Motor neurone disease

Motor neurone disease: assessment and management

Clinical guideline <...>

Appendices A – Q

September 2015

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
The Royal College of Surgeons of England
Royal College of General Practitioners
Royal College of Nursing
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Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SCOPE

1 Guideline title

Motor neurone disease: the assessment and management of motor neurone disease

1.1 Short title

Motor neurone disease

2 The remit

The Department of Health has asked NICE: 'to develop a clinical guideline on the assessment and management of motor neurone disease'.

3 Need for the guideline

3.1 Epidemiology

a) Motor neurone disease (MND) is a neurodegenerative condition which affects the brain and spinal cord and is primarily characterised by degeneration of the motor neurones and subsequent loss of motor neurone function.

b) MND presents in 4 main forms;

I. Amyotrophic lateral sclerosis (ALS) which results in upper and lower motor neurone damage with symptoms of wasting and weakness. This occurs in approximately two-thirds of people diagnosed with MND.

II. Progressive bulbar palsy, which is caused by lower motor neurone damage in the head and neck, leading to difficulties

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with swallowing and speech. Progressive bulbar palsy occurs in a quarter of people with MND.

III. Progressive muscular atrophy, which is due to lower motor nerve loss, resulting in weakness and wasting of muscles, especially in the arms. It affects 1 in 10 people with MND.

IV. Primary lateral sclerosis, in which upper motor neurone nerve loss causes increasing stiffness. With this slowly progressive form the prognosis is usually longer – an average of 10–15 years in total.

c) Although MND may initially present in one of the above forms, as the disease progresses the effects on each person vary as both lower and upper motor neurones can become affected in any part of the body. Most people lose the ability to walk, move their arms, swallow, speak and have difficulty breathing, eventually leading to death. Approximately 50% of people with MND show cognitive change, varying from mild frontal lobe changes, which may affect decision making, to frontal temporal dementia.

d) MND is thought to develop as a result of a complex interplay between genetic, environmental and lifestyle factors in the ageing brain.

e) The majority of people with MND do not have a family history of the disease (known as 'sporadic' MND), but approximately 5–10% have a close family relative who has the disease ('familial' MND). Of those who have familial MND, a large proportion have a mutation in the *C9orf72* gene and the other genes and proteins that are linked to familial MND, including *SOD1*, *TARDBP-43* and *FUS*.

f) It is estimated that there are up to 5,000 people with MND in the UK. Approximately 1,100 people are diagnosed annually in the UK, a diagnosis which has a wide-ranging impact not only on the person themselves but on their family and friends.

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g) The onset of disease occurs predominantly between the ages of 55 and 65 years, affecting slightly more men than women. MND is severely life-shortening, with 50% of people dying from respiratory failure within 3 years of developing their first symptoms. However, some people have a slower disease course and may survive for 10 years or more.

3.2 Current practice

a) Motor neurone disease is incurable and the management of symptoms varies across England and Wales. In addition to providing care, the multidisciplinary team may enable people with MND to make treatment preferences in advance, in case their preferences cannot be communicated at the advanced or end stages of the disease. Decisions at the early stages can include where treatment is to be given (at home or in a care home, hospice or hospital) and which medications or interventions should be given as the disease progresses.

b) Drugs can be used for symptom management, but riluzole is the only pharmacological drug licensed in the UK to slow the progression of MND. Other medications and interventions can be used to manage symptoms. For people who have difficulty breathing, non-invasive ventilation may be delivered through a nasal mask, oronasa mask or mouthpiece.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

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4.1 Population

4.1.1 Groups that will be covered

a) Adults (aged 18 and over) with MND.

b) People with frontal temporal dementia will be considered as a separate patient subgroup.

4.1.2 Groups that will not be covered

a) Children and young people (under 18 years).

b) Adults with other neurodegenerative disorders who do not have MND.

c) People diagnosed with Kennedy's disease.

4.2 Healthcare setting

a) All settings in which NHS care is provided.

4.3 Management

4.3.1 Key issues that will be covered

a) Timeliness of diagnosis, and communicating with patients and their families and carers about the diagnosis.

b) Communicating with patients and their families and carers about prognosis and ongoing care.

c) Monitoring and ongoing assessment, including:

- assessment of cognitive impairment
- coordination of care and support across health and social care
- disease progression.

d) Symptom management, including:

- muscle stiffness and cramp

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- muscle weakness
- communication problems
- swallowing difficulties and secretion management, including drooling
- nutrition, including weight management and timing of gastrostomy
- breathing difficulties, including cough assistance.

e) Psychosocial support for people with MND and their families and carers.

f) Identification of social care needs for people with MND and their carers.

g) Managing discontinuation of non-invasive ventilation.

h) Preparation for, and anticipation of, end of life.

4.3.2 Issues that will not be covered

i) Diagnosis, including investigations.

j) Complementary therapies.

k) Riluzole.

l) Tracheostomy.

m) Dietary supplements with the aim of modifying disease progression.

n) Enteral feeding.

4.4 Main outcomes

o) Health-related quality of life.

p) Patient and carer-reported outcomes, for example, symptoms, satisfaction and pain.

q) Function measured by disability scores.

