheni* or lambert-eaton syndrome or eaton-lambert syndrome or duchenne* or becker* or miyoshi or walker warburg syndrome toxic myoneural disorder* or myotonic disorder*).ti,ab.
9.	lambert-eaton myasthenic syndrome/
10.	((congenital or mitochondrial or drug-induced or alcoholic or endocrine inflammatory or infectious or metabolic) adj3 myopath*).ti,ab.
11.	or/1-10

7 Embase search terms

1.	neuromuscular disease/
2.	myasthenia gravis/
3.	exp myositis/
4.	exp muscular dystrophy/
5.	myositis.ti,ab.

6.	((neuromuscular or immobility) adj3 (disorder* or disease*)).ti,ab.
7.	(ischaemic infarction* adj3 muscle*).ti,ab.
8.	(muscular dystroph* or muscular atroph* or myositis or myastheni* or lambert-eaton syndrome or eaton-lambert syndrome or duchenne* or becker* or miyoshi or walker warburg syndrome toxic myoneural disorder* or myotonic disorder*).ti,ab.
9.	((congenital or mitochondrial or drug-induced or alcoholic or endocrine inflammatory or infectious or metabolic) adj3 myopath*).ti,ab.
10.	eaton lambert syndrome/
11.	or/1-10

1 CRD search terms

#1.	MeSH descriptor neuromuscular diseases
#2.	MeSH descriptor myasthenia gravis
#3.	MeSH descriptor myositis explode all trees
#4.	(myositis)
#5.	MeSH descriptor muscular dystrophies explode all trees
#6.	((neuromuscular or immobility) adj3 (disorder* or disease*)))
#7.	((ischaemic infarction* adj3 muscle*))
#8.	((muscular dystroph* or muscular atroph* or myositis or myastheni* or lambert-eaton syndrome or eaton-lambert syndrome or duchenne* or becker* or miyoshi or walker warburg syndrome toxic myoneural disorder* or myotonic disorder*))
#9.	MeSH descriptor lambert-eaton myasthenic syndrome
#10.	((congenital or mitochondrial or drug-induced or alcoholic or endocrine inflammatory or infectious or metabolic) adj3 myopath*))
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

G.2.2.24 Nervous system tumours

3 Medline search terms

1.	exp neuroma, acoustic/
2.	exp cranial nerve neoplasms/
3.	central nervous system neoplasms/
4.	exp spinal cord neoplasms/
5.	((brain or midbrain or brainstem or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system or (meninges or meningeal or leptomenigeal or pontine)) adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or sarcoma* or metastas* or secundar*).ti,ab.
6.	or/1-5 [only these lines used in dizziness question]
7.	((spinal or spine) adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or metastas* or secundar*).ti,ab.
8.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 myeloma*).ti,ab
9.	(neurosarcoma* or neurocytoma*).ti,ab.
10.	chordoma/
11.	(chordoma* or chordocarcinoma* or chordoepithelioma* or notochordoma*).ti,ab.
12.	(choroid plexus adj (carcinoma* or tumo?r* or neoplas* or malignan*).ti,ab.
13.	(acoustic adj1 neuroma*).ti,ab.
14.	(neurinoma* or neurofibroma* or neurilemmoma or schwannoma*).ti,ab.
15.	exp glioma/

16.	glioma*.ti,ab.
17.	(glioneuronal adj1 (cancer* or neoplas* or tumo?r* or carcinoma*)).ti,ab.
18.	(ependymal adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
19.	(ependymoblastoma* or glioblastoma* or glioneurocytoma*).ti,ab.
20.	(subependymoma* or sub-ependymoma*).ti,ab.
21.	(oligoastrocytoma* or oligo-astrocytoma*).ti,ab.
22.	(oligodendrogl* or oligodendrocytoma*).ti,ab.
23.	ganglioglioma*.ti,ab.
24.	exp astrocytoma/
25.	(ganglioglioma* or ganglioblastoma* or ganglioblastoma* or gangliocytoma* or ganglioneuroblastoma* or gliosarcoma*).ti,ab.
26.	exp astrocytoma/
27.	(astrocytoma* or astroblastoma* or astroglioma*).ti,ab.
28.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj2 ((germ cell adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)) or (germinoma* or dysgerminoma*))).ti,ab.
29.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 teratoma*).ti,ab.
30.	(haemangioblastoma* or hemangioblastoma*).ti,ab.
31.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 angioma*).ti,ab.
32.	(meningioma* or meningiosarcoma*).ti,ab.
33.	exp neuroectodermal tumors/
34.	pnet.ti,ab.
35.	(neuroectodermal* adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
36.	(medulloblastoma* or medulloctoma* or medullomyoblastoma* or pinealoma*).ti,ab.
37.	pinealoma/
38.	(pinealocytoma* or pineocytoma*).ti,ab.
39.	(pineal?blastoma* or pineoblastoma*).ti,ab.
40.	(pineal adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
41.	(craniopharyngioma* or cranio-pharyngioma*).ti,ab.
42.	pituitary neoplasms/
43.	(pituitary adj1 (cancer* or neoplas* or tumo?r* or adenoma* or carcinoma* or lymphoma*)).ti,ab.
44.	(rathkes*1 adj1 (pouch or cleft) adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
45.	(infratentorial adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
46.	(supratentorial adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
47.	spongioblastoma*.ti,ab.
48.	or/1-47

1 Embase search terms

1.	exp neuroma/
2.	exp cranial nerve tumor/
3.	central nervous system tumor/
4.	exp spinal cord tumor/

5.	((brain or midbrain or brainstem or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system or (meninges or meningeal or leptomeningeal or pontine)) adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or sarcoma* or metastas* or secundar*)).ti,ab.
6.	((spinal or spine) adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or metastas* or secundar*)).ti,ab.
7.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 myeloma*).ti,ab.
8.	(neurosarcoma* or neurocytoma*).ti,ab.
9.	chordoma/
10.	(chordoma* or chordocarcinoma* or chordoepithelioma* or notochordoma*).ti,ab.
11.	(choroid plexus adj (carcinoma* or tumo?r* or neoplas* or malignan*)).ti,ab.
12.	(acoustic adj1 neuroma*).ti,ab.
13.	(neurinoma* or neurofibroma* or neurilemmoma or schwannoma*).ti,ab.
14.	exp glioma/
15.	glioma*.ti,ab.
16.	(glioneuronal adj1 (cancer* or neoplas* or tumo?r* or carcinoma*)).ti,ab.
17.	(ependymal adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
18.	(ependymblastoma* or glioblastoma* or glioneurocytoma*).ti,ab.
19.	(subependymoma* or sub-ependymoma*).ti,ab.
20.	(oligoastrocytoma* or oligo-astrocytoma*).ti,ab.
21.	(oligodendrogl* or oligodendrocytoma*).ti,ab.
22.	ganglioglioma*.ti,ab.
23.	ganglioblastoma*.ti,ab.
24.	(ganglioglioma* or ganglioblastoma* or ganglioblastoma* or gangliocytoma* or ganglioneuroblastoma* or gliosarcoma*).ti,ab.
25.	exp astrocytoma/
26.	(astrocytoma* or astroblastoma* or astroglioma*).ti,ab.
27.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj2 ((germ cell adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)) or (germinoma* or dysgerminoma*))).ti,ab.
28.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 teratoma*).ti,ab.
29.	(haemangioblastoma* or hemangioblastoma*).ti,ab.
30.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 angioma*).ti,ab.
31.	(meningioma* or meningiosarcoma*).ti,ab.
32.	exp neuroectoderm tumor/
33.	pnet.ti,ab.
34.	(neuroectodermal* adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
35.	(medulloblastoma* or medulloctoma* or medullomyoblastoma* or pinealoma*).ti,ab.
36.	pineal body tumor/
37.	(pinealocytoma* or pineocytoma*).ti,ab.
38.	(pineal?blastoma* or pineoblastoma*).ti,ab.
39.	(pineal adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
40.	(craniopharyngioma* or cranio-pharyngioma*).ti,ab.
41.	hypophysis tumor/

42.	(pituitary adj1 (cancer* or neoplas* or tumo?r* or adenoma* or carcinoma* or lymphoma*)).ti,ab.
43.	(rathkes*1 adj1 (pouch or cleft) adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
44.	(infratentorial adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
45.	(supratentorial adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)).ti,ab.
46.	spongioblastoma*.ti,ab.
47.	or/1-46

1 CRD search terms

#1.	MeSH descriptor neuroma, acoustic explode all trees
#2.	MeSH descriptor cranial nerve neoplasms explode all trees
#3.	MeSH descriptor central nervous system neoplasms
#4.	MeSH descriptor spinal cord neoplasms explode all trees
#5.	((brain or midbrain or brainstem or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system or (meninges or meningeal or leptomeningeal or pontine)) adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or sarcoma* or metastas* or secundar*)))
#6.	((spinal or spine) adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma* or metastas* or secundar*)))
#7.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 myeloma*))
#8.	((neurosarcoma* or neurocytoma*))
#9.	MeSH descriptor chordoma
#10.	(chordoma)
#11.	((chordoma* or chordocarcinoma* or chordoepithelioma* or notochordoma*))
#12.	((choroid plexus adj (carcinoma* or tumo?r* or neoplas* or malignan*)))
#13.	((acoustic adj1 neuroma*))
#14.	((neurinoma* or neurofibroma* or neurilemmoma or schwannoma*))
#15.	MeSH descriptor glioma explode all trees
#16.	(glioma*)
#17.	((glioneuronal adj1 (cancer* or neoplas* or tumo?r* or carcinoma*)))
#18.	((ependymal adj1 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)))
#19.	((ependymoblastoma* or glioblastoma* or glioneurocytoma*))
#20.	((subependymoma* or sub-ependymoma*))
#21.	((oligoastrocytoma* or oligo-astrocytoma*))
#22.	((oligodendrogli* or oligodendrocytoma*))
#23.	(ganglioglioma*)
#24.	(ganglioblastoma*)
#25.	((ganglioglioma* or ganglioblastoma* or ganglioblastoma* or gangliocytoma* or ganglioneuroblastoma* or gliosarcoma*))
#26.	MeSH descriptor astrocytoma explode all trees
#27.	((astrocytoma* or astroblastoma* or astroglioma*))
#28.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj2 ((germ cell adj2 (cancer* or neoplas* or tumo?r* or carcinoma* or lymphoma*)) or (germinoma* or dysgerminoma*))))
#29.	((brain or intracranial or cranial or cerebell* or cerebr* or cns or central nervous system) adj1 (angioma*))

#30.	((meningioma* or meningiosarcoma*))
#31.	MeSH descriptor neuroectodermal tumors explode all trees
#32.	(pnet)
#33.	((neuroectodermal* adj1 (cancer* or neoplas* or tumor?r* or carcinoma* or lymphoma*)))
#34.	((medulloblastoma* or medulloctoma* or medullomyoblastoma* or pinealoma*))
#35.	MeSH descriptor pinealoma
#36.	((pinealocytoma* or pineocytoma*))
#37.	((pineal?blastoma* or pineoblastoma*))
#38.	((pineal adj1 (cancer* or neoplas* or tumor?r* or carcinoma* or lymphoma*)))
#39.	((craniopharyngioma* or cranio-pharyngioma*))
#40.	MeSH descriptor pituitary neoplasms
#41.	((pituitary adj1 (cancer* or neoplas* or tumor?r* or adenoma* or carcinoma* or lymphoma*)))
#42.	((rathkes*1 adj1 (pouch or cleft) adj1 (cancer* or neoplas* or tumor?r* or carcinoma* or lymphoma*)))
#43.	((infratentorial adj1 (cancer* or neoplas* or tumor?r* or carcinoma* or lymphoma*)))
#44.	((supratentorial adj1 (cancer* or neoplas* or tumor?r* or carcinoma* or lymphoma*)))
#45.	(spongioblastoma*)
#46.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45

G.2.2.15 Peripheral nerve disorders

2 Medline search terms

1.	exp peripheral nervous system diseases/
2.	(peripheral nerv* adj3 (disorder* or disease*)).ti,ab.
3.	(stiff person syndrome or isaacs syndrome or moersch woltmann syndrome or stiff-man syndrome or startle syndrome).ti,ab.
4.	carpal tunnel syndrome.ti,ab.
5.	polyneuropath*.ti,ab.
6.	mononeuropath*.ti,ab.
7.	causalgia.ti,ab.
8.	((cprs or complex regional pain syndrome) adj3 (type 1 or type one or type i or type two or type ii or type 2)).ti,ab.
9.	phantom limb/
10.	phantom limb.ti,ab.
11.	((plexus or root) adj3 (compression* or disorder*)).ti,ab.
12.	((radial or ulnar or median) adj3 lesion*).ti,ab.
13.	(neuropathies or neuropathy).ti,ab.
14.	or/1-13

3 Embase search terms

1.	peripheral neuropathy/
2.	(peripheral nerv* adj3 (disorder* or disease*)).ti,ab.
3.	(carpal tunnel syndrome or stiff person syndrome or isaacs syndrome).ti,ab.
4.	polyneuropath*.ti,ab.
5.	mononeuropath*.ti,ab.

6.	causalgia.ti,ab.
7.	((cprs or complex regional pain syndrome) adj3 (type 1 or type one or type i or type two or type ii or type 2)).ti,ab.
8.	phantom limb.ti,ab.
9.	((plexus or root) adj3 (compression* or disorder*)).ti,ab.
10.	((radial or ulnar or median) adj3 lesion*).ti,ab.
11.	(neuropathies or neuropathy).ti,ab.
12.	carpal tunnel syndrome/
13.	polyneuropathy/
14.	exp mononeuropathy/
15.	complex regional pain syndrome type ii/
16.	brachial plexus neuropathy/
17.	diabetic neuropathy/
18.	or/1-17

1 CRD search terms

#1.	MeSH descriptor peripheral nervous system diseases explode all trees
#2.	((peripheral nerv* adj3 (disorder* or disease*)))
#3.	((stiff person syndrome or isaacs syndrome or moersch woltmann syndrome or stiff-man syndrome or startle syndrome))
#4.	(carpal tunnel syndrome)
#5.	(polyneuropath*)
#6.	(mononeuropath*)
#7.	(causalgia)
#8.	((cprs or complex regional pain syndrome) adj3 (type 1 or type one or type i or type two or type ii or type 2)))
#9.	MeSH descriptor phantom limb
#10.	(phantom limb)
#11.	((plexus or root) adj3 (compression* or disorder*)))
#12.	((radial or ulnar or median) adj3 lesion*)
#13.	((neuropathies or neuropathy))
#14.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

G.2.2.26 Rare disorders

3 Medline search terms

1.	cerebral palsy/
2.	exp paralysis/
3.	(monoplegi* or hemiplegi* or paraplegi* or tetraplegi* or cerebral palsy or paralytic syndrome or werdnig hoffmann syndrome).ti,ab.
4.	(cerebrospinal fluid adj2 leak*).ti,ab.
5.	(diastematomyelia or dydromyelia or neuromyopath* or systematic atroph* or cerebral cyst* or benign intracranial hypertension or dysreflexia).ti,ab.
6.	polyradiculopath*.ti,ab.
7.	neurotoxicity syndromes/
8.	(toxic encephalopath* or neurotoxic* syndrome*).ti,ab.
9.	((postpoliomyelitis or post-polio or post polio or postpolio) adj1 syndrome) or disease).ti,ab.

10.	arnold-chiari malformation/
11.	(arnold-chiari adj1 (syndrome or malformation)).ti,ab
12.	aphasia/
13.	dysarthria/
14.	(dysarthria or aphasia or dysphasia or anarthria).ti,ab.
15.	exp dyslexia/
16.	agnosia/
17.	agnosia.ti,ab.
18.	dyslexia.ti,ab.
19.	exp apraxias/
20.	apraxia.ti,ab.
21.	(syringobulbia or syringomyelia).ti,ab.
22.	exp autonomic nervous system diseases/
23.	neurodegenerative diseases/
24.	((neurodegenerative or neuro-degenerative or neuro degenerative or autonomic nervous system) adj3 (disease* or disorder*)).ti,ab.
25.	or/1-24

1 Embase search terms

1.	exp paralysis/
2.	(monoplegi* or hemiplegi* or paraplegi* or tetraplegi* or cerebral palsy or paralytic syndrome or werdnig hoffmann syndrome).ti,ab.
3.	(cerebrospinal fluid adj2 leak*).ti,ab.
4.	(diastematomyelia or dydromyelia or neuromyopath* or systematic atroph* or cerebral cyst* or benign intracranial hypertension or dysreflexia).ti,ab.
5.	polyradiculopath*.ti,ab.
6.	*"toxicity and intoxication"/
7.	(toxic encephalopath* or neurotoxic* syndrome*).ti,ab.
8.	((postpoliomyelitis or post-polio or post polio or postpolio) adj1 (syndrome or disease)).ti,ab.
9.	arnold chiari malformation/
10.	(arnold-chiari adj1 (syndrome or malformation)).ti,ab.
11.	aphasia/
12.	dysarthria/
13.	(dysarthria or aphasia or dysphasia or anarthria).ti,ab.
14.	dyslexia/
15.	agnosia/
16.	agnosia.ti,ab.
17.	dyslexia.ti,ab.
18.	exp apraxia/
19.	"apraxia of speech"/
20.	apraxia.ti,ab.
21.	(syringobulbia or syringomyelia).ti,ab.
22.	exp autonomic neuropathy/
23.	exp degenerative disease/
24.	((neurodegenerative or neuro-degenerative or neuro degenerative or autonomic nervous system) adj3 (disease* or disorder*)).ti,ab.