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r) Hospital admissions (including unplanned admissions).

s) Mobility.

t) Survival.

4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

4.5.1 Timeliness of diagnosis

What is the time to diagnosis for people with MND in the UK and what are the main causes of delay?

4.5.2 Communicating with people with motor neurone disease and their families and carers

a) What are the best methods of communicating diagnosis to people with MND and their families and carers?

b) What are the best methods of communicating prognosis and choices of ongoing care to people with MND and their families and carers?

4.5.3 Monitoring and ongoing assessment

a) What are the most clinically and cost effective cognitive assessment tools for people with MND?

b) Does multidisciplinary team care, including social care, improve patient and carer outcomes in people with MND?

c) What are the most clinical and cost effective assessment tools for monitoring the progression of MND and what should be the frequency of assessment?

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d) What are the most effective and cost effective assessment tools for assessing the social care needs for people with MND and how often should these needs be reassessed?

4.5.4 Symptom management

a) What is the clinical and cost effectiveness of pharmacological treatments for managing muscle stiffness in people with MND?

b) What is the clinical and cost effectiveness of non-pharmacological treatments for managing muscle stiffness in people with MND?

c) What is the clinical and cost effectiveness of equipment for managing muscle stiffness in people with MND?

d) What is the clinical and cost effectiveness of pharmacological treatments for managing muscle cramps in people with MND?

e) What is the clinical and cost effectiveness of non-pharmacological treatments for managing muscle cramps in people with MND?

f) What is the clinical and cost effectiveness of pharmacological treatments for managing muscle weakness in people with MND?

g) What is the clinical and cost effectiveness of non-pharmacological treatments for managing muscle weakness in people with MND?

h) What is the clinical and cost effectiveness of equipment for managing muscle weakness in people with MND?

i) What is the clinical and cost effectiveness of systems for managing communication problems in people with MND?

j) What is the clinical and cost effectiveness of pharmacological treatments for secretion management in people with MND?

k) What is the clinical and cost effectiveness of non-pharmacological treatments for secretion management in people with MND?

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l) What is the clinical and cost effectiveness of treatments for managing swallowing difficulties in people with MND?

m) What is the clinical and cost effectiveness of treatments for weight management in people with MND?

n) What is the optimum timing of gastrostomy in people with MND?

o) What is the clinical and cost effectiveness of cough-assistance techniques for managing respiratory difficulties in people with MND?

p) What is the clinical and cost effectiveness of pharmacological treatments for managing breathing difficulties in people with MND?

4.5.5 Psychosocial and social support for people with motor neurone disease and their families and carers

a) What are the psychosocial and social care support needs of people with MND and their families and carers?

4.5.6 Preparation for, and anticipation of, end of life

a) How should the discontinuation of NIV be managed?

b) What are the best methods of communication and support to help people with MND and their families and carers prepare for, and anticipate, end of life?

4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

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4.7 Status

4.7.1 Scope

This is the final version of the scope.

4.7.2 Timing

The development of the guideline recommendations will begin in March 2014.

5 Related NICE guidance

5.1 Published guidance

5.1.1 NICE guidance to be updated

This guideline does not intend to update any existing NICE guidance.

5.1.2 NICE guidance to be amalgamated

Motor neurone disease: the use of non-invasive ventilation in the management of motor neurone disease. (NICE clinical guideline 105 (July 2010).

5.1.3 Other related NICE guidance

- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Infection control. NICE clinical guideline 139 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- End of life care for adults. NICE quality standard 13 (2011).
- Depression with a chronic physical health problem. NICE clinical guideline 91(2009).
- Functional electrical stimulation for drop foot of central neurological origin. NICE interventional procedure guidance 278 (2009).
- Nutrition support in adults. NICE clinical guideline 32 (2006).
- Riluzole (rilutek) for the treatment of motor neurone disease. NICE technology appraisal guidance 20 (2001).

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- End of life care for infants, children and young people NICE Clinical Guideline (publication date tbc)

5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Pressure ulcers. NICE clinical guideline. Published April 2014.
- Multiple sclerosis. NICE clinical guideline. Published October 2014.
- Medicines optimisation. NICE clinical guideline. Publication to be confirmed.
- Homecare. NICE social care guidance. Publication expected 2015.
- Transition between health and social care. Publication expected 2015.

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

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Appendix B: Declarations of interest

The May 2007 version (updated October 2008) of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

David Oliver (Chair)