25.	or/1-24
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1 **CRD search terms**

#1.	MeSH descriptor cerebral palsy
#2.	MeSH descriptor paralysis explode all trees
#3.	((monoplegi* or hemiplegi* or paraplegi* or tetraplegi* or cerebral palsy or paralytic syndrome or werdnig hoffmann syndrome))
#4.	((cerebrospinal fluid adj2 leak*)
#5.	((diastematomyelia or dydromyelia or neuromyopath* or systematic atroph* or cerebral cyst* or benign intracranial hypertension or dysreflexia))
#6.	(polyradiculopath*)
#7.	MeSH descriptor neurotoxicity syndromes
#8.	((toxic encephalopath* or neurotoxic* syndrome*))
#9.	((postpoliomyelitis or post-polio or post polio or postpolio) adj1 syndrome))
#10.	MeSH descriptor arnold-chiari malformation
#11.	((arnold-chiari adj1 (syndrome or malformation)))
#12.	MeSH descriptor aphasia
#13.	MeSH descriptor dysarthria
#14.	((dysarthria or aphasia or dysphasia or anarthria))
#15.	MeSH descriptor dyslexia explode all trees
#16.	MeSH descriptor agnosia
#17.	(agnosia)
#18.	(dyslexia)
#19.	MeSH descriptor apraxias explode all trees
#20.	(apraxia)
#21.	((syringobulbia or syringomyelia))
#22.	MeSH descriptor autonomic nervous system diseases explode all trees
#23.	MeSH descriptor neurodegenerative diseases
#24.	((neurodegenerative or neuro-degenerative or neuro degenerative or autonomic nervous system) adj3 (disease* or disorder*)))
#25.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

G.2.2.27 Sleep disorders

3 **Medline search terms**

1.	exp sleep wake disorders/ or exp restless leg syndrome/
2.	((sleep* or sleep-wake) adj1 (syndrome* or disorder*)).ti,ab.
3.	(sleep disorder* or insomnia or dyssomnia or hypersomnia or narcolepsy or somnolence or cataplex* or parasomnia* or sleep apnea or restless leg syndrome or klein-levin syndrome).ti,ab.
4.	or/1-3

4 **Embase search terms**

1.	exp sleep disorder/
2.	restless legs syndrome/
3.	(sleep* adj1 (syndrome* or disorder*)).ti,ab.

4.	(sleep disorder* or insomnia or dyssomnia or hypersomnia or narcolepsy or somnolence or cataplex* or parasomnia* or sleep apnea or restless leg syndrome or klein-levin syndrome).ti,ab.
5.	or/1-4

1 **CRD search terms**

#1.	MeSH descriptor sleep wake disorders explode all trees
#2.	MeSH descriptor restless legs syndrome explode all trees
#3.	((sleep* or sleep-wake) adj1 (syndrome* or disorder*)))
#4.	((sleep disorder* or insomnia or dyssomnia or hypersomnia or narcolepsy or somnolence or cataplex* or parasomnia* or sleep apnea or restless leg syndrome or klein-levin syndrome))
#5.	#1 or #2 or #3 or #4

G.2.2.28 Spinal atrophy

3 **Medline search terms**

1.	exp spinal cord diseases/
2.	exp polyradiculoneuropathy/
3.	(polyradiculopath* or polyradiculoneuropath* or guillain-barre syndrome or guillain barre synrome or fisher syndrome or brown-sequard* syndrome).ti,ab.
4.	(spinal cord adj3 (disease* or disorder* or compression* or degenerat* or malformation*)).ti,ab.
5.	or/1-4

4 **Embase search terms**

1.	exp spinal cord disease/
2.	spinal muscular atrophy/
3.	myelitis/
4.	(polyradiculopath* or polyradiculoneuropath* or guillain-barre syndrome or guillain barre synrome or fisher syndrome or brown-sequard* syndrome).ti,ab.
5.	(spinal cord adj3 (disease* or disorder* or compression* or degenerat* or malformation*)).ti,ab.
6.	or/1-5

5 **CRD search terms**

#1.	MeSH descriptor spinal cord diseases explode all trees
#2.	MeSH descriptor polyradiculoneuropathy explode all trees
#3.	((polyradiculopath* or polyradiculoneuropath* or guillain-barre syndrome or guillain barre synrome or fisher syndrome or brown-sequard* syndrome))
#4.	((spinal cord adj3 (disease* or disorder* or compression* or degenerat* or malformation*)))
#5.	#1 or #2 or #3 or #4

G.3 Study design and other filters search terms

G.3.1 Excluded study designs and publication types

8 The following study designs and publication types were removed from retrieved results using the NOT
9 operator.

10 **Medline search terms**

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

1 **Embase search terms**

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

G.32 Health economic studies (HE)

3 **Medline search terms**

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/

7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

1 **Embase search terms**

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3B Observational studies (OBS)

3 **Medline search terms**

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective (cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

4 **Embase search terms**

1.	clinical study/
2.	exp case control study/
3.	family study/

4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

G.3.14 Prognostic and prediction rule studies (PROG)

2 Medline search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and logistic models/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
9.	roc curve/
10.	or/1-9

3 Embase search terms

1.	predict.ti.
2.	(validat* or rule*).ti,ab.
3.	(predict* and (outcome* or risk* or model*)).ti,ab.
4.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
5.	decision*.ti,ab. and statistical model/
6.	(decision* and (model* or clinical*)).ti,ab.
7.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
8.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
9.	receiver operating characteristic/
10.	or/1-9

G.3.15 Signs and symptoms (SIGNS)

2 Medline search terms

1.	exp "signs and symptoms"/
2.	symptom assessment/
3.	diagnosis/ or prognosis/
4.	(clinical adj3 (manifest* or feature* or finding* or aspect* or marker*)).ti,ab.
5.	(presenting adj3 (feature* or finding* or factor*)).ti,ab.
6.	presentation*.ti,ab.
7.	(physical adj3 (manifest* or characteristic* or feature* or finding*)).ti,ab.
8.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
9.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
10.	or/1-9

3 Embase search terms

1.	symptom assessment/
2.	diagnosis/
3.	prognosis/
4.	(clinical adj3 (manifest* or feature* or finding* or aspect* or marker*)).ti,ab.
5.	(presenting adj3 (feature* or finding* or factor*)).ti,ab.
6.	((risk or prognostic) adj factor*).ti,ab.
7.	presentation*.ti,ab.
8.	(physical adj3 (manifest* or characteristic* or feature* or finding*)).ti,ab.
9.	(sign or signs or symptom* or recogni* or identif* or complain*).ti,ab.
10.	(diagnos* or prognos* or assess* or criteria* or predict*).ti,ab.
11.	or/1-10

G.4 Searches for specific questions

G.4.51 Head shape or size abnormalities

- 6 • In children and babies who present with abnormal head shape, what is the predictive accuracy of
7 accompanying signs and symptoms to support non-specialists in identifying neurological
8 problems?

9 Medline search terms

1.	Brain spinal injury [G.2.2.2]
2.	Cranial nerve diseases [G.2.2.3]
3.	Central nervous system diseases [G.2.2.4]
4.	Epilepsy [G.2.2.6]
5.	Headache [G.2.2.9]
6.	Motor neurone disease [G.2.2.10]
7.	Neuromuscular disease [G.2.2.13]
8.	Nervous system tumours [G.2.2.14]
9.	Peripheral nervous disorders [G.2.2.15]
10.	Rare disorders [G.2.2.16]
11.	Sleep disorders [G.2.2.17]
12.	Spinal atrophy [G.2.2.18]

13.	hydrocephalus/ or exp megalencephaly/ or microcephaly/ or exp hematoma, subdural/ or dandy-walker syndrome/
14.	neurocutaneous syndromes/
15.	Neurofibromatosis/
16.	(hydrocephalus or neurofibromatos* or phakomatos* or neurocutaneous syndrome* or macrocephal* or megalencephal* or plagiocephal* or microcephal* or microlissencephal* or dandy-walker or subdural haehorrag* or subdural haematoma* or subdural hematoma* or subdural hemorrhag*).ti,ab.
17.	spina bifida.ti,ab.
18.	or/1-17
19.	Children and babies [G.2.1.1]
20.	exp plagiocephaly/
21.	((uneven* or irregular* or abnormal* or parallelogram or unusual* or large* or small* or under-develop* or big* or flat* or mis-shape* or misshape*) adj2 (head* or skull* or cranium)).ti,ab.
22.	plagiocephal*.ti,ab.
23.	or/20-22
24.	18 and 19 and 23
25.	Excluded study designs and publication types [G.3.1]
26.	24 not 25
27.	Limit 26 to English language
	Date parameters: 1946 - 22 July 2016

1 Embase search terms

1.	Brain spinal injury [G.2.2.2]
2.	Cranial nerve diseases [G.2.2.3]
3.	Central nervous system diseases [G.2.2.4]
4.	Epilepsy [G.2.2.6]
5.	Headache [G.2.2.9]
6.	Motor neurone disease [G.2.2.10]
7.	Neuromuscular disease [G.2.2.13]
8.	Nervous system tumours [G.2.2.14]
9.	Peripheral nervous disorders [G.2.2.15]
10.	Rare disorders [G.2.2.16]
11.	Sleep disorders [G.2.2.17]
12.	Spinal atrophy [G.2.2.18]
13.	(hydrocephalus or neurofibromatos* or Phakomatos* or neurocutaneous syndrome* or macrocephal* or megalencephal* or plagiocephal* or microcephal* or microlissencephal* or dandy-walker or subdural haehorrag* or subdural haematoma* or subdural hematoma* or subdural hemorrhag*).ti,ab.
14.	hydrocephalus/ or Microcephaly/ or hematoma, Subdural/ or dandy-walker syndrome/
15.	phakomatosis/
16.	neurofibromatosis/
17.	Spina bifida.ti,ab.
18.	or/1-17
19.	Children and babies [G.2.1.1]
20.	plagiocephaly/

21.	((uneven* or irregular* or abnormal* or parallelogram or unusual* or large* or small* or under-develop* or big* or flat* or mis-shape* or misshape*) adj2 (head* or skull* or cranium)).ti,ab.
22.	plagiocephal*.ti,ab.
23.	or/20-22
24.	18 and 19 and 23
25.	Excluded study designs and publication types [G.3.1]
26.	24 not 25
27.	Limit 26 to English language
	Date parameters: 1974 - 22 July 2016

G.4.12 Facial pain, atraumatic

- 2 • In adults and young people who present with atraumatic facial pain, what is the predictive
3 accuracy of accompanying signs and symptoms to support non-specialists in identifying suspected
4 neurological conditions?

5 Medline search terms

1.	Cranial nerve diseases [G.2.2.3]
2.	Functional diseases [G.2.2.8]
3.	Rare disorders [G.2.2.16]
4.	multiple sclerosis/
5.	((multiple or disseminated) adj2 scleros*).ti,ab.
6.	myelitis, transverse/
7.	ms.ti.
8.	cluster headache/
9.	cluster headache*.ti,ab.
10.	((migraine* or headache*) adj3 (face or facial pain*)).ti,ab.
11.	or/1-10
12.	((facial or face or myofacial or orofacial or craniofacial or trigeminal or trifacial or occipital) adj3 (pain* or neuralgia or tenderness*)).ti,ab.
13.	Signs and symptoms filter [G.3.5]
14.	11 and 12 and 13
15.	facial pain/ or facial neuralgia/ or trigeminal neuralgia/
16.	((facial or face or myofacial or orofacial or craniofacial or trigeminal or trifacial or occipital) adj3 (pain* or neuralgia or tenderness)).ti.
17.	15 or 16
18.	11 and 17
19.	Study filters OBS [G.3.3] or PROG [G.3.4]
20.	(14 or 18) and 19
21.	Excluded study designs and publication types [G.3.1]
22.	20 not 21
23.	Limit 22 to English language
	Date parameters: 1946 – 14 July 2016

6 Embase search terms

1.	Cranial nerve diseases [G.2.2.3]
2.	Functional diseases [G.2.2.8]

3.	Rare disorders [G.2.2.16]
4.	multiple sclerosis/
5.	((multiple or disseminated) adj2 scleros*).ti,ab.
6.	myelitis, transverse/
7.	ms.ti.
8.	cluster headache/
9.	cluster headache*.ti,ab.
10.	((migraine* or headache*) adj3 (face or facial pain*)).ti,ab.
11.	or/1-10
12.	((facial or face or myofacial or orofacial or craniofacial or trigeminal or trifacial or occipital) adj3 (pain* or neuralgia or tenderness*)).ti,ab.
13.	Signs and symptoms filter [G.3.5]
14.	11 and 12 and 13
15.	face pain/
16.	trigeminal neuralgia/
17.	((facial or face or myofacial or orofacial or craniofacial or trigeminal or trifacial or occipital) adj3 (pain* or neuralgia or tenderness)).ti.
18.	or/15-17
19.	11 and 18
20.	Study filters OBS [G.3.3] or PROG [G.3.4]
21.	(14 or 19) and 20
22.	Excluded study designs and publication types [G.3.1]
23.	21 not 22
24.	Limit 23 to English language
	Date parameters: 1974 - 14 July 2016

G.4.13 Dizziness

- 2 • In adults and young people who present with dizziness, what is the predictive accuracy of
3 accompanying signs and symptoms to support non-specialists in identifying neurological
4 conditions?

5 Medline search terms

1.	Cranial nerve diseases [G.2.2.3]
2.	Epilepsy [G.2.2.6]
3.	Functional diseases [G.2.2.8]
4.	Headache [G.2.2.9]
5.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
6.	Nervous system tumours [G.2.2.14]
7.	Rare disorders [G.2.2.16]
8.	or/1-8
9.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed* or light headed* or orthostasis or orthostatic hypotension or vertigo or tinnitus).ti,ab.
10.	Signs and symptoms filter [A.3.5]
11.	8 and 9 and 10
12.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed or light headed or orthostasis or orthostatic hypotension or vertigo or tinnitus).ti.
13.	dizziness/ or vertigo/ or tinnitus/

14.	12 or 13
15.	8 and 14
16.	Study filters OBS [A.3.3] or PROG [A.3.4]
17.	(11 or 15) and 16
18.	Excluded study designs and publication types [A.3.1]
19.	17 not 28
20.	Limit 19 to English language
	Date parameters: 1946 – 5 July 2016

1 Embase search terms

1.	Cranial nerve diseases [G.2.2.3]
2.	Epilepsy [G.2.2.6]
3.	Functional diseases [G.2.2.8]
4.	Headache [G.2.2.9]
5.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
6.	Nervous system tumours [G.2.2.14]
7.	Rare disorders [G.2.2.16]
8.	or/1-8
9.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed or light headed or orthostasis or orthostatic hypotension or vertigo or tinnitus).ti,ab.
10.	Signs and symptoms filter [G.3.5]
11.	8 and 9 and 10
12.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed or light headed or orthostasis or orthostatic hypotension or vertigo or tinnitus).ti.
13.	*dizziness/ or *vertigo/ or *tinnitus/
14.	12 or 13
15.	8 and 14
16.	Study filters OBS [G.3.3] or PROG [G.3.4]
17.	(11 or 15) and 16
18.	Excluded study designs and publication types [G.3.1]
19.	17 not 18
20.	Limit 19 to English language
	Date parameters: 1974 – 5 July 2016

G.424 Headaches in children

- 3 • In children and babies under 12 who present with headache, what is the predictive accuracy of
4 accompanying signs and symptoms to support non-specialists in identifying suspected
5 neurological conditions?

6 Medline search terms

1.	Central nervous system diseases [G.2.2.4]
2.	Developmental disorders [G.2.2.5]
3.	Functional diseases [G.2.2.8]
4.	Headache [G.2.2.9]
5.	Nervous system tumours [G.2.2.14]
6.	Rare disorders [G.2.2.16]
7.	or/1-6

8.	Children and babies [G.2.1.1]
9.	7 and 8
10.	(migraine* or headache*).ti,ab.
11.	Signs and symptoms filter [G.3.5]
12.	9 and 10 and 11
13.	exp headache/ or exp headache disorders/
14.	(migraine* or headache*).ti.
15.	13 or 14
16.	9 and 15
17.	Study filters OBS [G.3.3] or PROG [G.3.4]
18.	(12 or 16) and 17
19.	Excluded study designs and publication types [G.3.1]
20.	18 not 19
21.	Limit 20 to English language
	Date parameters: 1946 – 20 July 2016

1 Embase search terms

1.	Central nervous system diseases [G.2.2.4]
2.	Developmental disorders [G.2.2.5]
3.	Functional diseases [G.2.2.8]
4.	Headache [G.2.2.9]
5.	Nervous system tumours [G.2.2.14]
6.	Rare disorders [G.2.2.16]
7.	or/1-6
8.	Children and babies [G.2.1.1]
9.	7 and 8
10.	(headache* or migraine*).ti,ab.
11.	Signs and symptoms filter [G.3.5]
12.	9 and 10 and 11
13.	exp "headache and facial pain"/
14.	(headache* or migraine*).ti.
15.	13 or 14
16.	9 and 15
17.	Study filters OBS [G.3.3] or PROG [G.3.4]
18.	(12 or 16) and 17
19.	Excluded study designs and publication types [G.3.1]
20.	18 not 19
21.	Limit 20 to English language
	Date parameters: 1974 – 20 July 2016

G.4.5 HINTS test

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

6 Medline search terms

1.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed* or light headed* or orthostasis or orthostatic hypotension or vertigo* or tinnitus).ti,ab.
2.	dizziness/ or exp vertigo/ or tinnitus/
3.	1 or 2
4.	((head impulse or nystagmus or skew) adj1 (test* or exam*)).ti,ab.
5.	head impulse nystagmus test of skew.ti,ab.
6.	head impulse test/
7.	hints.ti,ab.
8.	or/4-7
9.	3 and 8
10.	Excluded study designs and publication types [G.3.1]
11.	9 not 10
12.	Limit 11 to English language
	Date parameters: 1946 – 26 September 2016

1 Embase search terms

1.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed* or light headed* or orthostasis or orthostatic hypotension or vertigo* or tinnitus).ti,ab.
2.	positional dizziness/ or dizziness/ or exp vertigo/ or tinnitus/
3.	1 or 2
4.	((head impulse or nystagmus or skew) adj1 (test* or exam*)).ti,ab.
5.	head impulse nystagmus test of skew.ti,ab.
6.	head impulse test/
7.	hints.ti,ab.
8.	or/4-7
9.	3 and 8
10.	Excluded study designs and publication types [G.3.1]
11.	9 not 10
12.	Limit 11 to English language
	Date parameters: 1974 – 26 September 2016

2 Cochrane search terms

#1.	(dizzy or dizziness or dizzyness or lightheaded* or light-headed* or light headed* or orthostasis or orthostatic hypotension or vertigo* or tinnitus):ti,ab
#2.	MeSH descriptor: [dizziness] this term only
#3.	MeSH descriptor: [vertigo] explode all trees
#4.	MeSH descriptor: [tinnitus] this term only
#5.	(or #1-#4)
#6.	((head impulse or nystagmus or skew) next (test* or exam*)):ti,ab
#7.	head impulse nystagmus test of skew:ti,ab
#8.	MeSH descriptor: [head impulse test] this term only
#9.	hints:ti,ab
#10.	(or #6-#9)
#11.	#5 and #10
	Date parameters: Inception: 1974 – 26 September 2016

G.4.16 Memory tests

- 2 • In people under 40 with suspected (or under investigation for) memory failure, what is the
3 negative predictive value of neuropsychological assessments in ruling out organic memory
4 failure?

5 Medline search terms

1.	exp dementia/
2.	memory/ or exp memory disorders/
3.	((memory or cognitive or cognition) adj2 (failure or impairment*)).ti,ab.
4.	(memory adj2 problems).ti,ab.
5.	exp cognition disorders/
6.	((young or working age or frontotemporal or fronto-temporal) adj1 dementia).ti,ab.
7.	(early onset adj1 (dementia or alzheimer*)).ti,ab.
8.	or/1-7
9.	(6cit or cognitive impairment test* or 7 minute screen or seven minute screen).ti,ab.
10.	mini mental state exam*.ti,ab.
11.	(mmse adj4 (test* or assess* or diagnos*)).ti,ab.
12.	gpcog.ti,ab.
13.	(general practitioner assessment adj2 cognition).ti,ab.
14.	mini-cog.ti,ab.
15.	(addenbrooke* cognitive exam* or ace-3 or ace3 or ace-r).ti,ab.
16.	or/9-15
17.	exp physicians, primary care/
18.	exp family practice/
19.	exp physicians, family/
20.	exp general practice/
21.	primary health care/
22.	(family practi* or family doctor* or family physician* or gp* or general practi* or gp* surger* or primary care centre*).ti,ab.
23.	((primary or primary health) adj care).ti,ab.
24.	or/17-23
25.	8 and 16 and 24
26.	Excluded study designs and publication types [G.3.1]
27.	25 not 26
28.	Limit 27 to English language
	Date parameters: 1946 – 19 October 2016

6 Embase search terms

1.	memory assessment/ or memory test/ or memory/ or memory disorder/
2.	((memory or cognitive or cognition) adj2 (failure or impairment*)).ti,ab.
3.	(memory adj2 problems).ti,ab.
4.	cognitive defect/
5.	exp dementia/
6.	((young or working age or frontotemporal or fronto-temporal) adj1 dementia).ti,ab.
7.	(early onset adj1 (dementia or alzheimer*)).ti,ab.
8.	or/1-7
9.	(6cit or cognitive impairment test* or 7 minute screen or seven minute screen).ti,ab.

10.	mini mental state exam*.ti,ab.
11.	mini mental state examination/
12.	(mmse adj4 (test* or assess* or diagnos* or screen* or detect*)):ti,ab.
13.	gpcog.ti,ab.
14.	(general practitioner assessment adj2 cognition).ti,ab.
15.	mini-cog.ti,ab.
16.	(addenbrooke* cognitive exam* or ace-3 or ace3 or ace-r).ti,ab.
17.	or/9-16
18.	exp general practitioners/
19.	exp general practice/
20.	primary health care/
21.	(family practi* or family doctor* or family physician* or gp* or general practi* gp surgeon* or primary care centre*).ti,ab.
22.	((primary or primary health) adj care).ti,ab.
23.	or/18-22
24.	8 and 17 and 23
25.	Excluded study designs and publication types [G.3.1]
26.	24 not 25
27.	Limit 26 to English language
	Date parameters: 1974 – 19 October 2016

1 Cochrane search terms

#1.	MeSH descriptor: [dementia] explode all trees
#2.	MeSH descriptor: [memory] this term only
#3.	MeSH descriptor: [memory disorders] explode all trees
#4.	((memory or cognitive or cognition) near/2 (failure or impairment*)):ti,ab
#5.	(memory near/2 problems):ti,ab
#6.	MeSH descriptor: [cognition disorders] explode all trees
#7.	((young or "working age" or frontotemporal or fronto-temporal) next dementia):ti,ab
#8.	("early onset" next (dementia or alzheimer*)):ti,ab
#9.	(or #1-#8)
#10.	(6cit or ("cognitive impairment" next test*) or "7 minute screen" or "seven minute screen"):ti,ab
#11.	mini mental state next exam*:ti,ab
#12.	(mmse near/4 (test* or assess* or diagnos*)):ti,ab
#13.	gpcog:ti,ab
#14.	("general practitioner assessment") near/2 (cognition):ti,ab
#15.	mini-cog or "mini cog":ti,ab
#16.	(addenbrooke* next "cognitive" next exam* or ace-3 or ace3 or ace-r):ti,ab
#17.	(or #10-#16)
#18.	MeSH descriptor: [physicians, primary care] explode all trees
#19.	MeSH descriptor: [family practice] explode all trees
#20.	MeSH descriptor: [physicians, family] explode all trees
#21.	MeSH descriptor: [general practice] explode all trees
#22.	MeSH descriptor: [primary health care] this term only

#23.	("family" next practi* or "family" next doctor* or "family" next physician* or gp* or "general" next practi* or gp* surger* or "primary care" next centre*):ti,ab
#24.	((primary or "primary health") next care):ti,ab
#25.	(or #18-#24)
#26.	#8 and #17 and #25
#27.	Date parameters: Inception – 19 October 2016

G.4.17 Motor developmental delay (CK test)

- 2 • In children and infants under 10 who present with motor developmental delay, is a Creatine
3 Kinase test accurate in identifying whether muscular dystrophy is present as compared to no test
4 (and as indicated by the reference standard, diagnosis at follow-up)?

5 Medline search terms

1.	muscular dystrophies/
2.	developmental disabilities/ or motor skills/
3.	((motor* or develop*) adj2 (delay* or disorder*)):ti,ab.
4.	(milestone* adj2 (miss* or delay*)):ti,ab.
5.	(musc* dystrop* or duchenne*):ti,ab.
6.	or/1-5
7.	Children and babies [G.2.1.1]
8.	creatine kinase/ or creatine kinase, mm form/
9.	(creatine kinase or creatine k or creatine phosphokinase or ck or phospho-creatine kinase or cpk or creatine phosphotransferase or phosphocreatine phosphotransferase or isoenzyme cpk mb or mm creatine or muscle creatine):ti,ab.
10.	8 or 9
11.	6 and 7 and 10
12.	Excluded study designs and publication types [G.3.1]
13.	11 not 12
14.	Limit 13 to English language
	Date parameters: 1946 – 02 September 2016

6 Embase search terms

1.	muscular dystrophy/
2.	developmental disorder/ or motor performance/ or motor development/
3.	((motor* or develop*) adj2 (delay* or disorder*)):ti,ab.
4.	(milestone* adj2 (miss* or delay*)):ti,ab.
5.	(musc* dystrop* or duchenne*):ti,ab.
6.	or/1-5
7.	Children and babies [G.2.1.1]
8.	creatine kinase/
9.	creatine kinase mm/
10.	(creatine kinase or creatine k or creatine phosphokinase or ck or phospho-creatine kinase or cpk or creatine phosphotransferase or phosphocreatine phosphotransferase or isoenzyme cpk mb or mm creatine or muscle creatine):ti,ab.
11.	or/8-10
12.	6 and 7 and 11
13.	Excluded study designs and publication types [G.3.1]

14.	12 not 13
15.	Limit 14 to English language
	Date parameters: 1974 - 02 September 2016

1 Cochrane search terms

#1.	MeSH descriptor: [muscular dystrophies] explode all trees
#2.	MeSH descriptor: [developmental disabilities] explode all trees
#3.	MeSH descriptor: [motor skills] explode all trees
#4.	((motor* or develop*) near/2 (delay* or disorder*)):ti,ab
#5.	(milestone* near/2 (miss* or delay*)):ti,ab
#6.	(musc* dystrop* or duchenne*):ti,ab
#7.	(or #1-#6)
#8.	Children and babies [G.2.1.1]
#9.	("creatine kinase" or "creatine k" or "creatine phosphokinase" or ck or "phosphocreatine kinase" or cpk or "creatine phosphotransferase" or "phosphocreatine phosphotransferase" or "isoenzyme cpk mb" or "mm creatine" or "muscle creatine"):ti,ab
#10.	MeSH descriptor: [creatine kinase] this term only
#11.	MeSH descriptor: [creatine kinase, mm form] this term only
#12.	(or #9-#11)
#13.	#7 and #8 and #12
	Inception – 02 September 2016

G.4.2 Blackouts and other paroxysmal events

- 3 • In children and babies who present with paroxysmal events, what is the predictive accuracy of
4 accompanying signs and symptoms to support non-specialists in identifying suspected
5 neurological conditions?

6 Medline search terms

1.	Children and babies [G.2.1.1]
2.	seizures/
3.	seizures, febrile/
4.	((non-epileptic or non epileptic or nonepileptic or nonepilepsy or non-epilepsy or non epilepsy or paroxysmal or complex or pyrexial* or dissociative) adj2 (seizure* or attack* or disorder* or event* or convulsion* or spell* or fit* or episode* or blackout*)):ti,ab.
5.	((psychogenic or physiological or psychological or psychosomatic or somatoform) adj2 (seizure* or convulsion* or blackout* or fit*)):ti,ab.
6.	(febrile adj1 (convulsion* or seizure* or fit*)):ti,ab.
7.	or/2-6
8.	Signs and symptoms filter [G.3.5]
9.	1 and 7 and 8
10.	Study filters OBS [G.3.3] or PROG [G.3.4]
11.	9 and 11
12.	Excluded study designs and publication types [A.3.1]
13.	11 not 12
14.	Limit 13 to English language
	Date parameters: 1946 – 25 August 2016

7 Embase search terms

1.	Children and babies [G.2.1.1]
2.	seizure/
3.	febrile convulsion/
4.	((non-epileptic or non epileptic or nonepileptic or nonepilepsy or non-epilepsy or non epilepsy or paroxysmal or complex or pyrexial* or dissociative) adj2 (seizure* or attack* or disorder* or event* or convulsion* or spell* or fit* or episode* or blackout*).ti,ab.
5.	((psychogenic or physiological or psychological or psychosomatic or somatoform) adj2 (seizure* or convulsion* or blackout* or fit*).ti,ab.
6.	(febrile adj1 (convulsion* or seizure* or fit*).ti,ab.
7.	or/2-6
8.	Signs and symptoms filter [G.3.5]
9.	1 and 7 and 8
10.	Study filters OBS [G.3.3] or PROG [G.3.4]
11.	9 and 11
12.	Excluded study designs and publication types [A.3.1]
13.	11 not 12
14.	Limit 13 to English language
	Date parameters: 1974 – 25 August 2016

G.4.19 Sensory symptoms such as tingling or numbness

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

5 Medline search terms

1.	Epilepsy [G.2.2.6]
2.	Functional diseases [G.2.2.8]
3.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
4.	Myelopathies and radiculopathies (G.2.2.12)
5.	Nervous system tumours [G.2.2.14]
6.	Peripheral nervous disorders (G.2.2.15)
7.	Rare disorders [G.2.2.16]
8.	or/1-7
9.	(tingl* or alter* sens* or electric shock* or prickl* or numb or numbness or paresthesia* or paraesthesia* or formication*).ti,ab.
10.	(pin* adj2 needle*).ti,ab.
11.	or/9-10
12.	Signs and symptoms filter [G.3.5]
13.	8 and 11 and 12
14.	(tingl* or alter* sens* or electric shock* or prickl* or numb or numbness or paresthesia* or paraesthesia* or formication*).ti.
15.	(pin* adj2 needle*).ti.
16.	paresthesia/
17.	or/14-16
18.	8 and 17
19.	Study filters OBS [G.3.3] or PROG [G.3.4]
20.	(13 or 18) and 19

21.	Excluded study designs and publication types [G.3.1]
22.	20 not 21
23.	Limit 22 to English language
	Date parameters: 1946 – 28 July 2016

1 **Embase search terms**

1.	Epilepsy [G.2.2.6]
2.	Functional diseases [G.2.2.8]
3.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
4.	Myelopathies and radiculopathies (G.2.2.12)
5.	Nervous system tumours [G.2.2.14]
6.	Peripheral nervous disorders (G.2.2.15)
7.	Rare disorders [G.2.2.16]
8.	or/1-7
9.	(tingl* or alter* sens* or electric shock* or prickl* or numb or numbness or paresthesia* or paraesthesia* or formication*).ti,ab.
10.	(pin* adj2 needle*).ti,ab.
11.	or/9-10
12.	Signs and symptoms filter [G.3.5]
13.	8 and 11 and 12
14.	(tingl* or alter* sens* or electric shock* or prickl* or numb or numbness or paresthesia* or paraesthesia* or formication*).ti.
15.	(pin* adj2 needle*).ti.
16.	paresthesia/
17.	or/15-16
18.	8 and 17
19.	Study filters OBS [G.3.3] or PROG [G.3.4]
20.	(13 or 18) and 19
21.	Excluded study designs and publication types [G.3.1]
22.	20 not 21
23.	Limit 22 to English language
	Date parameters: 1974 – 28 July 2016

G.4.10 Tremor

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

6 **Medline search terms**

1.	Ataxia (G.2.2.1)
2.	Developmental disorders [G.2.2.5]
3.	Extrapyramidal diseases (G.2.2.7)
4.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
5.	Neuromuscular disease (G.2.2.13)
6.	Nervous system tumours [G.2.2.14]
7.	Rare disorders [G.2.2.16]
8.	or/1-7

9.	tremor*.ti,ab.
10.	Signs and symptoms filter [G.3.5]
11.	8 and 9 and 10
12.	tremor/
13.	essential tremor/
14.	tremor*.ti.
15.	or/12-14
16.	8 and 15
17.	Study filters OBS [G.3.3] or PROG [G.3.4]
18.	(11 or 16) and 17
19.	Excluded study designs and publication types [G.3.1]
20.	18 not 19
21.	Limit 20 to English language
	Date parameters: 1946 – 03 June 2016

1 Embase search terms

1.	Ataxia (G.2.2.1]
2.	Developmental disorders [G.2.2.5]
3.	Extrapyramidal diseases (G.2.2.7)
4.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
5.	Neuromuscular disease (G.2.2.13)
6.	Nervous system tumours [G.2.2.14]
7.	Rare disorders [G.2.2.16]
8.	or/1-7
9.	tremor*.ti,ab.
10.	Signs and symptoms filter [G.3.5]
11.	8 and 9 and 10
12.	tremor/
13.	essential tremor/
14.	tremor*.ti.
15.	or/12-14
16.	8 and 15
17.	Study filters OBS [G.3.3] or PROG [G.3.4]
18.	(11 or 16) and 17
19.	Excluded study designs and publication types [G.3.1]
20.	18 not 19
21.	Limit 20 to English language
	Date parameters: 1974 – 03 June 2016

G.5 Health economics search terms

G.5.1 Health economic [HE] reviews

4 Economic searches were conducted in Medline, Embase and NHS EED and HTA databases hosted by
5 CRD.

6 Medline & Embase search terms

1.	Ataxia [G.2.2.1]
2.	Cranial nerve diseases [G.2.2.3]
3.	Central nervous system diseases [G.2.2.4]
4.	Developmental disorders [G.2.2.5]
5.	Epilepsy [G.2.2.6]
6.	Extrapyramidal diseases (G.2.2.7)
7.	Functional diseases [G.2.2.8]
8.	Headache [G.2.2.9]
9.	Motor neurone disease (G.2.2.10)
10.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
11.	Myelopathies and radiculopathies (G.2.2.12)
12.	Neuromuscular disease (G.2.2.13)
13.	Nervous system tumours [G.2.2.14]
14.	Peripheral nervous disorders (G.2.2.15)
15.	Rare disorders [G.2.2.16]
16.	Sleep disorders (G.2.2.17)
17.	Spinal atrophy (G.2.2.18)
18.	or/1-17
19.	Study filter HE [G.3.2]
20.	18 and 19
21.	Excluded study designs and publication types [G.3.1]
22.	20 not 21
23.	Limit 22 to English language
	Date parameters: 2015 – 9 March 2017