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	Sponsored attendance (by scientific organising committee, not pharmaceutical company) to MND symposium, World congress of Neurology, Congress of European Federation of Neurological Societies, Austrian Society for Neurology.	Non-specific personal pecuniary interest	Declare and participate
	Involvement (not Principal investigator) of study of withdrawal of NIV, funded by the MND Association.	Specific non-personal pecuniary interest	Declare and participate
	Member of Board of European Association for Palliative Care (EAPC). Chair of EAPC Taskforce of Neurological Palliative Care - publication of; Palliative care for Patients with Progression Neurological Disease: A consensus paper based on available evidence'.	Specific personal non-pecuniary interest	Declare and participate
	Honorary President of Mid-Kent Branch of MND Association. Member of Research advisory committee of MND Association.	Specific personal non-pecuniary interest	Declare and participate
	Author of MND A Family Affair, Principal author/editor of Palliative care for ALS - From diagnosis to bereavement.	Specific personal pecuniary interest	Declare and participate
	Editor of End of Life Care in Neurological Disease. Many papers on MND published in 2010.	Specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
(29.7.14)			
Fifth GDG meeting (24.9.14)	Gave a lecture to the MND Association of Australia Conference. Received funding for travel from MND Association of Australia, and funding for travel from MND Association of Victoria.	Specific personal pecuniary interest	Declare and participate
	Gave advice to Motor Neurone Disease Association on whether to update leaflet on death and dying.	Specific personal non-pecuniary interest	Declare and participate
Sixth GDG meeting (10.12.14)	Involvement in MND Association End of life guide 2012-13 (before GDG). Spoken of at the MND symposium in December 2014.	Specific personal non-pecuniary interest	Declare and participate
	Involvement in a project on withdrawal of NIV, in particular the effects on professionals, with a hospice in Leicester. Funded by the MNDA. This is study 'involvement of healthcare professionals in withdrawal of MND' organised by Christina Faull at LOROS.	Specific non-personal pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	Speaking on 'Ethical and Clinical Dilemmas in MND ventilation' at Primary Care and Public Health 2015, NEC, Birmingham, 21 May 2015. No payment except expenses.	Reasonable travel expenses	Declare and participate
	I designed the original 'Just in Case' box and suggested the	Non-specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	idea to the MND Association. I was involved in the leaflets originally and have commented on updates.		
	Papers published in 2014/15: Veronese S, Valle A, Chio A, Calvo A, Oliver D. the last months of life of people with amyotrophic lateral sclerosis in mechanical invasive ventilation: a qualitative study. ALS and FTD 2014: 15:499-504. Watermeyer TJ, Brown RG, Sidle KCL, Oliver DJ, Allen C, Karlsson J, Ellis CM, Shaw CE, Al-Chalabi A, Goldstein LH. Executive dysfunction predicts social cognition impairment in amyotrophic lateral sclerosis. J Neurol. 2015; DOI 10.1007/s00415-015-7761-0 Oliver D. Reflections on neurological palliative care - editorial. European Journal of Palliative Care 2014; 21:2. Oliver D. Palliative care and neurology. Kongress Highlights. Neurologisch Supplementum 3 / 2014. Oliver D. Palliative care for people with progressive neurological disease: what is the role? Journal of Palliative Care 2014; 30: 298-301. Speaking in 2014/ 2015: Speaker at Special Interest group 11th Conference of Austrian Society for Neurology Salzburg March 2014 Speaker on Palliative Care Guidelines EFNS / ENS Congress in	Specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	Istanbul Speaker of Neurological palliative care JPN meeting on Neurodegenerative disease Amsterdam Palliative care speaker at Curtin University, Perth, Australia MND Ask the Experts afternoon, Harry Perkins Institute of Medical research, Perth Planning ahead – dynamic changes and pathways of care 7th National MND Conference of MND Association of Australia Gold Coast, Australia Association for Palliative Medicine Neurological Palliative Care Special Interest Group Manchester Ethical dilemmas in Non-invasive ventilation in MND Breathing matters – conference on NIV		
Thirteenth GDG meeting (10.11.15)			