1 CRD search terms

#1.	Ataxia [G.2.2.1]
#2.	Cranial nerve diseases [G.2.2.3]
#3.	Central nervous system diseases [G.2.2.4]
#4.	Developmental disorders [G.2.2.5]
#5.	Epilepsy [G.2.2.6]
#6.	Extrapyramidal diseases (G.2.2.7)
#7.	Functional diseases [G.2.2.8]
#8.	Headache [G.2.2.9]
#9.	Motor neurone disease (G.2.2.10)
#10.	Multiple sclerosis and inflammatory disorders [G.2.2.11]
#11.	Myelopathies and radiculopathies (G.2.2.12)
#12.	Neuromuscular disease (G.2.2.13)
#13.	Nervous system tumours [G.2.2.14]
#14.	Peripheral nervous disorders (G.2.2.15)
#15.	Rare disorders [G.2.2.16]
#16.	Sleep disorders (G.2.2.17)
#17.	Spinal atrophy (G.2.2.18)
#18.	or/1-17
	Date parameters: Inception – 9 March 2017

1

1 Appendix H: Clinical evidence tables

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

H.1.1 Dizziness and vertigo including the HINTS test in adults

H.1.1.1 Dizziness and vertigo

Reference	Navi BB <i>et al.</i> 2012. Rate and Predictors of Serious Neurologic Causes of Dizziness in the Emergency Department. <i>Mayo Clinic Proc.</i> 87(11): 1080-1088		
Study type and analysis	<ul style="list-style-type: none"> Retrospective cohort Multivariable logistic regression 		
Number of participants and characteristics	<p>n=907 collated from a single source by reviewing an electronic database of medical records for consecutive patients presenting with dizziness, vertigo or imbalance to a single centre (emergency department of tertiary care hospital)</p> <p>Eligible records were randomly assigned to 1 of 6 data abstractors, who were all neurologists (4 board-certified fellows and 2 third-year neurology residents). Variables that were missing or not mentioned in clinical notes were considered not to be present.</p> <p>Serious neurologic diagnoses were defined as any of the following: ischemic stroke, TIA, intracerebral haemorrhage, subarachnoid haemorrhage, subdural haemorrhage, epidural haemorrhage, brain neoplasm, seizure, demyelinating disease, and brain abscess or meningitis.</p> <p>Other diagnoses included: peripheral vertigo, benign paroxysmal positional vertigo, vestibular neuronitis, Meniere’s disease, concussion, migraine, gait disorder, orthostasis or presyncope, syncope, dizziness, psychiatric disorder, arrhythmia, acute coronary syndrome, stable angina, congestive heart failure exacerbation, hypertensive emergency, drug or substance ingestion or withdrawal, hypoglycaemia, electrolyte disorder, anaemia or gastrointestinal bleeding and systemic infection.</p>		
	Serious neurological diagnoses (n=49)	Other diagnoses (n=858)	Total (n=907)
Risk factor			
Migraines	3	51	54
Nausea or vomiting	19	402	421
Light-headedness	19	290	309

Reference	Navi BB <i>et al.</i> 2012. Rate and Predictors of Serious Neurologic Causes of Dizziness in the Emergency Department. Mayo Clinic Proc. 87(11): 1080-1088			
	Headache	9	181	190
	Gait disturbance	23	130	153
	Visual disturbance besides diplopia	7	92	99
	Dyspnoea	4	76	80
	URI symptoms	2	67	69
	Sensory disturbance	6	62	68
	Chest pain	2	67	69
	Psychiatric symptoms	1	65	66
	Tinnitus	6	48	54
	Syncope	3	47	50
	Confusion	3	37	40
	Hearing loss	1	35	36
	Speech disturbance	10	15	25
	Diplopia	7	16	23
	Unilateral weakness	9	8	17
	Dix–Hallpike manoeuvre documented (abnormal)	4 (1)	145 (81)	149 (82)
	<p>Inclusion criteria: people aged 18 years or older who visited the emergency department between January 2007 and December 2009, with any of the following reported triage symptoms as the primary symptom: dizzy, dizziness, vertigo, spinning, imbalance, or disequilibrium.</p> <p>Exclusion criteria: primary symptoms not included in the above list (determined by independent review by 2 neurologists). Additional eligible emergency department visits by a person already included in the study were not recorded.</p> <p>Additional population details: 628 people (69%) presented with a triage symptom of 'dizzy' or 'dizziness', 240 (26%) with 'vertigo' or 'spinning', and 39 (4%) with 'imbalance' or 'disequilibrium'. Isolated dizziness was present in 169 (19%) and nystagmus in 81 (9%) people Laboratory evaluation was performed in 703 (78%), ECG in 612 (68%) and neuroimaging in 321 (28%) patients</p>			

Reference	Navi BB <i>et al.</i> 2012. Rate and Predictors of Serious Neurologic Causes of Dizziness in the Emergency Department. Mayo Clinic Proc. 87(11): 1080-1088		
	<p>Diagnosis: there was 72% agreement on the diagnosis of serious neurologic disease between the 2 assessors (disagreements resolved by a third reviewer)</p> <p>Mean (SD) age: of 59 (19) years</p> <p>Male/female: 42/58%</p> <p>Median duration of symptoms: 1 day (IQR: 0-2 days)</p> <p>Previous episodes of dizziness: 295 (33%)</p>		
	Serious neurological diagnoses (n=49)	Other diagnoses (n=858)	Total (n=907)
	Comorbidities		
	36	411	447
	24	227	251
	7	124	131
	10	81	91
	8	69	77
	8	46	54
	1	24	25
	1	9	10
Clinical predictors	<p><i>A priori</i> potential predictors of outcome were:</p> <ul style="list-style-type: none"> • age • diabetes mellitus • Dix–Hallpike manoeuvre • focal examination abnormalities (any neurologic sign besides nystagmus, for example, gait disturbance, limb or facial weakness, limb ataxia) • imbalance as the reference triage symptom • isolated dizziness symptoms • positional symptoms • previous stroke. 		

Reference	Navi BB <i>et al.</i> 2012. Rate and Predictors of Serious Neurologic Causes of Dizziness in the Emergency Department. Mayo Clinic Proc. 87(11): 1080-1088
Confounders OR stratification strategy	See predictors above (also considered as confounders) Only predictors that were significantly ($p < 0.10$) associated with the outcome in univariate analysis were included in the final multivariate model: <ul style="list-style-type: none"> • age • imbalance as the triage symptom • isolated dizziness • previous stroke • focal examination abnormalities.
Outcomes and effect sizes	Odds ratios (95% CI) for serious neurologic disease versus other diagnosis in multivariate analysis Focal examination abnormality: 5.9 (3.1-11.2) Age ≥ 60 years: 5.7 (2.5-13.4) Imbalance as triage symptom: 5.9 (2.3-15.2) Previous stroke: 2.0 (0.8-5.0) Isolated dizziness: 0.2 (0.0-0.7)
Comments	Risk of bias assessments: Selection bias – VERY HIGH (not all plausible confounders considered; for example, headache, vomiting, nystagmus and intermittency of dizziness are absent from the analysis, and just less than 10 events per variable) Detection bias – MODERATE (6 raters assessed the risk factors and lack of adjustment for inter-rater measurements errors but data abstraction used standardised forms optimised for reliability of data abstraction and a data dictionary provided for reference to answer potential queries) Attrition bias – LOW Overall: very serious risk of bias

H.1.112 HINTs test

Study	Chen 2011¹²⁷
Study type	Cohort study
Number of studies (number of participants)	1 (n=24)

Study	Chen 2011¹²⁷
Country and setting	Australia. Emergency department.
Funding	Not stated (the authors have no conflict of interest to disclose)
Duration of study	1 year
Age, gender, family origin	Mean age: 64 years (SD 13 years; range 42-83 years) Gender: 63% M/37% F Family origin: Not stated
Patient characteristics	<p>People who presented with acute isolated vertigo to the emergency department were identified by referral. The indications for referral were uncertain diagnosis, presence of vascular risk factors (smoking, hypertension, diabetes, dyslipidaemia, atrial fibrillation and recent neck trauma) and failure of symptoms improvement for safe discharge.</p> <p>Inclusion criteria: acute prolonged rotatory vertigo associated with nausea or vomiting, without other brainstem signs.</p> <p>Exclusion criteria: tinnitus; antecedent viral illness; prior diagnosis or attacks suggestive of Meniere's disease; vestibular migraine; corticospinal tract dysfunction; appendicular and truncal cerebellar signs; hemianopia or other visual field defect; Horner's syndrome; sensory disturbance; facial palsy; bulbar dysfunction and dysarthria; dense motor signs – 3, 4 or 6 nerve palsy, internuclear ophthalmoplegia, gaze palsy.</p> <p>n=20 vestibular group: all VN (n=10/10) had positive h-HIT and unidirectional nystagmus, but 1 patient had SD and abnormal vertical smooth pursuit (SP). In all the strokes (n=10/10), 1 of the following signs suggesting of central lesion was present: negative h-HIT, central-type nystagmus, SD or abnormal vSP.</p> <p>n=4 cochleovestibular group, all had normal DWI, but 3 patients had central ocular motor signs (abnormal vertical SP and SD)</p>
Index test	4-step ocular motor signs examination (h-HIT, directionality of nystagmus, SD and vertical smooth pursuit)
Reference standard	Neuroimaging (MRI with diffusion-weighted imaging, DWI)
Target condition	Stroke
Results:	
TP	10
FP	4
FN	0

Study	Chen 2011 ¹²⁷
TN	10
Sensitivity	100%
Specificity	90%
Other measures as agreed with the Committee:	
PPV	
NPV	
Positive likelihood ratio	
Negative likelihood ratio	
Area under the curve	
General limitations (according to QUADAS-2)	Very high risk of bias because of patient selection (very small sample size; sampling from a high-risk population)

Study	Kattah 2009 ²⁵⁹
Study type	Prospective cross-sectional
Number of studies (number of participants)	1 (n=101)
Country and setting	USA. Hospital.
Funding	Grants from the National Institute for Health and Agency for Healthcare Research and Quality
Duration of study	9 years
Age, gender, family origin	Mean age: 62 years (SD 13 years; range 26-92 years) Gender: 65% M/35% F Family origin: Not stated

Study	Kattah 2009 ²⁵⁹
Patient characteristics	<p>Inclusion: people with acute vestibular syndrome (AVS), characterised by the rapid onset (over seconds to hours) of vertigo, nausea or vomiting, and gait unsteadiness in association with head-motion intolerance and nystagmus lasting days to weeks; people with at least 1 stroke risk factor (such as smoking, hypertension, diabetes, hyperlipidaemia, atrial fibrillation, eclampsia, hypercoagulable state, recent cervical trauma, or prior stroke or myocardial infarction)</p> <p>Exclusion: people with a history of recurrent vertigo with or without auditory symptoms</p> <p>n=25 peripheral lesion, n=76 central lesion (69 ischemic strokes, 4 haemorrhages, 2 demyelinating disease, 1 anticonvulsant toxicity)</p>
Index test	HINTS (normal h-HIT, direction-changing nystagmus and skew deviation)
Reference standard	Neuroimaging (MRI with diffusion-weighted imaging, DWI)
Target condition	Central lesion
Results:	
TP	76
FP	1
FN	0
TN	24
Sensitivity	100%
Specificity	96%
Other measures as agreed with the Committee:	
PPV	
NPV	
Positive likelihood ratio	25 (3.66-170.59)
Negative likelihood ratio	0.00 (0.00-0.11)
Area under the curve	

Study	Kattah 2009 ²⁵⁹
General limitations (according to QUADAS-2)	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)

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Study	Kerber 2015 ²⁶³
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=272; n=202 had full HINTS test)
Country and setting	USA. Tertiary medical centre.
Funding	Grant from the Agency for Healthcare Research and Quality
Duration of study	4 years
Age, gender, family origin	Median age, years (IQR): people with stroke, 60.6 (51.0-71.3); people without stroke 56.1 (48.6-66.5) Gender: 47% M/53% F Family origin: 78% White non-Hispanic; 13% Black non-Hispanic; 5% Asian; 10% Hispanic; 1% Other race or culture
Patient characteristics	Inclusion criteria: Dizziness as a principal reason for the medical encounter; continuous dizziness symptoms at the time of the study examination; nystagmus (spontaneous or gaze-evoked) or objective and subjective new imbalance when walking. The minimum requirement for objective imbalance was the inability to take 10 steps in tandem without a side step, after up to 2 attempts. Exclusion criteria: Age<18 years, prisoners, people not fluent in English or unable to provide informed consent because of cognitive or psychiatric impairment; more than 14 days since onset of continuous dizziness at the time of study examination;

Study	Kerber 2015 ²⁶³
	<p>chronic recurrent dizziness (defined as ≥ 5 prior episodes similar in quality, intensity, and duration to the current symptoms, with at least 1 episode more than 1 year prior and 1 within the past year); history of multiple sclerosis; dizziness thought to be the result of trauma, orthostatic hypotension, medication or drug intoxication, or a known medical or neurologic disorder (for example, hepatic encephalopathy, hydrocephalus); posterior canal benign paroxysmal positional vertigo (that is, characteristic transient upbeat-torsional nystagmus on the Dix–Hallpike test performed and interpreted by a study clinician) unless spontaneous or gaze-evoked nystagmus was also present; moderate to severe, new, CNS examination abnormalities (for example, hemiparesis, hemisensory loss, axial ataxia, gaze palsy); people with a contraindication to MRI. People with possible or only mild abnormalities (for example, small deviations on coordination testing, mild dysarthria, or sensory symptoms) were not excluded. Screening examinations performed and interpreted by a study or treating clinician. The examiner’s judgment was used to determine whether the finding was consistent with a CNS abnormality and whether the severity was more than a possible or mild abnormality.</p> <p>n=29 (11%) with acute stroke confirmed by MRI n=243 (89%) without acute stroke confirmed by MRI</p> <p>n=202 had full HINTS test</p>
Index test	HINTS (normal h-HIT, direction-changing nystagmus, and skew deviation)
Reference standard	MRI
Target condition	Stroke
<p>Results:</p> <p>TP</p> <p>FP</p> <p>FN</p> <p>TN</p> <p>Sensitivity (calculated)</p> <p>Specificity (calculated)</p>	<p>20</p> <p>100</p> <p>4</p> <p>78</p> <p>83 (63-95)%</p> <p>44 (36-51)%</p>

Study	Kerber 2015 ²⁶³
Other measures as agreed with the Committee:	
PPV	
NPV	
Positive likelihood ratio	
Negative likelihood ratio	
Area under the curve	0.77 (0.69-0.84)
General limitations (according to QUADAS-2)	High risk of bias (unclear whether the index test results were interpreted with knowledge of the results of the reference standard)

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Study	Newman-Toker 2013 ³⁵¹
Study type	Cross-sectional study
Number of studies (number of participants)	1 (n=190)
Country and setting	USA. Emergency department.
Funding	No commercial support has been accepted related to the development or publication of these activities. A grant from the Swiss National Science Foundation supported the efforts of Dr Mantokoudis.
Duration of study	3 months
Age, gender, family origin	Median age: 61.0 years (range 18-92 years; IQR 52.0-70.0) Gender: 60.5% M/39.5% F Family origin: 90% White non-Hispanic; 6.3% Black or African American; 3.7% Other race or culture
Patient characteristics	Inclusion criteria: people with at least 1 hour of acute, persistent, continuous vertigo or dizziness with spontaneous or gaze-evoked nystagmus, plus nausea or vomiting, head motion intolerance, and new gait unsteadiness (that is, AVS), presenting

Study	Newman-Toker 2013 ³⁵¹
	<p>within 1 week of symptom onset. People were required to have 1 or more stroke risk factor (such as smoking, hypertension, diabetes, hyperlipidaemia, atrial fibrillation, eclampsia, hypercoagulable state, recent cervical trauma, prior stroke, or myocardial infarction).</p> <p>Exclusion criteria: if the symptom(s) abated prior to 24 hours (n=0), as the technical definition of AVS requires 24 hours of symptoms; history of multiple attacks of recurrent vertigo or dizziness compatible with Meniere’s disease, vestibular migraine, idiopathic recurrent vertigo, or if they were successfully treated for benign paroxysmal positional vertigo (BPPV) by Canalith Repositioning Procedure; lethargy sufficient to prevent participation in examination.</p> <p>Men and women with AVS were equally likely to have vestibular neuritis (35.7% versus 33.3%, chi-square p=0.74). Men were slightly more likely than women to have stroke were (64.3% versus 52.0%, chi-square p=0.09), and women were much more likely to have other central causes (0.0% versus 14.7%, chi-square p<0.001).</p> <p>n=66 (34.7%) vestibular neuritis n=113 (59.5%) posterior fossa stroke (n=105 (92.2%) infarction; n=8 (7.1%) haemorrhage</p>
Index test	HINTS (normal h-HIT, direction-changing nystagmus, and skew deviation)
Reference standard	Neuroimaging (MRI with diffusion-weighted imaging, DWI)
Target condition	Stroke
Results:	
TP	109
FP	1
FN	4
TN	65
Sensitivity	96.5 (91.7-98.9)%
Specificity	84.4 (75.0-91.3)%