1 **Sharon Abrahams (co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	Received a grant for cognitive change and ALS staging, funded by the ALSA to the University of Edinburgh.	Non-specific non-personal pecuniary interest	Declare and participate
	Attended the MNDA training day on cognitive change in MND (November 2014). Assisted with producing MNDA literature on the subject.	Non-specific personal non-pecuniary interest	Declare and participate
	Involved in a small research project for MND Scotland looking at barriers to cognitive screening for MND in Scotland. This involves some interviews of patients and healthcare professionals on their views on cognitive screening, with the aim of identifying any problems they perceive which would hinder more widespread implementation of cognitive screening in Scotland. There has been no money involved. This is based on a screening measure we have developed that is currently being used in many centres across Europe.	Non-specific personal non-pecuniary interest	Declare and participate
	Worked on consensus documents (peer reviewed publications) on management guidelines for MND.	Specific personal non-pecuniary interest	Declare and participate
	On the committee of ENCALS group – European cognitive screening.	Non-specific personal non-pecuniary interest	Declare and participate
	On the editorial board for ALS journal.	Non-specific personal non-pecuniary interest	Declare and participate
	Supervises a number of PhD students funded by university centres and charities.	Non-specific personal non-pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
(10.3.15)			
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Robert Angus**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	In receipt of a grant from the small business research initiative through NHS England to look at remote monitoring of ventilation and respiratory symptoms	Non-specific personal pecuniary interest	Declare and participate
Sixth GDG meeting (10.12.14)	Continuing work on telemedicine/telemonitoring funded by a grant from NHS England.	Non-specific personal pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Steven Bloch**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	Chair of the MNDA AAC best practice guidelines group. These best practice guidelines for AAC/MND were produced independently by a group of clinicians in 2012. There was no funding or commercial interest. The MNDA agreed to site them on their own website: http://www.mndassociation.org/forprofessionals/aac-for-mnd/. The guidelines remain available for public access.	Specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Julie Brignall-Morley**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	Regularly attends local MNDA meetings and meets with the Regional Care Advisor to discuss local issues and needs.	Specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Angeline Brooks (co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	I have been asked by the MNDA to contribute to an online learning module being developed by Northampton University for carers, aimed at increasing their knowledge around nutritional support in dysphagia. There is no financial reward for this project.	Specific personal non-pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG	No change to existing	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
meeting (14.1.15)	declarations.		
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Caroline Brown**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	Involved in writing ACPRC/BTS Guidelines 2009 on respiratory complications in neuromuscular disease Section G.	Specific personal non-pecuniary interest	Declare and participate
	Attended a training day on E70 (a type of cough assist device) organised by Responics (free event organised for clinicians) (November 2012).	Non-specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	Teaching for 2 days at the Department of Health and Rehabilitation at Keele University delivering on their ATMRP MSc module on the topic of managing respiratory	Specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	complications in Neuromuscular Disease. In return, the Therapies Directorate at the University Hospital of North Staffordshire received a free place on the module for one of their physiotherapists. To ensure that the delegates could not interpret the content of the lecture as reflecting in any way the content of the NICE MND Guideline, my colleague delivered the theory lecture and I taught on the practical techniques workshops. A PowerPoint slide was used at the beginning of the lecture to clarify to delegates that the content of the presentation did not reflect the content of the NICE MND Guidelines but was based on the BTS/ACPRC Physiotherapy Guidelines (2009) for the spontaneously breathing adult, Section 6, managing respiratory complications in neuromuscular disease.		
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	Accepted a request to sit as an expert on a project of guideline consensus development for the ENMC (European Neuro-Muscular Centre). The project includes 20 world experts for a 2-3 days closed doors meeting. The conference will be held in the Netherlands, all flights and accommodations (hotel, restaurant) will be covered by the ENMC. The guidelines topic is 'Airway clearance techniques in NMDs'.	Specific personal non-pecuniary interest	Declare and participate
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Annette Edwards**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	I am co-director of Leeds MND Care Centre, jointly with Dr Jung, consultant neurologist. My post does not receive any funding. However the MNDA fund sessions of a dietician, Speech and Language Therapist, physiotherapist and Care Centre Co-ordinator.	Specific personal non-pecuniary interest	Declare and participate
	Leeds MND Care Centre has a new post for specialist wheelchair provision (occupational therapist). The money came from the DOH through the MNDA to Leeds teaching hospitals to appoint a postholder (started in November 2013).	Non-specific non-personal pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	As a palliative care consultant with an interest in MND, and as coordinator of the palliative care in progressive neurological disease special interest forum, I am involved with other palliative care	Specific non-personal pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	professionals in audits. These include: 1a. Looking to identify triggers for end of life in patients with progressive neurological disease 1b. Looking at practices for managing discontinuation of ventilation in MND. This was an addendum to a wider piece of work "Withdrawal of Assisted Ventilation at the Request of a Patient with Motor Neurone Disease: Guidance for Professionals" The Guidance was supported by a grant from the MNDA and endorsed by the Association for Palliative Medicine of Great Britain and Ireland. I have only been involved in the group meeting to draw up the audit proforma. This has involved a face to face meeting and ongoing work by email / teleconference. I have not been on the group responsible for developing the guidance itself. The whole document is currently out for consultation.		
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting			

GDG meeting	Declaration of interest	Classification	Action taken
(10.11.15)			

1 **Karen James (co-opted expert adviser)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Roch Maher**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	I support the aims of the group Dignity in Dying on whose behalf I submitted an affidavit in support of their aim in the Nicholson/Lamb/Martin case. The case is currently under consideration in the Supreme Court having been heard in December. Judgement is due by the end of April.	Non-specific personal non-pecuniary interest	Declare and participate
	I am a member of the local branch (West London and Middlesex) of the MND Association. I support the overall aims of the association and occasionally speak on behalf of the organisation. I also review documents for the organisation's Personal Guide before publication. I have given evidence on behalf of the organisation to the All Party Parliamentary Group investigation into palliative care.	Specific personal non-pecuniary interest	Declare and participate
	I am a member of the user panel at the Princess Alice Hospice in Esher.	Non-specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG	No change to existing	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
meeting (10.3.15)	declarations.		
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	Resigned from GDG	N/A	N/A
Thirteenth GDG meeting (10.11.15)	Resigned from GDG	N/A	N/A

1 **Rachael Marsden**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	My post has funding from the MNDA through Oxford University, and is under a 4-yearly contract. The MNDA pay the University; the University pay the OUH who pay me.	Non-specific personal pecuniary interest	Declare and participate
	Director of Living Experience, a very small training company for care assistances in the community (local level).	Non-specific personal non-pecuniary interest	Declare and participate
	Holds a few shares in GW Pharmaceuticals.	Non-specific personal pecuniary interest	Declare and participate
	Research nurse for DIPALS trial.	Non-specific personal non-pecuniary interest	Declare and participate
	Various publications: Savulescu J. Marsden R. Hope T (1998) Sex, drugs and the invasion of privacy. BMY 316 921 -4 Kevin Talbot and Rachael Marsden. Motor neuron disease: the Facts. Oxford University Press, Jan 2008, ISBN-13: 978-0-19-920691-9 Ex-PLISSIT study: Marsden R, Botell R (2010) Discussing Sexuality with patients in a motor neurone disease clinic.	Specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	Nursing standard. 25, 15-17 Martin R Turner, Jakub Scaber, John A Goodfellow, Rachael Marsden, Melanie E Lord, Kevin Talbot. The diagnostic pathway and prognosis in bulbar-onset amyotrophic lateral sclerosis. J Neurol Sci. 2010. Epub ahead of press Turner MR, Brockington A, Scaber J, Hollinger H, Marsden R, Shaw PJ, Talbot K. Pattern of spread and prognosis in lower limb-onset ALS. Amyotroph Lateral Sclerosis. [Epub ahead of press] Marsden R (2011) Motor Neuron disease: an overview. Primary Health Care. 21,10, 31-36 Kevin Talbot, Martin Turner, Rachael Marsden and Rachel Botell. Motor neuron disease: a practical manual. Oxford University Press, ISBN-10 019954736X		
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	I have been an advisor to the BBC for 5 episodes of Casualty. I have only advised on how an actor would portray a person living with MND. I also suggested the story line for giving a person living with MND oxygen with bad effect.	Non-specific personal non-pecuniary interest	Declare and participate
	I am an advisor for the ITV soap Hollyoaks.	Non-specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	We are starting a study which is being sponsored by GlaxoSmithKline (GSK) in collaboration with McLaren Applied Technologies (MAT). The purpose of this study is to test the use of a device (sensor and electrodes) to measure participant's movement, activity and heart rate as it relates to their amyotrophic lateral sclerosis (ALS). The study will also measure certain aspects of participant's speech, and how that relates to their ALS. There is no treatment provided in this study. It is jointly funded by GSK & McLaren; funds go to the university.	Specific non-personal pecuniary interest	Declare and participate
	I am reading the TV scripts for Doctors (a daytime drama which will feature a person living with MND), Casualty and Hollyoaks. No payment is received for this.	Non-specific personal non-pecuniary interest	Declare and participate
Thirteenth GDG meeting (10.11.15)			