Study	Newman-Toker 2013 ³⁵¹
Other measures as agreed with the Committee:	
PPV	
NPV	
Positive likelihood ratio	6.19 (3.86-10.42)
Negative likelihood ratio	0.04 (0.02-0.11)
Area under the curve	0.995 (0.985-1.000)
General limitations (according to QUADAS-2)	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)

H.112 Facial pain, atraumatic

2 No relevant clinical studies were identified.

H.113 Memory failure in adults (Memory tests)

4 No relevant clinical studies were identified.

H.154 Sensory symptoms such as tingling and numbness in adults

6 No relevant clinical studies were identified.

H.175 Tremor in adults

8 No relevant clinical studies were identified.

H.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

H.2.21 Head shape or size abnormalities

3 No relevant clinical studies were identified.

H.2.22 Headaches

5 No relevant clinical studies were identified.

H.2.23 Motor developmental delay (creatine kinase tests)

7 No relevant clinical studies were identified.

H.2.24 Paroxysmal events

9 No relevant clinical studies were identified.

1 Appendix I: Health economic evidence tables

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

I.1.131 Dizziness and vertigo including the HINTS test in adults

I.1.141 Dizziness and vertigo

5 No relevant health economic studies were identified.

I.1.162 HINTS test

7 No relevant health economic studies were identified.

I.1.182 Facial pain, atraumatic

9 No relevant health economic studies were identified.

I.1.103 Memory failure in adults (Memory tests)

11 No relevant health economic studies were identified.

I.1.124 Sensory symptoms such as tingling or numbness in adults

13 No relevant health economic studies were identified.

I.1.145 Tremor in adults

15 No relevant health economic studies were identified.

I.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

I.2.1 Blackouts and other paroxysmal events

3 No relevant health economic studies were identified.

I.2.2 Headache

5 No relevant health economic studies were identified.

I.2.3 Head shape or size abnormalities

7 No relevant health economic studies were identified.

I.2.4 Motor developmental delay and unsteadiness (creatine kinase tests)

9 No relevant health economic studies were identified.

I.2.5 Sensory symptoms such as tingling and numbness in children

11 No relevant health economic studies were identified.

Appendix J: GRADE tables

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

J.1.1 Dizziness and vertigo including the HINTS test in adults

J.1.1.1 Dizziness and vertigo

Table 2: Risk factors for serious neurological diagnoses

Quality assessment							Adjusted effects	Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations , including publication bias where possible	Effect with 95% CIs	
Focal examination abnormality for predicting serious neurological diagnoses (adjusted ORs)								
1	Cohort studies	very serious ^a	no serious inconsistency	serious ^b	No serious imprecision	None	Adjusted OR[95% CI]: 5.9 [3.1, 11.2]	VERY LOW
Imbalance as triage symptom for predicting serious neurological diagnoses (adjusted ORs)								
1	Cohort studies	very serious ^a	no serious inconsistency	serious ^b	No serious imprecision	None	Adjusted OR[95% CI]: 5.9 [2.3, 15.2]	VERY LOW
Isolated dizziness for predicting serious neurological diagnoses (adjusted ORs)								
1	Cohort studies	very serious ^a	no serious inconsistency	serious ^b	No serious imprecision	None	Adjusted OR[95% CI]: 0.2 [0.0, 0.7]	VERY LOW

^a 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).

^b Outcome definition does not match our protocol and misclassification of final diagnosis possible

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Table 3: Sensitivity and specificity of the HINTS test in patients presenting with dizziness

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%.

J.1.12 Facial pain, atraumatic

12 No relevant clinical studies were identified.

J.1.13 Memory failure in adults (Memory tests)

14 No relevant clinical studies were identified.

J.1.14 Sensory symptoms such as tingling or numbness in adults

16 No relevant clinical studies were identified.

J.1.15 Tremor in adults

18 No relevant clinical studies were identified.

J.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

J.2.1 Blackouts and other paroxysmal events

No relevant clinical studies were identified.

J.2.2 Headache

No relevant clinical studies were identified.

J.2.3 Head shape or size abnormalities

No relevant clinical studies were identified.

J.2.4 Motor developmental delay and unsteadiness (creatine kinase tests)

No relevant clinical studies were identified.

J.2.5 Sensory symptoms such as tingling or numbness in children

No relevant clinical studies were identified.

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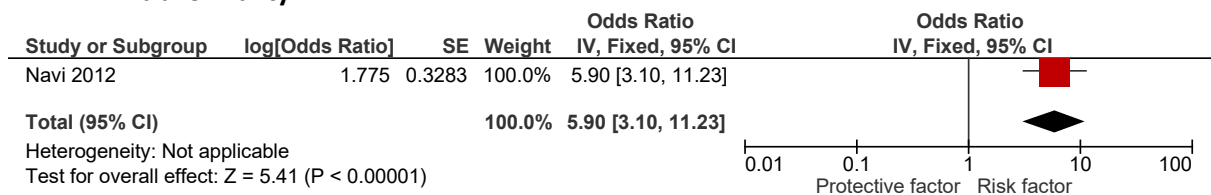
1 Appendix K: Forest plots

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

K.1.1 Dizziness and vertigo including the HINTS test in adults

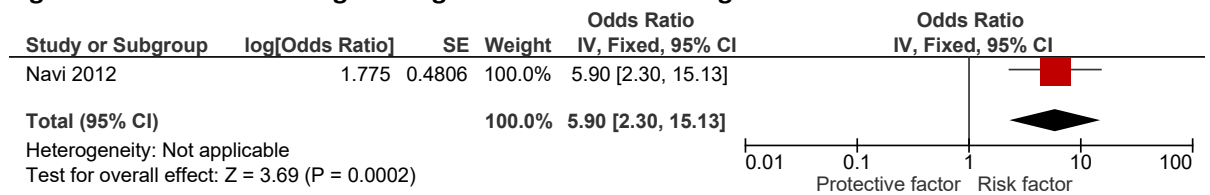
K.1.1.1 Dizziness and vertigo

Figure 12: Serious neurological diagnoses versus other diagnoses – Risk factor: focal examination abnormality



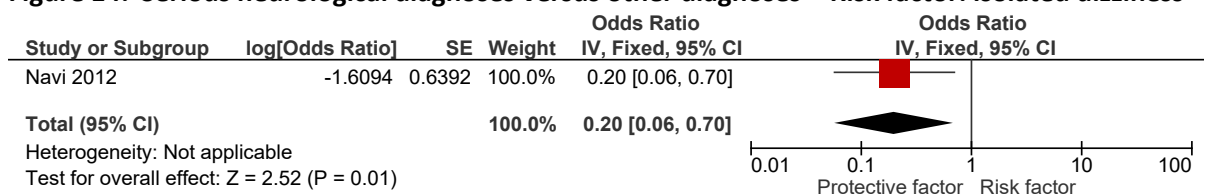
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Figure 13: Serious neurological diagnoses versus other diagnoses – Risk factor: imbalance



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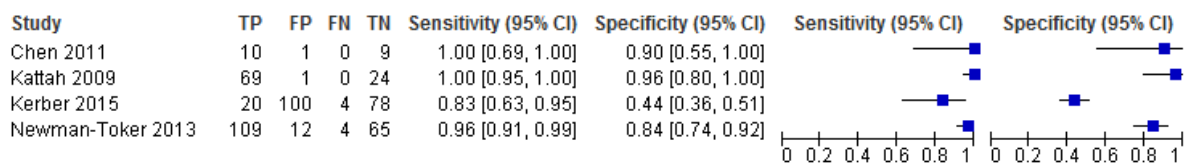
Figure 14: Serious neurological diagnoses versus other diagnoses – Risk factor: isolated dizziness



K.1.1.2 HINTS test

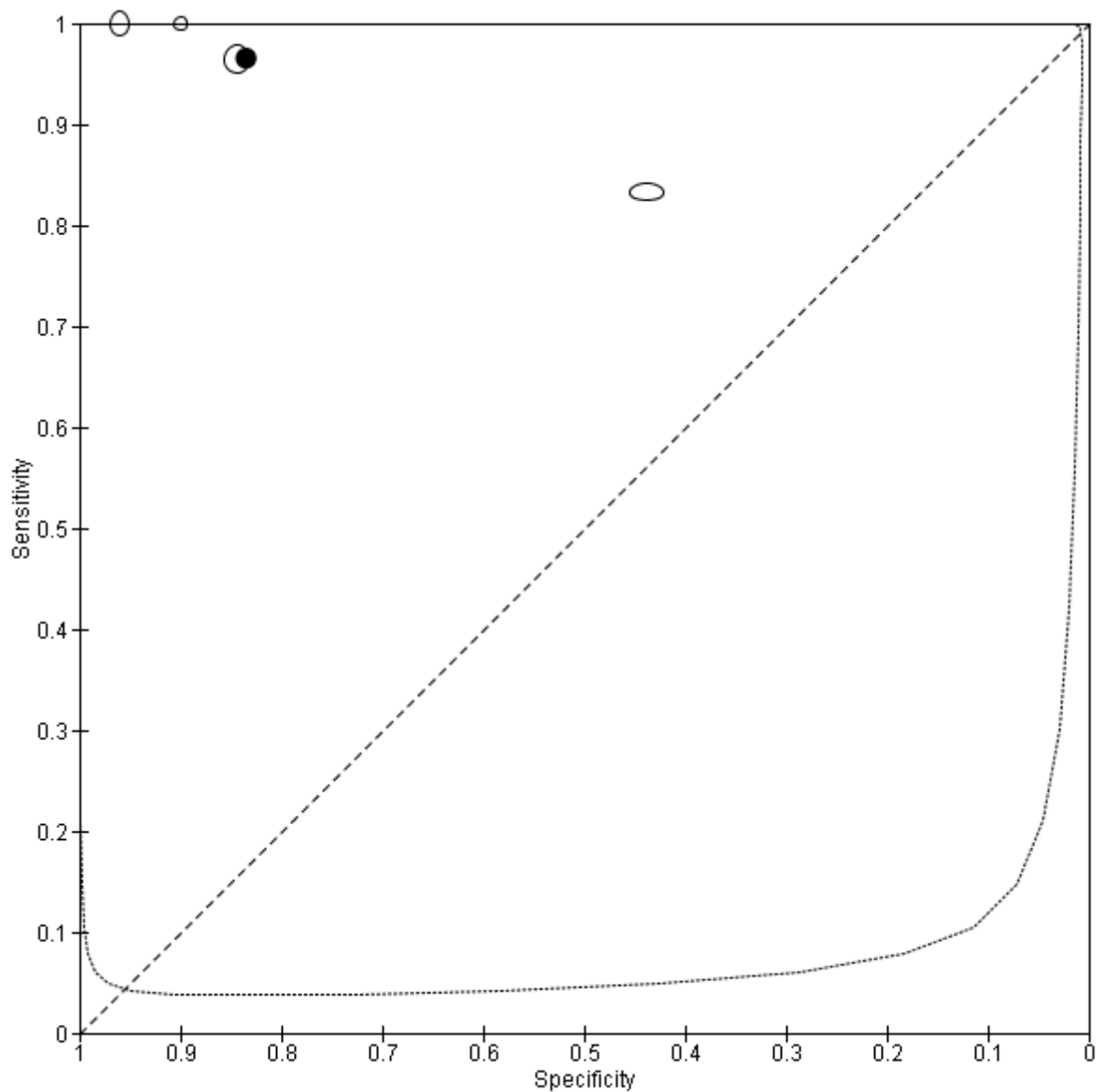
K.1.1.2.1 Coupled sensitivity and specificity forest plots

Figure 15: HINTS test Coupled sensitivity and specificity



K.1.1.2.2 Pooled estimate of sensitivity and specificity

Figure 16: Graph of pooled estimate of sensitivity and specificity with 95% confidence intervals



K.12 Facial pain, atraumatic

3 No relevant clinical studies were identified.

K.13 Memory failure in adults (Memory tests)

5 No relevant clinical studies were identified.

K.14 Sensory symptoms such as tingling or numbness in adults

7 No relevant clinical studies were identified.

K.15 Tremor in adults

9 No relevant clinical studies were identified.

K.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

2

K.2.1 Blackouts and other paroxysmal events

4 No relevant clinical studies were identified.

K.2.2 Headache

6 No relevant clinical studies were identified.

K.2.3 Head shape and size abnormalities

8 No relevant clinical studies were identified.

K.2.4 Motor developmental delay and unsteadiness (creatine kinase tests)

10 No relevant clinical studies were identified.

K.2.5 Sensory symptoms such as tingling or numbness in children

12 No relevant clinical studies were identified.

1 Appendix L: Excluded clinical studies

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

L.1.1 Dizziness and vertigo including the HINTS test in adults

L.1.1.1 Dizziness and vertigo

Reference	Reason for exclusion
Preuss, 2015 ³⁸⁷	Incorrect population: children; diagnosed with intracranial neoplasms (not non-specialist); not presenting with dizziness
Jelavoc 2015 ³³⁶	Incorrect population: presentation of syncope; incorrect setting: specialist
O'Mahony 1998 ³⁵⁶	Incorrect population: presentation of dizziness in 20% (results not stratified); incorrect study type: no multivariate or prognostic analysis
Colledge 1996 ¹³⁴	Incorrect study type: distinguishing dizzy versus non-dizzy and no multivariate or prognostic analysis
Salmito 2015 ⁴¹⁶	Incorrect study type: no multivariate or prognostic analysis and no link to neurological problems
Lee 2012 ²⁹²	Incorrect study type: no multivariate or prognostic analysis and no link to neurological problems
Kentala, 2000 ²⁶²	Incorrect setting: specialist centre
Obermann, 2015 ³⁵⁸	Incorrect study type: assessing improvement in dizziness score over time
Mahringer, 2014 ³¹⁴	Incorrect intervention: non-listed predictor (vHIT and bHIT tests)
Kroenke, 1994 ²⁸¹	Incorrect study type: assessing improvement in dizziness over time; no linking of symptoms and neurological problems
Olusesi, 2016 ³⁶³	Incorrect study type: no multivariate or prognostic analysis and no link to neurological problems
Newman-Toker, 2013 ³⁵¹	Incorrect study type: no multivariate or prognostic analysis

L.1.1.2 HINTS test

Reference	Reason for exclusion
Cohn 2014 ¹³³	Incorrect study design (systematic review with different protocol, includes reference standard other than MRI)
Lee 2015 ²⁹⁵	Incorrect study design (non-systematic review)
Newman-Toker 2013 ³⁵³	Proof of concept study looking at diagnostic accuracy of video-oculography device based on HINTS to help diagnose stroke. Not looking directly at the accuracy of the HINTS test itself. Evidence is not directly applicable for use as a basis for recommendations.
Newman-Toker 2013 ³⁵²	Abstract only (conference abstract, not a full paper)
Newman-Toker 2015 ³⁵⁰	Incorrect study design (non-systematic review)
Saber Tehrani 2014 ⁴¹²	Subgroup analysis for small strokes of the same data published in Newman-Toker 2013 ³⁵¹
Thomas 2016 ⁴⁴¹	Incorrect study design (letter to editor)

L.172 Facial pain, atraumatic

Reference	Reason for exclusion
Agbelusi 2005 ⁸	Addresses a different question
Aggarwal 2010 ⁹	No association of symptoms
Agius 2010 ¹¹	No association of symptoms
Agius 2010 ¹⁰	No association of symptoms
Akhter 2011 ¹⁵	Univariate analysis only
Ali 2008 ¹⁹	No association of symptoms
Ammori 2013 ²⁴	Addresses a different question
Balasa 2010 ⁵¹	No association of symptoms
Bhaskaracharya 2015 ⁷⁵	Univariate analysis only
Burchiel 1993 ⁹⁴	No relevant analysis
Campbell 1985 ⁹⁸	Addresses a different question
Ciancaglini 1999 ¹³¹	No association of symptoms
Cooper 2007 ¹³⁷	No association of symptoms
Cruccu 2009 ¹⁴⁰	No association of symptoms
Dupont Jr 2003 ¹⁶⁶	No association of symptoms
Fitzek 2001 ¹⁸³	No association of symptoms
Foley 2013 ¹⁸⁷	Unadjusted data only
Fujarra 2016 ¹⁹²	Addresses a different question
Fujii 2002 ¹⁹³	No association of symptoms
Gui 2013 ²¹¹	Invalid study design
Hamlyn 1992 ²¹³	Invalid study design
Hassett 2013 ²¹⁸	Addresses a different question
Inoue 2009 ²⁴¹	No association of symptoms
Jo 2013 ²⁵⁰	Addresses a different question
Juniper 1999 ²⁵³	Univariate analysis only
LeResche 2007 ²⁹⁸	No association of symptoms
Maarbjerg 2014 ³¹¹	Addresses a different question
Matsushima 2004 ³¹⁹	No association of symptoms
Mayne 2014 ³²¹	Invalid population
Mora 2009 ³³⁵	Traumatic injury
Moyaho-Bernal 2010 ³³⁷	Univariate analysis only
Obermann 2010 ³⁵⁹	Univariate analysis only
Osterberg 2005 ³⁶⁵	Univariate analysis only
Otuyemi 2000 ³⁶⁶	Univariate analysis only
Perez 2013 ³⁷⁹	Invalid study design (epidemiological, cross sectional study)
Raphael 2000 ³⁹⁶	Univariate analysis only
Rasmussen 1991 ³⁹⁷	Univariate analysis only
Vickers 2000 ⁴⁶⁰	Invalid study design (review)
von Piekartz 2015 ⁴⁶⁴	No association of symptoms
Zakrzewska 1999 ⁴⁸³	No association of symptoms

L.183 Memory failure in adults (Memory tests)

Reference	Reason for exclusion
Abdel-Aziz, 2015 ¹	Incorrect population: not early presentation
Arabi, 2013 ³⁵	Incorrect population: not early presentation
Belmin, 2007 ⁶²	Incorrect population: not early presentation
Borson, 2000 ⁸²	Incorrect population: not early presentation
Bottino, 2013 ⁸⁵	Abstract: incorrect population (not early presentation)
Brodsky, 2002 ⁹⁰	Incorrect population: not early presentation
Brooke, 1999 ⁹¹	Incorrect population: includes confirmed dementia; not early presentation
Carnero-Pardo, 2013 ¹⁰⁹	Incorrect population: not early presentation
Cervilla, 2004 ¹¹⁷	Incorrect population (not early presentation) and analysis
Chan, 2015 ¹²¹	Incorrect population: not early presentation
Chan, 2016 ¹²⁰	Incorrect population: not early presentation
Damian, 2011 ¹⁴²	Incorrect population: not early presentation
Dash, 2006 ¹⁴⁴	Insufficient information - no population details, insufficient reporting of outcome statistics
Davis, 2015 ¹⁴⁶	Review: not early presentation; incorrect index tests
Dougherty Jr, 2010 ¹⁶²	Incorrect population: not early presentation
Fage, 2015 ¹⁷⁹	Review: not early presentation; not primary care
Ferri, 2012 ¹⁸²	Abstract: insufficient information
Fuchs, 2012 ¹⁹¹	Incorrect population: not early presentation
Goldschmidt, 1983 ²⁰⁴	Incorrect population: age range not disclosed; incorrect study design: reference standard not performed on those negative on index test
Golstein, 2015 ²⁰⁵	Abstract: incorrect population (not early presentation)
Grober, 2008 ²⁰⁹	Incorrect population: not early presentation
Grober, 2014 ²⁰⁸	Incorrect population: not early presentation
Harrison, 2014 ²¹⁵	Review: not early presentation; incorrect index tests
Haubois, 2013 ²¹⁹	Incorrect population: not early presentation
Hessler, 2014 ²²⁶	Incorrect population: not early presentation
Jessen, 2011 ²⁴⁷	Incorrect population: not early presentation
Jimenez, 2015 ²⁴⁹	Abstract: insufficient information
Johansson, 2014 ²⁵¹	Incorrect population: not early presentation
Kamenski, 2009 ²⁵⁴	Incorrect population (not early presentation); incorrect reference standard
Kuslansky, 2002 ²⁸⁵	Incorrect population (not early presentation); incorrect index tests
Larner, 2014 ²⁸⁸	Incorrect population (not early presentation); incorrect index tests
Lee, 2009 ²⁹¹	Abstract: incorrect population (not early presentation)
Lischka, 2012 ³⁰²	Review: not early presentation; insufficient study information
Mitchell, 2009 ³³²	Review: Incorrect population (not early presentation)
Mitchell, 2010 ³³³	Incorrect index tests
Navarro Espigares, 2009 ³⁴²	Abstract: insufficient information
O'Sullivan, 2016 ³⁵⁷	Narrative review
Papageorgiou, 2014 ³⁶⁸	Incorrect population: not early presentation
Pezzotti, 2008 ³⁸⁰	Incorrect population: not early presentation

Reference	Reason for exclusion
Pirani, 2015 ³⁸¹	Abstract: incorrect population (not early presentation)
Ranson, 2015 ³⁹⁴	Abstract: insufficient information
Rous, 2014 ⁴¹⁰	Abstract: insufficient information
Sager, 2006 ⁴¹⁴	Incorrect population: not early presentation
Shaik, 2016 ⁴²⁵	Incorrect population: not early presentation
Solomon, 1998 ⁴³¹	Incorrect population: not early presentation
Sorbi, 2012 ⁴³²	Review: not early presentation; insufficient study information
Stein, 2015 ⁴³³	Incorrect population: not early presentation
Takechi, 2010 ⁴³⁷	Incorrect population: not early presentation; Incorrect study design: case-control
Tierney, 2000 ⁴⁴⁴	Incorrect population: not early presentation
Tierney, 2003 ⁴⁴³	Incorrect population: not early presentation
Trustram Eve, 2014 ⁴⁴⁸	Incorrect tests; no diagnostic data
Upadhyaya, 2010 ⁴⁵¹	Incorrect population: not early presentation
Velayudhan, 2014 ⁴⁵⁵	Review: not early presentation; insufficient study information
Wolfsgruber, 2014 ⁴⁷⁸	Not in English language
Yokomizo, 2014 ⁴⁸¹	Abstract: incorrect population (not early presentation)
Yokomizo, 2014 ⁴⁸²	Review: not early presentation; insufficient study information

L.194 Sensory symptoms such as tingling or numbness in adults and children

Reference	Reason for exclusion
Anekstein 2012 ²⁷	Addresses a different question
Ansari 2009 ³¹	Addresses a different question
Antunes 2000 ³³	Invalid study design (review)
Atroshi 2003 ⁴¹	Addresses a different question
Bares 2001 ⁵³	Non-English language
Barnes 2006 ⁵⁴	Addresses a different question
Baron 2009 ⁵⁵	Univariate analysis
Bastyr 2005 ⁵⁶	Validation of a questionnaire
Beck 2012 ⁵⁷	Addresses a different question
Beck 2013 ⁵⁸	Addresses a different question
Beghi 1989 ⁵⁹	Univariate analysis
Beijers 2015 ⁶⁰	Addresses a different question
Beiske 2004 ⁶¹	Univariate analysis
Berini 2014 ⁶⁸	Univariate analysis
Boorugu 2014 ⁸⁰	Addresses a different question
Borhani-Haghighi 2006 ⁸¹	Univariate analysis
Bozek 2001 ⁸⁶	Unavailable but from the abstract it appears to be a univariate analysis
Brenaut 2015 ⁸⁷	No association of symptoms. Questionnaire based exploratory study
Bridgeman 2007 ⁸⁸	Univariate analysis
Buonocore 2006 ⁹³	Addresses a different question
Caliandro 2006 ⁹⁷	Addresses a different question
Carlson 2010 ¹⁰⁷	Addresses a different question
Caro 2008 ¹¹⁰	Univariate analysis

Reference	Reason for exclusion
Casale 1989 ¹¹³	Addresses a different question
Castillo 1999 ¹¹⁵	Addresses a different question
Chang 2001 ¹²²	Univariate analysis
Chow 2005 ¹³⁰	Addresses a different question (differential diagnosis of carpal tunnel syndrome and cervical spondylosis)
Copeman 1988 ¹³⁸	Univariate analysis
Davis 2014 ¹⁴⁷	Univariate analysis
de Campos 2004 ¹⁴⁹	No association of symptoms
Denard 2010 ¹⁵¹	Univariate analysis
Dones 2003 ¹⁶¹	Univariate analysis (review of 27 cases of Chiari I malformation)
Duby 2004 ¹⁶⁵	Systematic review
Duston 1989 ¹⁶⁷	Univariate analysis
Elrefai 2009 ¹⁷²	Univariate analysis (prevalence of neuropathy in feet of diabetic patients)
Flores 2015 ¹⁸⁴	Univariate analysis
Franse 2000 ¹⁸⁹	Addresses a different question
Fu 2014 ¹⁹⁰	Addresses a different question (predictive factors for neurological complications in liver transplantation patients)
Gell 2005 ¹⁹⁶	No association of symptoms
Goh 2011 ²⁰³	Univariate analysis only
Gorson 1999 ²⁰⁶	Addresses a different question
Hird 2010 ²²⁷	Addresses a different question
Horowitz 1979 ²²⁹	Addresses a different question
Iqal 2015 ²⁴²	Unavailable but from abstract it appears to be a univariate analysis (Peripheral neuropathy: Incidence and clinical presentation in the cases of diabetic mellitus)
Jacovides 2014 ²⁴³	Univariate analysis
Jepsen 2006 ²⁴⁶	Addresses a different question
Ji 2012 ²⁴⁸	Addresses a different question
Jones Jr 2010 ²⁵²	No multivariate analysis
Karam 2014 ²⁵⁷	Addresses a different question (outcome predictors of post-traumatic syringomyelia)
Kendall 2009 ²⁶⁰	Incorrect population (children with human T-cell lymphotropic virus type 1)
Keniston 1997 ²⁶¹	Mixed population (not all participants had CTS)*
Kesler 2000 ²⁶⁵	Addresses a different question (complications of essential thrombocytosis)
Kim 2016 ²⁶⁸	Univariate analysis (in students with backpack palsy)
Kleiner-Fisman 2007 ²⁷²	Addresses a different question
Konen 1996 ²⁷⁴	No multivariate analysis
Kratz 2016 ²⁷⁹	Addresses a different question
Lauder 2000 ²⁸⁹	Addresses a different question
Lauder 2000 ²⁹⁰	Addresses a different question (prediction of electrodiagnostic outcomes)
Lee 2012 ²⁹⁶	No multivariable analysis (identification of carpal tunnel syndrome in Behçet's disease)

Reference	Reason for exclusion
Lee 2015 ²⁹³	Addresses a different question (neurologic adverse events following influenza A in children)
Li 2016 ³⁰⁰	Addresses a different question. Univariate analysis
Lin 2011 ³⁰¹	Addresses a different question
Lucchetta 2012 ³¹⁰	Incorrect population
McKillop 2014 ³²⁴	Systematic review
Miles 2015 ³³⁰	Systematic review
Nakatani 2011 ³⁴⁰	Univariate analysis only. Looking at prevalence of symptoms
Neopane 2003 ³⁴⁶	Univariate analysis. Incorrect population
Neumann 1995 ³⁴⁷	Addresses a different question
Newland 2014 ³⁴⁹	Univariate analysis
Ntani 2013 ³⁵⁴	Addresses a different question
Orita 2015 ³⁶⁴	Invalid population
Overgaard 2004 ³⁶⁷	Univariate analysis (tingling and numbness in the hands of computer users)
Rae-Grant 1999 ³⁹⁰	No multivariable analysis
Rana 2014 ³⁹³	Addresses a different question. Looking at predictors of pain and not pain as a predictor
Rathore 2002 ³⁹⁹	Univariate analysis only
Rauck 2013 ⁴⁰⁰	Addresses a different question
Reading 2003 ⁴⁰²	Univariate analysis only
Rico 2014 ⁴⁰⁴	Addresses a different question
Rubino 2007 ⁴¹¹	Univariate analysis of diabetic peripheral neuropathy symptoms
Sawaya 2006 ⁴¹⁸	Addresses a different question. No multivariable analysis (peripheral neuropathy in thalassemia)
Schifitto 2002 ⁴¹⁹	No multivariable analysis
Shian 1994 ⁴²⁶	Univariate analysis only
Siva 2009 ⁴²⁸	Addresses a different question
Smart 2012 ⁴²⁹	Addresses a different question
Solomon 2011 ⁴³⁰	Addresses a different question
Tabatabaei-Malazy 2011 ⁴³⁶	Univariate analysis (prevalence of diabetic peripheral neuropathy and related factors)
Tamburin 2008 ⁴⁴⁰	No association of symptoms*
Thomas 2012 ⁴⁴²	Invalid study type (narrative review)
Tietjen 1993 ⁴⁴⁵	Addresses a different question. Predictive factors for antiphospholipid immunoreactivity in transient focal neurological events
Vegosen 2012 ⁴⁵⁴	Invalid population
Vrethem 2002 ⁴⁶⁵	Univariate analysis (analysis of data from a questionnaire follow-up study in patients with neuroborreliosis)
Whitworth 2010 ⁴⁷³	Addresses a different question

L.105 Tremor in adults

Reference	Reason for exclusion
Benito-Leon 2015 ⁶³	Incorrect population
Chase 2015 ¹²³	Incorrect study design

Reference	Reason for exclusion
Deuschl 2015 ¹⁵⁵	No association of symptoms
Diamond 2014 ¹⁵⁷	Not guideline condition
Dogu 2005 ¹⁶⁰	No association of symptoms
Duarte 1995 ¹⁶⁴	Incorrect study design
Duval 2006 ¹⁶⁸	Incorrect population
Erer 2009 ¹⁷⁴	Prevalence only
Gelb 1999 ¹⁹⁵	Incorrect study design
Gironell 2001 ¹⁹⁹	Not available
Hely 1995 ²²⁴	No association of symptoms
Hely 1999 ²²⁵	Not relevant analysis
Hughes 1992 ²³⁵	Test accuracy data
Lou 1991 ³⁰⁵	Unadjusted data only
Louis 1996 ³⁰⁸	Unadjusted data only
Louis 1998 ³⁰⁹	No association of symptoms
Louis 2011 ³⁰⁶	Incorrect study design
Louis 2013 ³⁰⁷	No association of symptoms
Mahlknecht 2015 ³¹²	Incorrect population
Martinelli 1987 ³¹⁶	Unadjusted data only
McDermott 1995 ³²²	Not relevant analysis
Meneghini 1992 ³²⁷	Test accuracy data
Montgomery 2000 ³³⁴	No association of symptoms
Mutch 1991 ³³⁸	Unadjusted data only
Parkinson Study Group 1989 ³⁷⁰	No association of symptoms
Patel 2015 ³⁷¹	Incorrect study design
Pearce 1968 ³⁷⁴	No association of symptoms
Post 2007 ³⁸⁵	Systematic review (included studies were assessed)
Poston 2009 ³⁸⁶	No association of symptoms
Quagliato 2009 ³⁸⁹	No association of symptoms
Rao 2003 ³⁹⁵	Systematic review (included studies were assessed)
Salemi 1998 ⁴¹⁵	Environmental associations
Sun 2006 ⁴³⁵	Incorrect study design
Tallon-Barranco 1997 ⁴³⁹	Incorrect population
Vesela 2002 ⁴⁵⁹	Not in English
Wenning 2000 ⁴⁷¹	Not relevant analysis
Whaley 2007 ⁴⁷²	Incorrect population

L12 Part 2: Children aged under 16 – signs, symptoms and investigative tests

12

L.2.31 Blackouts and paroxysmal events

Reference	Reason for exclusion
Abe 1982 ²	No multivariate analysis. Addresses a different question. An investigation into how the behaviours manifested at 3 years of age have changed after 5 years' follow-up
Abend 2011 ³	Univariate analysis only. Retrospective analysis of children identified from a prospective paediatric stroke registry to define the incidence of seizures as presenting symptom of arterial ischemic stroke
Adelow 2009 ⁷	No multivariate analysis
Akhtar 2002 ¹⁴	People previously diagnosed with epilepsy underwent ECG to determine how many children may have cardiovascular anomalies. Authors only present the number of people with possible alternative diagnoses to epilepsy. No multivariate analysis
Alam 2012 ¹⁸	Narrative literature review
Altunbasak 2007 ²⁰	2-year prognosis of epilepsy
An 2010 ²⁵	Logistic regression only used for predictors of prognosis
Anderson 1989 ²⁶	Addresses a different question
Annegers 2000 ²⁸	Univariate analysis
Annegers 1998 ²⁹	No multivariate analysis
Annegers 1987 ³⁰	Addresses a different question. Prognostic factors of unprovoked seizures after febrile convulsions
Apakama 2006 ³⁴	Addresses a different question. Video monitoring in children referred for an outpatient EEG
Arango 2012 ³⁶	No multivariate analysis
Arndt 2016 ³⁸	Narrative review. No extractable data
Attumalil 2011 ⁴²	Variables in the multivariate analysis were only looking at birth and neonatal aspects. No predictors of interest to our review were included
Austin 2015 ⁴⁴	Addresses a different question. The variables included in the multivariate analysis include parent variables, child behaviours problems and seizure occurrence, which are not predictors of interest to our review question
Austin 2001 ⁴⁵	Addresses a different question. The variables included in the multivariate analysis are our outcomes of interest not the predictors
Austin 2011 ⁴⁶	Addresses a different question. The variables included in the multivariate analysis include demographic, seizure risk factors and family risk factors, which are not predictors of interest to our review question
Bademosi 1989 ⁵⁰	Case control study with no multivariate analysis
Berg 1998 ⁶⁴	Addresses a different question. Looks at the influence of the onset of unprovoked seizures in the recurrence of seizures in children after febrile seizures
Berg 1996 ⁶⁵	No multivariate analysis
Berg 1999 ⁶⁶	Identification of differences between children with epilepsy with and without febrile seizures
Bergamo 2015 ⁶⁷	Univariate analysis only
Bertelsen 2016 ⁶⁹	Abstract only