1 **Christopher McDermott**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG	Subsistence received from	Non-specific personal non-	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
meeting (12.3.14)	Synapse Biomedical (manufacturer of diaphragm pacing) following a training session on diaphragm pacing.	pecuniary interest	
	Expenses received from MNDA for overnight accommodation when speaking.	Reasonable travel expenses	Declare and participate
	Support for cough assist trial (free devices) from Respironics.	Specific personal non-pecuniary interest	Declare and participate
	Support for diaphragm pacing study (free devices) from Synapse biomedical.	Specific personal non-pecuniary interest	Declare and participate
	Support for telehealth study from Cogent Healthcare Systems.	Non-specific non-personal pecuniary interest	Declare and participate
	Inventor of a new head support, seeking a commercial partner.	Specific personal non-pecuniary interest	Declare and participate
	MNDA, MRC, JPND, NIHR grant support for MND-related research programmes.	Specific non-personal pecuniary interest	Declare and participate
	Various publications on care for MND: 1: McGeachan AJ, Hobson EV, Shaw PJ, McDermott CJ. Developing an outcome measure for excessive saliva management in MND and an evaluation of saliva burden in Sheffield. Amyotroph Lateral Scler Frontotemporal Degener. 2015 Mar;16(1-2):108-13. doi: 10.3109/21678421.2014.951942. Epub 2014 Sep 16. PubMed PMID: 25225845. 2: Jenkins TM, Hollinger H, McDermott CJ. The evidence for symptomatic treatments in amyotrophic lateral sclerosis. Curr Opin Neurol. 2014 Oct;27(5):524-31. doi: 10.1097/WCO.0000000000000135. Review. PubMed PMID: 25110934.	Specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	3: Stavroulakis T, Baird WO, Baxter SK, Walsh T, Shaw PJ, McDermott CJ. The impact of gastrostomy in motor neurone disease: challenges and benefits from a patient and carer perspective. BMJ Support Palliat Care. 2014 May 21. pii: bmjspcare-2013-000609. doi: 10.1136/bmjspcare-2013-000609. [Epub ahead of print] PubMed PMID: 24848262. 4: Stavroulakis T, Baird WO, Baxter SK, Walsh T, Shaw PJ, McDermott CJ. Factors influencing decision-making in relation to timing of gastrostomy insertion in patients with motor neurone disease. BMJ Support Palliat Care. 2014 Mar;4(1):57-63. doi: 10.1136/bmjspcare-2013-000497. Epub 2013 Dec 11. PubMed PMID: 24644772. 5: Lenglet T, Lacomblez L, Abitbol JL, Ludolph A, Mora JS, Robberecht W, Shaw PJ, Pruss RM, Cuvier V, Meininger V; Mitotarget study group. A phase II-III trial of olesoxime in subjects with amyotrophic lateral sclerosis. Eur J Neurol. 2014 Mar;21(3):529-36. doi: 10.1111/ene.12344. Epub 2014 Jan 21. PubMed PMID: 24447620.6. 6. Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort studY, ProGas Study Group. Lancet Neurology 2015 DOI: http://dx.doi.org/10.1016/S1474-4422(15)00104-0		
Second GDG meeting	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
(29.4.14)			
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	Has been asked to write an article for a GP magazine on MND, for which an honorarium will be paid to the department.	Specific non-personal pecuniary interest	Declare and participate
Sixth GDG meeting (10.12.14)	Article published in Current opinion in neurology on management of MND. Honorarium paid to department.	Specific non-personal pecuniary interest	Declare and participate
	Multiple presentations on care management at Brussels international MNDA symposium. No payment was received for this.	Specific personal non-pecuniary interest	Declare and participate
	In receipt of departmental funding for telehealth study from Abbott pharmaceuticals.	Non-specific non-personal pecuniary interest	Declare and participate
	MNDA funding for collar project (departmental).	Specific non-personal pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	Investigator in study on use of MDT for people with MND (Aridegbe, 2013).	Specific personal non-pecuniary interest	Declare and acted as an expert adviser for the GDG
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	Involvement in a publication on experiences of withdrawal of NIV.	Specific personal non-pecuniary interest	Declare and participate
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Aleks Radunovic**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	Director of Barts MND Care Centre. Whilst I don't receive any funding for my role, the MND Association funds care centre coordinator time to support the centre.	Specific personal non-pecuniary interest	Declare and participate
	Member of the MND Association Outcomes Standards Sub-group.	Specific personal non-pecuniary interest	Declare and participate
	Member of the Royal College of General Practitioners MND Red Flags Steering Group.	Specific personal non-pecuniary interest	Declare and participate
	Member of the Association of British Neurologists' Neuromuscular Section; recently developed the MND Quality Statements.	Specific personal non-pecuniary interest	Declare and participate
	Member of the Data Monitoring and Ethics Committee for "A randomised controlled trial evaluating NeuRx/4 Diaphragm Pacing in patients with respiratory muscle weakness due to Motor Neurone Disease".	Specific personal non-pecuniary interest	Declare and participate
	Chair of the Palliative Care Network for Rare and Rapidly Progressing Neurodegenerative Diseases in Essex, Herts and North East London.	Specific personal non-pecuniary interest	Declare and participate
	Member of the St Joseph's Hospice Steering Group for Managing medication towards the end of life: local consensus guidance for professionals.	Specific personal non-pecuniary interest	Declare and participate
	Principal Investigator, Modulation of muscle stem cell function in motor neurone disease and other neuromuscular disorders (funded by Barts and the London Charity and AR was a signatory).	Non-specific non-personal pecuniary interest	Declare and participate
	Principal Investigator, Phase IIb Multi-national, Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety, Tolerability and	Non-specific non-personal pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	Efficacy of CK-2017357 in Patients with Amyotrophic Lateral Sclerosis (ALS), Protocol no CY 4026 (funded by Cytokinetics and AR was a signatory).		
	Principal Investigator, A prospective multi-centre evaluation of gastrostomy in patients with MND (funded by MND Association and AR was not a signatory).	Specific non-personal pecuniary interest	Declare and participate
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Jennifer Rolfe**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	I have worked with the MND Association on the development of a prescription for a powered wheelchair specifically to meet the needs of people living with MND or other deteriorating neurological conditions. This is funded by DoH and has involved working with manufacturers: Invacare, Sunrise medical and Ottobock. Each has donated powered wheelchairs to the MNDA to use with MND clients through their wheelchair services project. The manufacturers have provided funding towards lunch for 3 study days hosted by the Oxford MND Care and Research Centre which is where I work.	Specific non-personal non-pecuniary interest	Declare and participate
	Ottobock has funded my travel costs to Naidex where I am presenting the clinical aspects of the development of the Neuro powered wheelchair prescription.	Reasonable travel expenses	Declare and participate
	I am presenting at the specialist interest Posture and Mobility Group national training event in April 2014 on the Neuro Powered Wheelchair involving the three manufacturers. I will submit an abstract for presentation of this project at the International Symposium on MND/ALS (Belgium, December 2014).	Specific personal non-pecuniary interest	Declare and participate
	I was funded by Oxford Brookes University in October 2013 to go to MND team in Utrecht to look at the management of head drop in ALS/MND. Oxford Brookes University were funded by a private donation from Edgar Smith. As a result of the Utrecht visit I	Specific non-personal pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	have worked with the orthotics department at the Oxford Universities NHS trust on the design of a customised head support currently provided by them (NHS provision). This work will also be written up and submitted to the British Journal of Occupational Therapists. There is reference made to the fact that NICE are developing guidelines for MND in the article. I am a joint author on this article with the lecturer from Oxford Brookes University.		
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	Recruiting for the TONiC (Trajectories of Outcome in Neurological Conditions) study under Oxford site PI Professor Kevin Talbot (study PI is Professor C A Young – the Walton Centre). This involves gaining consent from participants to give them a questionnaire to complete and returning it to TONiC study staff (commenced recruiting on 23 July 2014).	Non-specific personal non-pecuniary interest	Declare and participate
	Provided clinical advice to MND Association to inform their review of their published advice to NHS wheelchair services on the provision of wheelchairs for people living with MND. The document is a detailed clinical support tool not a guideline.	Specific personal non-pecuniary interest	Declare and participate
	MND Association sit on the NHS England Wheelchair Summit & Alliance. They have shared some data from this for my clinical advice and feedback.	Specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
Seventh GDG meeting (11.12.14)	Interviewed on my clinical involvement in wheelchair provision for people living with MND by Wendy Grey from NHS Improving Quality for the NHS England wheelchair summit.	Non-specific personal non-pecuniary interest	Declare and participate
	Attended the International Symposium on MND/ALS and presented a poster on my work with the MNDA on development of Neuro Wheelchair.	Specific personal non-pecuniary interest	Declare and participate
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	Have been a professional reviewer for a research vignette submitted to National Institute for Health Research – which was for a vignette titled: "Intervention to improve the psychological health of people living with MND and their carers".	Specific personal non-pecuniary interest	Declare and participate
	The MNDA have been shortlisted for a Health Service Journal Award for Value and Improvement in Specialist Services category for the Powered Neuro Wheelchair project I have been involved with them. There is no personal financial gain from this award.	Specific personal non-pecuniary interest	Declare and participate
Thirteenth GDG meeting (10.11.15)			

1 **Ian Smith**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	There has been an offer of an unconditional educational grant to fund a fellow under his supervision from B and D Electromedical Ltd who manufacture ventilatory support devices. This is not linked to any particular study as yet and is likely to fund work relating to sleep apnoea.	Non-specific non-personal pecuniary interest	Declare and participate
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Sandra Smith**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	Trustee of the MNDA and member of the Trustee Care Committee and Chair of Engagement Committee.	Specific personal non-pecuniary interest	Declare and participate
	One of 14 Campaign contacts for MNDA (Chair of the Merseyside branch of MNDA. Association Visitor for MNDA (all voluntary capacity).	Specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	Gave a presentation at Manchester University for student nurses on 'being a carer for someone living with MND and FTD'. No payment or expenses were received.	Specific personal non-pecuniary interest	Declare and participate
	I am involved with MND Association renewing and updating information literature with regards to MND and cognitive impairment and FTD.	Specific personal non-pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Rachel Starer**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	I will be talking to a group of healthcare professionals about integrated care between primary and secondary services with reference to MND organised by the Oxford MND Centre on 18 March 2015. There is no payment for the event.	Specific personal non-pecuniary interest	Declare and participate
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
(21.4.15)			
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Jean Waters**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	I chair the Gloucestershire branch of the MND Association and External member MND Association care committee.	Non-specific personal non-pecuniary interest	Declare and participate
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	Speaking at GlaxoSmithKline on 08 October 2014 at an ALS seminar on personal experience of living with MND. An honorarium will be paid.	Non-specific personal pecuniary interest	Declare and participate
	Patient representative for NHS England Wheelchair Action Plan – Better Commissioning & Procurement.	Non-specific personal non-pecuniary interest	Declare and participate
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	Appointed to the Wheelchair Leadership Alliance, which is chaired by Baroness Grey-Thompson and supported by NHSIQ, charged with campaigning to redevelop NHS	Non-specific personal non-pecuniary interest	Declare and participate

GDG meeting	Declaration of interest	Classification	Action taken
	wheelchair services.		
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

1 **Christine Strohmeier (MNDA peer reviewer)**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
Eleventh GDG meeting (21.4.15)	No change to existing declarations.	N/A	N/A
Twelfth GDG meeting (12.5.15)	I am employed by the Motor Neurone Disease Association as a Regional Care Development Adviser in South London.	Specific personal financial pecuniary interest	Declare and participate
Thirteenth GDG meeting (10.11.15)			

1 **NCGC team**

GDG meeting	Declaration of interest	Classification	Action taken
First GDG meeting (12.3.14)	None	N/A	N/A
Second GDG meeting (29.4.14)	No change to existing declarations.	N/A	N/A
Third GDG meeting (24.6.14)	No change to existing declarations.	N/A	N/A
Fourth GDG meeting (29.7.14)	No change to existing declarations.	N/A	N/A
Fifth GDG meeting (24.9.14)	No change to existing declarations.	N/A	N/A
Sixth GDG meeting (10.12.14)	No change to existing declarations.	N/A	N/A
Seventh GDG meeting (11.12.14)	No change to existing declarations.	N/A	N/A
Eight GDG meeting (14.1.15)	No change to existing declarations.	N/A	N/A
Ninth GDG meeting (10.3.15)	No change to existing declarations.	N/A	N/A
Tenth GDG meeting (20.4.15)	No change to existing declarations.	N/A	N/A
Eleventh GDG meeting	No change to existing declarations.	N/A	N/A

GDG meeting	Declaration of interest	Classification	Action taken
(21.4.15)			
Twelfth GDG meeting (12.5.15)	No change to existing declarations.	N/A	N/A
Thirteenth GDG meeting (10.11.15)			

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Appendix C: Review protocols