Reference	Reason for exclusion
Beslow 2013 ⁷¹	Addresses a different question. Risk factors for seizures and epilepsy in children. No multivariate analysis
Beslow 2010 ⁷²	Addresses a different question. Features of children with intracerebral haemorrhage and predictors of short-term outcomes
Bessiso 1990 ⁷³	No multivariate analysis
Betts 1992 ⁷⁴	Addresses a different question
Bhattacharyya 2014 ⁷⁶	Univariate analysis only
Bonkowsky 2009 ⁷⁹	No multivariate analysis
Bosson 2014 ⁸³	Addresses a different question. Risk of apnoea in patients with seizures. Multivariate analysis includes age, medicated in the field, seizure on PED arrival and seizure disorder
Bosson 2014 ⁸⁴	Addresses a different question. Risk factors for apnoea not apnoea as a risk factor
Brown 1996 ⁹²	Narrative review. No extractable data
Bye 1994 ⁹⁵	Clinical description of complex partial seizures. No multivariate analysis
Bye 2000 ⁹⁶	No multivariate analysis. Ten-year retrospective study of non-epileptic paroxysmal events in children
Canavese 2012 ⁹⁹	Addresses a different question. Clinical and video-EEG-polymyographic study of paroxysmal non-epileptic motor events
Canpolat 2014 ¹⁰²	No multivariate analysis
Cansu 2007 ¹⁰³	No association of symptoms. Not clear if patients had paroxysmal events and one of the predictors or not
Caplan 2004 ¹⁰⁴	Addresses a different question. Looking at the role of cognition, language, seizure and demographic variables in the psychopathology of complex partial seizures
Caraballo 2003 ¹⁰⁵	Univariate analysis
Caraballo 2011 ¹⁰⁶	Clinical description of EEG in childhood absences
Carman 2013 ¹⁰⁸	Multivariate analysis does not include any predictors relevant to the review question. Mostly looked at socio-demographic, birthweight, consanguinity, and parents' age and education
Carvalho 2001 ¹¹²	No multivariate analysis
Casetta 2002 ¹¹⁴	Investigation of pre-, mid- and post-natal risk factors for cryptogenic and idiopathic epilepsy
Chahine 2006 ¹¹⁸	Narrative review. No extractable data
Chahine 2006 ¹¹⁹	Narrative review. No extractable data
Chen 2010 ¹²⁵	Univariate analysis
Chen 2015 ¹²⁶	Univariate analysis
Chiaretti 2000 ¹²⁸	Univariate analysis
Ciceri 2011 ¹³²	Review
Covanis 1992 ¹³⁹	Univariate analysis. Early prognostic signs of absence epilepsy
Dai 2006 ¹⁴¹	Narrative review. No extractable data
Daoud 2003 ¹⁴³	Univariate analysis
Datta 2005 ¹⁴⁵	Addresses a different question. To determine which factors contribute most to psychopathology in children with epilepsy. No predictors of interest in the multivariate analysis (sociodemographic, treatments, seizure variables including type, duration and frequency)
Dennis 1978 ¹⁵³	Book chapter

Reference	Reason for exclusion
Dhiman 2014 ¹⁵⁶	Clinical description and suggestion for new classification
DiMario 2006 ¹⁵⁸	Narrative review. No extractable data
Ellenberg 1986 ¹⁷⁰	Addresses a different question. The impact of seizures on children's intellectual performance
Ellenberg 1978 ¹⁷¹	Addresses a different question. Investigates whether intellectual deterioration is caused by seizures in children
Emam 2009 ¹⁷³	Addresses a different question. Pattern, risk factors, diagnosis and outcome of stroke. Does not present the results of a multivariate analysis
Espeche 2010 ¹⁷⁵	No multivariate analysis
Espeche 2011 ¹⁷⁶	No multivariate analysis. Analysis of electro-clinical features and evolution of patients with benign infantile seizures associated with paroxysmal dyskinesia
Ettinger 1999 ¹⁷⁸	Wrong population (adults)
Fattal-Valevski 2013 ¹⁸⁰	Addresses a different question. Clinical description of paediatric brain tumours that present with seizures
Fois 1982 ¹⁸⁵	No multivariate analysis
Fois 1988 ¹⁸⁶	No multivariate analysis
Geelhoed 2005 ¹⁹⁴	Addresses a different question. Accuracy of models in predicting long-term outcome of epilepsy
Graves 2012 ²⁰⁷	Narrative summary. Recommendations for practice
Hamati-Haddad 1998 ²¹²	Addresses a different question. Incidence of febrile convulsions in an epilepsy clinical population and relates presence and characteristics of febrile convulsions to the localisation of subsequent epilepsy
Hansen 2015 ²¹⁴	Survey. No multivariate analysis
Hauser 1970 ²²⁰	Narrative summary. No extractable data
Heijbel 1980 ²²³	Univariate analysis only
Horrocks 2005 ²³⁰	Addresses a different question. Clinical description of the features of a series of children with anoxic-epileptic seizures
Hrastovec 2012 ²³¹	No multivariate analysis
Huang 1998 ²³³	No multivariate analysis
Huguenard 2016 ²³⁶	No multivariate analysis
Kamiishi 1994 ²⁵⁵	No multivariate analysis. Follow-up of childhood absence epilepsy with a history of febrile convulsions
Kannoth 2009 ²⁵⁶	Wrong population. Includes adults and children (mean age 32 years, range 6–85)
Karasalihoglu 2003 ²⁵⁸	Multivariate analysis does not include variables of interest (for example, history of birth asphyxia, type of seizure, polypharmacy)
Kim 2012 ²⁶⁹	Addresses a different question. Clinical and video-EEG-polymyographic study of paroxysmal non-epileptic motor event
King 1999 ²⁷⁰	Addresses a different question. Looking at whether MRI and EEG would reveal abnormal clinical features of benign partial seizures of adolescents
Kirkpatrick 1998 ²⁷¹	Narrative literature review
Koo 1993 ²⁷⁵	No multivariate analysis
Korff 2005 ²⁷⁷	Addresses a different question. Eye closure during paroxysmal events and link to seizures
Kristensen 1992 ²⁸⁰	No multivariate analysis
Krumholz 1983 ²⁸²	No multivariate analysis

Reference	Reason for exclusion
Ku 2014 ²⁸³	Long-term (11 years) follow-up of children with febrile seizures. Logistic regression includes sex, urbanisation and occupation as variables. No predictors of interest to our review question
Lal 2014 ²⁸⁶	Univariate analysis only
Lee 2016 ²⁹⁴	Long-term follow-up to identify prognostic factors that can predict epilepsy in children with febrile seizures
Lee 1989 ²⁹⁷	Univariate analysis only
Mallick 2014 ³¹⁵	Univariate analysis. Epidemiology and clinical features of childhood arterial ischemic stroke
Matsumoto 1985 ³¹⁷	Addresses a different question. Predictors of long-term outcomes if convulsive disorders
Matsumoto 2013 ³¹⁸	Unobtainable
Metrick 1991 ³²⁸	No multivariate analysis
Miano 2010 ³²⁹	Univariate analysis only
Neligan 2012 ³⁴³	Prospective cohort study looking at long-term risk of developing epilepsy after febrile seizures (follow-up to 20 years)
Nelson 1978 ³⁴⁴	Addresses a different question. Looking at death, motor disabilities and recurrence of seizure. No multivariate analysis
Nevo 1995 ³⁴⁸	Addresses a different question. Risk factors for seizures not seizures as risk factors. Multivariate analysis includes cerebral palsy, mental retardation, febrile seizures and prematurity as variables
O'Brien 1981 ³⁵⁵	Narrative summary. No multivariate analysis or extractable data
Ogunniyi 1987 ³⁶⁰	No multivariate analysis. Risk factors investigated include febrile seizures, head trauma, previous immunisation, use of psychotropic drugs and stimulants, haemoglobinopathy and syphilis
Ogunrin 2014 ³⁶¹	Cross sectional case-control study. No multivariate analysis
Park 2015 ³⁶⁹	Univariate analysis
Patel 2007 ³⁷²	Univariate analysis. Compares clinical features of non-epileptic seizures between <13 year olds and >13 year olds
Pavlidou 2013 ³⁷³	Long-term follow-up of children with febrile seizures. No association of symptoms
Pearce 1979 ³⁷⁵	No multivariate analysis. Looking at risk factors as long-term predictors in children with convulsive disorder
Per 2014 ³⁷⁶	No multivariate analysis
Plioplys 2014 ³⁸²	Psychogenic non-epileptic seizures. Only data reported from logistic regression is somatic psychiatric and adversity variables. No predictors relevant to our review question
Plioplys 2016 ³⁸³	Addresses a different question. Risk factors for comorbid psychopathology in youth with psychogenic non-epileptic seizures
Proulx 1993 ³⁸⁸	No multivariate analysis. Addresses a different question. Assessment of BP measurement in children admitted to PICU for hypertensive crisis or status epilepticus to determine whether this can differentiate between the 2 conditions. Reports sensitivity, specificity, NPV and PPV
Rossiter 1977 ⁴⁰⁹	Univariate analysis only. Descriptive statistics of convulsions in the first year of life
Saemundsen 2007 ⁴¹³	No multivariate analysis
Saltik 2003 ⁴¹⁷	No multivariate analysis
Sehgal 1979 ⁴²²	Univariate analysis. Recurrence of febrile seizures

Reference	Reason for exclusion
Seki 1981 ⁴²³	Univariate analysis only
Sfaihi 2012 ⁴²⁴	Epidemiological study. Univariate analysis only
Silver 2008 ⁴²⁷	Addresses a different question
Trinka 2002 ⁴⁴⁷	No multivariate analysis
Ueoka 1980 ⁴⁵⁰	Abstract on follow-up of children with febrile convulsions
Vaghani 2013 ⁴⁵²	No multivariate analysis
Verduyn 1992 ⁴⁵⁶	Descriptive study. No extractable data
Verity 1991 ⁴⁵⁷	No multivariate analysis
Verrotti 2000 ⁴⁵⁸	No multivariate analysis
Vincentiis 2006 ⁴⁶¹	No multivariate analysis. Risk factors for psychogenic non-epileptic seizures in children already diagnosed with epilepsy
Visser 2010 ⁴⁶²	Investigates the prenatal and perinatal factors that may predict the incidence of paroxysmal epileptic and non-epileptic disorders within the first year of life. No predictors of interest in the multivariate analysis
Visser 2012 ⁴⁶³	No predictors of interest in the multivariate analysis (examples include maternal indicators and birthweight)
Wakamoto 2011 ⁴⁶⁶	Clinical characteristics of childhood absences
Wallace 1984 ⁴⁶⁸	Narrative review. No extractable data
Wallace 1979 ⁴⁶⁹	No multivariate analysis
Wang 2008 ⁴⁷⁰	Looked at scoring system based on frequency of seizures. Data not relevant to our review question
Wiebe 2008 ⁴⁷⁴	Systematic review
Yang 1995 ⁴⁷⁹	No multivariate analysis
Yilmaz 2013 ⁴⁸⁰	Unobtainable

L.2.2 Headache

Reference	Reason for exclusion
Abu-Arafeh 2004 ⁴	No association of symptoms
Abu-Arafeh 2005 ⁵	No association of symptoms
Abu-Arafeh 2010 ⁶	No association of symptoms
Ahmed 2010 ¹²	No multivariable analysis
Ahmed 1996 ¹³	No association of symptoms
Akyuz 2000 ¹⁶	Unadjusted data only
Al-Twajiri 2002 ¹⁷	No association of symptoms
Amarilyo 2011 ²¹	Not relevant analysis
Anttila 2002 ³²	No association of symptoms. Question about causes of tension type headaches not headache as a predictor of our outcomes of interest.
Atiq 2006 ⁴⁰	No association of symptoms
Aui-Aree 2010 ⁴³	Invalid populations (only 10% had a headache)
Auvichayapat 2007 ⁴⁷	Univariate analysis only
Babar 2012 ⁴⁹	Unavailable
Balottin 2005 ⁵²	No association of symptoms
Bertoli 2007 ⁷⁰	Invalid population (aged 4–18 years)
Brna 2005 ⁸⁹	Unadjusted data only

Suspected neurological conditions
Excluded clinical studies

Cannavo 2003 ¹⁰⁰	Invalid population (aged over 12 years), no association of symptoms
Canpolat 2015 ¹⁰¹	Invalid study design (case series)
Carotenuto 2005 ¹¹¹	Not relevant condition
Cavestro 2014 ¹¹⁶	Univariate analysis only
Conicella 2008 ¹³⁶	Unadjusted analyses only
de Ribaupierre 2008 ¹⁵⁰	No association of symptoms
Deng 2015 ¹⁵²	No association of symptoms
Esposito 2012 ¹⁷⁷	Unadjusted analyses only
Fernandez-Mayoralas 2010 ¹⁸¹	No association of symptoms
Foroughipour 2011 ¹⁸⁸	Univariate analysis only
Genizi 2013 ¹⁹⁷	Outcomes, ADHD and learning disabilities (might need further checking)
Genizi 2016 ¹⁹⁸	No data provided
Gladstein 1993 ²⁰⁰	Univariate analysis only
Glatstein 2015 ²⁰¹	Unadjusted data only
Glueck 1986 ²⁰²	Not relevant analysis
Harrison 1982 ²¹⁶	Unadjusted data only
Holden 1994 ²²⁸	Not adjusted for identified predictors
Hsiao 2014 ²³²	Univariate analysis only
Hussain 1995 ²³⁷	Prevalence of headache types
Jaffe 1985 ²⁴⁴	Invalid population (not headache)
Kernick 2009 ²⁶⁴	Unadjusted data only
Khan 2015 ²⁶⁶	No association of symptoms
Kienbacher 2006 ²⁶⁷	Not relevant analysis
Klitbo 2011 ²⁷³	Unadjusted data only
Kranick 2013 ²⁷⁸	Invalid population (stroke)
Kung 2009 ²⁸⁴	Unadjusted data only
Lanphear 2014 ²⁸⁷	Unadjusted data only
Lewis 2000 ²⁹⁹	Unadjusted data only, invalid population (under 18 year olds)
Medina 2001 ³²⁶	Cost-effectiveness analysis
Nelson 2010 ³⁴⁵	No association of symptoms
Preuss 2015 ³⁸⁷	Univariate analysis only
Raieli 2015 ³⁹¹	Univariate analysis only
Rains 2008 ³⁹²	Invalid study design (review)
Rasul 2009 ³⁹⁸	Invalid population (neurological deficit)
Ravid 2013 ⁴⁰¹	Unadjusted data only
Reulecke 2008 ⁴⁰³	No data provided
Robbins 2010 ⁴⁰⁵	Invalid population (aged over 12 years)
Rossi 1989 ⁴⁰⁷	Invalid study design (review)
Rossi 1992 ⁴⁰⁸	Univariate analysis only
Uche 2013 ⁴⁴⁹	Univariate analysis only
Waldie 2014 ⁴⁶⁷	No association of symptoms
Wilne 2012 ⁴⁷⁵	Addresses a different question. Evolution of clinical features of brain tumours
Wilne 2007 ⁴⁷⁶	Systematic review

Wilne 2006 ⁴⁷⁷	Invalid population (aged 15 weeks to 17 years)
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L.23 Head shape and size abnormalities

Reference	Reason for exclusion
Aring 2007 ³⁷	No association of symptoms
Boere-Boonekamp 2001 ⁷⁸	Univariate analysis only
Collett 2011 ¹³⁵	Not adjusted for any of the listed confounders
Day 1979 ¹⁴⁸	No association of symptoms
Huang 1998 ²³⁴	Invalid study design
Hutchison 2004 ²³⁸	No association of symptoms
Hutchison 2009 ²³⁹	Univariate analysis only
Hutchison 2011 ²⁴⁰	No association of symptoms
Jansen 1982 ²⁴⁵	No association of symptoms
Kordestani 2005 ²⁷⁶	No association of symptoms
Lorber 1981 ³⁰³	Univariate analysis only
Losee 2007 ³⁰⁴	Univariate analysis only
Mawji 2014 ³²⁰	No association of symptoms
McElrath 2010 ³²³	Invalid population
McKinney 2008 ³²⁵	Invalid study design
Miller 2000 ³³¹	No relevant analysis
Oh 2009 ³⁶²	Data not reported
Pomatto 2006 ³⁸⁴	No association of symptoms
Roddi 1995 ⁴⁰⁶	Invalid study design
Seal 2013 ⁴²⁰	Invalid study design
Talebian 2013 ⁴³⁸	Univariate analysis only
Tomlinson 2007 ⁴⁴⁶	No association of symptoms
Van Dommelen 2015 ⁴⁵³	Diagnostic test accuracy data

L.24 Motor developmental delay and unsteadiness (creatine kinase tests)

Reference	Reason for exclusion
Amato 198 ²²	No relevant analysis
Ambegaonkar 2011 ²³	No relevant analysis
Aston 1984 ³⁹	No relevant analysis
Avaria 2012 ⁴⁸	Not available
Birdi 2005 ⁷⁷	No relevant analysis
Chen 1983 ¹²⁴	No relevant analysis
Chien 2011 ¹²⁹	No relevant analysis
Diniz 2014 ¹⁵⁹	No relevant analysis
Drousiotou 1998 ¹⁶³	No relevant analysis
Edwards 1984 ¹⁶⁹	No relevant analysis
Gruemer 1984 ²¹⁰	No relevant analysis
Hashim 2011 ²¹⁷	Invalid population
Heath 1984 ²²²	Invalid population
Mahoney 1977 ³¹³	No relevant analysis

Reference	Reason for exclusion
Nagappa 2013 ³³⁹	No relevant analysis
Percy 1979 ³⁷⁷	No relevant analysis
Percy 1984 ³⁷⁸	No relevant analysis
Seay 1978 ⁴²¹	No relevant analysis
Stubgen 1993 ⁴³⁴	No relevant analysis
Zatz 1978 ⁴⁸⁶	No relevant analysis
Zatz 1980 ⁴⁸⁵	No relevant analysis
Zatz 1991 ⁴⁸⁴	No relevant analysis
Zhang 2012 ⁴⁸⁷	No relevant analysis

17 Appendix M: Excluded health economic studies

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

M.1.01 Dizziness and vertigo including the HINTS test in adults

M.1.11 Dizziness and vertigo

22 No relevant health economic studies were identified for exclusion.

M.1.12 HINTS test

24 No relevant health economic studies were identified for exclusion.

M.1.2 Facial pain, atraumatic

26 No relevant health economic studies were identified for exclusion.

M.1.3 Memory failure in adults (Memory tests)

28 No relevant health economic studies were identified for exclusion.

29 Sensory symptoms such as tingling or numbness in adults. No relevant health economic studies were identified for exclusion.
30

M.1.4 Tremor in adults

32 No relevant health economic studies were identified for exclusion.

M.2 Part 2: Children aged under 16 – signs, symptoms and investigative tests

M.2.1 Blackouts and other paroxysmal events

36 No relevant health economic studies were identified for exclusion.

M.2.2 Headache

38 No relevant health economic studies were identified for exclusion.

M.2.3 Head shape and size abnormalities

40 No relevant health economic studies were identified for exclusion.

M.2.4 Motor developmental delay and unsteadiness (creatine kinase tests)

42 No relevant health economic studies were identified for exclusion.

43 **Appendix N: Cost impact of neurological**
44 **outpatient attendances**

45 For each recommendation, the committee considered the additional pressures that additional
46 referrals could place on neurological services. To give the committee a reference point for what
47 impact the recommendations could have, it was presented with the annual total number of
48 neurological referrals along with the total cost to the NHS. The following outpatient attendance
49 numbers were taken from the Hospital Episode Statistics (HES) for England 2014/15.²²¹

50 The HES show the number of first-time outpatient attendances split by age group. It was felt that this
51 number would capture all of the attendances that arise from referral for a neurological symptom.

52 For children and young people under 17 years of age, the HES showed data for individuals attending
53 neurological services and paediatric neurological services separately. These data are shown in Table 4
54 below. For young people and adults above 16 years of age, the data showed the number attending
55 paediatric neurological services (336) was <0.1% of total appointments and is therefore not shown
56 below.

57 Overall, the data show that in 2014/15 there were:

- 58 • 24,696 first-time outpatient visits for a neurological-related problem for children under the age of
59 17
- 60 • 493,110 first-time outpatient visits for a neurological-related problem for young people and
61 adults over the age of 16.

62 NHS reference costs (2015/16) show that a consultant-led neurological outpatient attendance costs
63 £178.94. A consultant-led paediatric neurological outpatient visit costs £380.16.¹⁵⁴

64 If we apply the NHS reference costs to all neurological outpatient visits for those under 16, the total
65 cost to the NHS is between £7,944,183 and £9,388,337. The range of costs depends on the cost of
66 neurological services for children who do not see a paediatric neurologist, which the data below
67 suggest occurs in 29% of people under 17 years of age.

68 If we apply the cost of an average neurological outpatient visit to all neurological outpatient
69 attendances to those over 16 years of age, the cost to the NHS is £88,303,003.

70 Therefore, if first-time neurological attendances for children were to be increased by 10%, this would
71 cost the NHS approximately £1,000,000. If first-time neurological attendances for adults increase by
72 1%, this would cost the NHS approximately £900,000.

73 The committee was presented with these data and used them to make judgements about the
74 potential health economic impact of recommendations within this guideline.

Table 4: Number of first-time outpatient attendances for individuals under 17 years

Type of service accessed	Age (years)						TOTAL
	0	1-4	5-9	10-14	15	16	
Neurology	508	927	890	1,005	365	3,482	7,177
Paediatric neurology	1,255	4,721	5,275	4,631	1,072	565	17,519
							24,696

Table 5: Number of first-time neurological outpatient attendances for individuals over 16 years

Age	17	18	19	20-24	25-29	30-34	35-39	40-44	45-49	50-54
Number of attendances	5,048	5,148	4,934	27,577	32,078	33,787	34,420	39,557	46,075	47,527
Age (continued)	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90-120	TOTAL	
Number of attendances	42,464	38,068	40,848	34,239	29,235	19,325	9,571	2,873	492,774	

Appendix O: Rationale for categorising symptoms

Summary of committee decisions and rationales for prioritising signs and symptoms (scope section 1.5, Q1.1 and Q1.2: Indications for referral).

Table 6: Signs and symptoms relevant for adults

Symptom	Decision	Rationale
Acute confusion	Initial decision: Cross-refer to existing guidance Final decision: Not prioritised	The committee initially thought it would cross-refer or adapt recommendations from the delirium guideline to non-specialist, non-institutional settings. However, after further consideration, it was decided that because delirium is only one cause of confusion and most causes of confusion are general medical problems rather than neurological problems, there would be no contention with the fact that any acute onset of unexplained confusion that cannot be managed in primary care would be referred for neurological assessment.
Blackouts (TLOC)	Cross-refer to existing guidance	Cross-refer to TLOC guideline as the recommendations adequately cover recognition and referral for adults.
Coma	Not prioritised for inclusion in guideline	Not prioritised as adults presenting with coma would always be referred immediately to secondary care as an emergency.
Distortion or disturbance of eyesight	Not prioritised for inclusion in guideline	Not prioritised as most referrals are to ophthalmology units.
Dizziness and vertigo	Evidence review	This is a commonly presenting symptom with numerous causes, some benign and some indicating potentially serious neurological disease. A key issue is how to differentiate central nervous system causes from peripheral vestibular disorders. Evidence to support recommendations in this area would be helpful.
Facial pain, atraumatic	Evidence review	This is a common presentation in primary care. It is widely misdiagnosed as people with atraumatic facial pain are often treated for trigeminal neuralgia, which can be managed in primary care. Atraumatic facial pain should sometimes be referred. A key issue is therefore the signs and symptoms that help differentiate trigeminal neuralgia from other causes. Evidence to support the committee's decision-making would be helpful.

Symptom	Decision	Rationale
Gait unsteadiness	Consensus recommendations and cross-refer to existing guidance	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.
Handwriting difficulties	Consensus recommendations	Adults who have new-onset difficulty writing should always be referred.
Limb or facial weakness	Consensus recommendations and cross-refer to existing guidance	Assessment and referral depends on clinical skills and established ground rules which are uncontentious. Cross-refer to MND and stroke guideline, as the recommendations adequately cover recognition and referral for adults. There is a need to define circumstances in which radiculopathy requires referral.
Memory failure	Consensus recommendations	Concentration difficulties are commonly misconstrued as memory problems. There is a need for guidance for non-specialists on how to recognise the effects of anxiety, as patients are often inappropriately referred. There is a parallel issue of under-referral and delayed diagnosis of younger patients with dementia.
Posture distortion	Consensus recommendations	Dystonia often remains unrecognised in primary care, yet it is often readily treated with botulinum toxin in specialist clinics. Guidance for non-specialists on how to diagnose and refer is required.
Sensory symptoms such as tingling or numbness	Evidence review	This is a common presentation in primary care and there is uncertainty as to when patients should be referred. A key issue is what the clinical features of functional neurological disorders are, which features indicate physical disease, and how urgently these require expert assessment. The committee agreed that an evidence review to support their decision-making would be helpful.
Sleep disorders	Consensus recommendations	There is a need for guidance for non-specialists on which sleep disorders to refer to secondary care. Common problems are sleep behaviour disorders and sleep apnoea. However, this is unlikely to be an area of contention and therefore an evidence review may not add value.
Smell or taste problems	Consensus recommendations	Loss of sense of taste or smell is unusual but very disturbing to patients. There is a need for guidance in primary care on how to recognise anosmia that requires referral because it could be associated with potentially serious neurological disorders. There is also a need for guidance for non-specialists on referral of post-traumatic anosmia, which can usually be managed successfully in primary care.
Speech problems	Consensus recommendations	Onset of disrupted speech is a serious symptom, which always requires expert assessment.

Symptom	Decision	Rationale
Tics and involuntary movements	Consensus recommendations	Spasms and facial dystonias are often misconstrued as tics. Facial dystonias and hemi-facial spasm should be referred for consideration of botulinum toxin treatment; tics should be managed in primary care unless they are very severe. Delayed referrals for hemifacial spasms and facial dystonias is common, implying guidance for non-specialists in this area will be valuable.
Tremor	Evidence review	A key issue is how non-specialists can differentiate a parkinsonian tremor from an essential tremor. A parkinsonian tremor needs to be referred, while an essential tremor can initially be managed in primary care. Guidance for non-specialist on how to differentiate these 2 types of tremor will be valuable. The committee agreed that an evidence review to support their decision-making would be helpful.

1 **Table 7: Signs and symptoms relevant for children**

Symptom	Decision	Rationale
Attention, concentration and memory problems	Consensus recommendations and cross-refer to existing guidance	Memory failure as an isolated symptom in children is very unusual unless they have an established neurological disorder affecting memory function. It is occasionally seen following a head injury. Concentration difficulties are more common, and the key diagnosis to consider is ADHD. Cross-refer to ADHD guideline as the recommendations adequately cover recognition and referral.
Blackouts and other paroxysmal events	Evidence review	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 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.
Clumsiness	Not prioritised for inclusion in the guideline	Not prioritised as clumsiness in isolation usually does not have serious organic cause and will be picked up as part of standard developmental assessment for which there are already referral pathways in place. If serious, recommendations for motor developmental delay will apply.
Coma	Not prioritised for inclusion in guideline	Not prioritised, as children presenting with a coma would always be referred immediately to secondary care as an emergency.

Symptom	Decision	Rationale
Confusion, acute	Consensus recommendations	The delirium guideline does not cover children or young adults. Children presenting with acute confusion should always be referred. Recommendations to consolidate clinical practice would be helpful so that clear guidance is available as some underlying conditions can be life-threatening.
Developmental and intellectual regression	Not prioritised for inclusion in the guideline	Not prioritised, as children with developmental and intellectual regression should always be referred to secondary care (either hospital or community paediatrician). Any delays in diagnosis and management are more likely to occur at the secondary care level. There are many potential causes, including some rare possibilities.
Distortion or disturbance of eyesight	Not prioritised for inclusion in guideline	Not prioritised because children with visual problems usually present in the first instance to an optician, who would then refer those requiring further assessment to ophthalmology.
Dizziness and vertigo	Consensus recommendations	Dizziness from a neurological disorder is not a frequent presentation in children. Common causes include postural hypotension and migraine.
Facial pain, atraumatic	Not prioritised for inclusion in guideline	Not prioritised, as this is not a common presentation in children.
Gait unsteadiness	N/A – covered under motor developmental delay and unsteadiness.	–
Global developmental delay	Not prioritised for inclusion in the guideline	Not prioritised as referral pathways are already in place. A child identified with global developmental delay at any stage in early childhood – by a GP, health visitor or community paediatrician – will initially be referred to developmental paediatric services and then potentially on to tertiary services for investigations if required.
Handwriting difficulties	Not prioritised for inclusion in the guideline	Not prioritised, as there are pathways already in place. Schools refer to community paediatrician. Children with motor developmental problems such as cerebral palsy, which put them at risk of writing disorders, would already have been identified and diagnosed earlier in childhood.
Head shape or size abnormalities	Evidence review	Some children with abnormal head shape or size 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. A key issue is therefore 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.
Headache	Evidence review	The headache guideline does not cover under 12s, so there is a need for guidance regarding this population. Migraine is a common presentation, but there are

Symptom	Decision	Rationale
		<p>concerns about under referral, delayed diagnosis, 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.</p> <p>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:</p> <ul style="list-style-type: none"> • red flags for urgent referral • clinical features of migraine in children under 12 • features commonly seen with headaches that might indicate a brain tumour in children. <p>The committee agreed that an evidence review to support their decision-making would be helpful.</p>
Hypotonia ('floppiness')	Consensus recommendations	Children presenting with hypotonia should always be referred (benign symptoms would be a diagnosis of exclusion). Severe hypotonia is often picked up in the neonatal period. Health visitors and GPs would pick up less severe hypotonia at 6-week baby check. Hypotonia presenting later in childhood would be accompanied by motor developmental delay and is easily recognised. Depending on its severity, children would be referred either to developmental paediatrician or to paediatric neurology.
Limb or facial weakness	Consensus recommendations	Children presenting with limb or facial weaknesses should always be referred. There are occasional benign causes such as pressure palsies from sitting with crossed legs or using an ill-fitting heavy rucksack, but these would be diagnosed after excluding other causes.
Motor developmental delay and unsteadiness	Consensus recommendations and creatine kinase test review	Boys not walking by 18 months should be referred. The important differential diagnosis is Duchenne muscular dystrophy (DMD). A creatine kinase is a good screening test for Duchenne. The necessity to make this diagnosis early is to allow genetic counselling for family members, consideration of steroid therapy, and allowing children the opportunity to participate in drug trials. Other peripheral neuromuscular disorders can also present with motor developmental delay but are much less common than Duchenne. Onset of gait abnormalities in children would always merit referral but does not always have a neurological cause. Guidance is

Symptom	Decision	Rationale
		<p>needed for non-specialists to know where to refer the child and with what degree of urgency.</p> <p>Creatine kinase is an inexpensive test available to non-specialists that may aid referral decisions. The committee therefore prioritised the investigative test aspect of this question for a systematic review, the key issue being the sensitivity and specificity of creatine kinase in diagnosing muscular dystrophies in children.</p>
Posture distortion	Consensus recommendations and cross-refer to existing guidance	Distortion of posture should not be referred if transient. Although dystonia in children does occur, it is usually a part of a dystonic cerebral palsy. Primary dystonia is rare in children, and there is often a delay in diagnosis. Some children are initially thought to have functional disorders. Cross-refer to cerebral palsy and spasticity guidelines.
Sensory symptoms such as tingling or numbness	Evidence review	Tingling or altered body sensation in children is an unusual presentation. 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.
Sleep disorders	Consensus recommendations	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.
Smell or taste problems	Not prioritised for inclusion in guideline	Not prioritised, as this is not a common presentation in children.
Speech developmental delay	N/A – covered under speech problems	–
Speech problems	Consensus recommendations	There is a need for guidance for non-specialists to help differentiate acute onset from speech developmental delay. Pathways into speech therapy are already in place for speech developmental delay.
Squint	Consensus recommendations	Referral pathways to ophthalmology are already in place for squint. Ophthalmology may then refer to neurology. Focal signs should be referred urgently to neurology. A key issue for non-specialists is around the urgency of referrals and to whom to refer.
Tics and involuntary movements	Consensus recommendations	Isolated tic disorders can be managed in primary care. If tics are not isolated, very severe, or the child has anxiety, then referral is appropriate. Key issues in this area are identifying the associated features of tic disorders that necessitate specialist

Symptom	Decision	Rationale
		input and treatment. There is also an issue around where the referral should be made – to psychology, paediatrics or paediatric neurology?
Tremor	Consensus recommendations	Tremor in children is most often seen as part of a motor disorder such as cerebral palsy or developmental dyspraxia. There is already a well-established referral pathway to a developmental paediatrician or occupational therapist. Tremor as a symptom of a progressive neurological disorder is rarely seen in isolation and would be referred for neurological assessment. Tremor can be a presenting sign of hyperthyroidism in children. This would be recognised in primary care and referred.

1 Appendix P: Targeted engagement exercise

P.1 Targeted engagement exercise external experts

Name	Job Title
Lisa Adams	Physiotherapist
Ahmed Al-Dahiri	General Practitioner Partner
Eleanor Au	General Practitioner
Pyari Bose	Consultant Neurologist
Pieter Adriaan Bothma	Consultant in Anaesthesia and Intensive Care
Shachi Buch	Consultant Community Paediatrician specialising in Palliative Care
Susan Bush	Neurophysiotherapist
Mark Coley	General Practitioner
Paul Cooper	Consultant Neurologist
Jon Dickson	General Practitioner
Giles Elrington	Consultant Neurologist
Hedley Emsley	Consultant Neurologist
Will Evans	General Practitioner
Lauren Fratalia	Consultant Neurologist
Gill (Stern) Gallick	Consultant Paediatric Neurophysiotherapist
Vijeya Ganesan	Senior Lecturer in Paediatric Neurology
Kirsty Harkness	Consultant Neurologist
Abigail Henderson	Paediatric Physiotherapist
Ram Kumar	Consultant Paediatric Neurologist specialising in Neurorehabilitation, Spasticity and Movement Disorder Management
Helen Lewis	Consultant Community Paediatrician
Nick Merrifield	General Practitioner Partner
Leena Mewasingh	Consultant Paediatric Neurologist
Karen O'Connor	General Practitioner
Poornima Pandey	Consultant Paediatrician
Prab Prabhakar	Consultant Paediatric Neurologist
Waqar Rashid	Consultant Neurologist
Karen Robson	Community Paediatric Physiotherapist
Styliani Spyridi	Psychiatrist
Andrew Webber	Paramedic Practice Lecturer
William Whitehouse	Clinical Associate Professor; Honorary Consultant Paediatric neurologist
Gabriel Whitlingum	Consultant Paediatrician specialising in Neurodisability and Autism

3 Appendix Q: NICE technical team

Name	Role
Martin Allaby	Clinical Advisor
Ben Doak	Guideline Commissioning Manager
Jane Lynn	Resource Impact Lead

Name	Role
Judith McBride	Editor
Bhash Naidoo	Health Economist
Kay Nolan	Guideline Lead
Jill Peacock	Guideline Coordinator
Toni Tan	Technical Lead

1

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