C.1 Recognition and referral

Table 1: Review protocol: Timeliness of diagnosis

Review question	What factors impact upon timeliness of diagnosis in people with MND in the UK?
Objectives	To establish what factors impact upon timeliness of diagnosis in people with MND in the UK
Criteria	**Population:** Adults (aged ≥18 years) with MND and their families and carers. **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND and their families and carers. For background information for the technical team, areas of relevance may include timeliness in: Identification of MND Referral to neurologist Carrying out relevant investigations Obtaining results of investigations People seeking help **Setting** Any setting where patients receive NHS care The review will include only papers from the UK because we consider this relevant to the UK health service.
Search criteria	**Databases:** Medline, Embase, CINAHL and PsychINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Qualitative studies (for example interviews, focus groups) Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** Stratify by people with/without frontotemporal dementia Subgroup by type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)

C.2 Information and support at diagnosis

Table 2: Review protocol: Knowledge to communicate diagnosis and prognosis

Review question	What specific MND knowledge do patients, their carers and health professionals consider is required in order to communicate diagnosis of MND, its prognosis, and choices of ongoing care appropriately?

Objectives	To identify what knowledge specifically relating to MND patients, carers and health professionals consider is required in order to appropriately communicate the diagnosis of MND, its prognosis, and choices of ongoing care
Criteria	**Population:** Adults (aged ≥18 years) with MND Family and carers of adults with MND Health professionals who support patients with MND **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND, their families and carers and health professionals. For background information for the technical team, areas of relevance may include specific knowledge of: Diagnosis, all forms of MND and disease progression Potential for cognitive change in MND and how this relates to different forms of MND and prognosis Care and management options for people with MND including social and healthcare provision and voluntary services The importance of follow up support post diagnosis **Setting** Any setting where patients receive NHS care International studies will be included
Search criteria	**Databases:** Medline, Embase, CINAHL and PsychINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Qualitative studies (for example interviews, focus groups) Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** Stratify by people with/without frontotemporal dementia

C.3 Cognitive assessments

Table 3: Review protocol: Optimum frequency of assessing cognitive function

Review question	What is the optimum frequency of assessing cognitive function in patients with MND?
Objectives	To assess when and how often assessment for cognitive impairment should take place in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND **Interventions:** Cognitive assessment at time points as specified by included studies **Comparison:** To be compared against each other **Outcomes:** Critical:

	• Health related quality of life • Timeliness of identifying cognitive change • Patient/carer/healthcare professional satisfaction with diagnostic process • Patient/carer knowledge/understanding of cognitive change (that is, allowing clearer discussion of care/options, advice for carers and thus more appropriate care/decision making) **Setting:** All settings in which NHS care is provided
Search criteria	**Databases:** Medline, Embase, The Cochrane Library, CINAHL and PsycInfo. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for cohort studies
Review strategy	**Data analysis:** • The population will be stratified from the outset by people with cognitive impairment including frontal temporal dementia (at diagnosis) • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by: o Type of assessment (that is, structured clinical interview, questionnaire, neuropsychological tests, routine clinical assessment) o Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)

C.4 Prognostic factors

Table 4: Review protocol: Prognostic tools for estimating survival

Review question	What are the most accurate prognostic tools for estimating survival in people with MND?
Objectives	To find the best tool to estimate survival in patients with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND **Interventions:** Any externally validated tools for predicting survival in people with MND **Outcomes:** Critical: Accuracy at predicting survival
Search criteria	**Databases:** Embase and Medline. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Prospective/retrospective prognostic tool studies
Review strategy	**Data analysis:** The population will be stratified from the outset by people with cognitive impairment including frontal temporal dementia; people who are at the end of life; people with swallowing difficulties (with or without gastronomy) If no externally validated risk tools are found then a risk factor review will be undertaken.

Table 5: Review protocol: Risk factors to predict survival

Review question	What risk factors predict survival in people with MND?
Objectives	To establish which risk factors are significant predictors of survival in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND **Presence/ absence of prognostic variable** Functional measurement scales (amyotrophic lateral sclerosis functional rating scale or amyotrophic lateral sclerosis functional rating scale revised only) Weight loss (pre/post 10% weight loss as preference, >/< 18.5 BMI if % weight loss not reported) Respiratory function measurement (sniff nasal inspiratory pressure [SNIP], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], carbon dioxide [CO2], oxygen saturation only) Cough/ability to clear secretions (peak cough flow) **Outcomes:** Critical: Mortality
Search criteria	**Databases:** Medline and Embase. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Prospective/retrospective prognostic studies. These could be: Prospective and retrospective cohorts Randomised trials Case control studies Systematic reviews of the above
Review strategy	**Data analysis** **Stratification:** People with cognitive impairment including frontotemporal dementia; Where studies begin with a NIV population Where studies begin with a gastrostomy population

C.5 Organisation of care

Table 6: Review protocol: Organisation of care

Review question	What is the most clinically- and cost-effective approach for coordinating care and support across health and social care for people with motor neurone disease and their families and carers?
Objectives	To identify the most appropriate approach for coordinating care and support for people with MND and their families and carers
Criteria	**Population:** Adults (aged ≥18 years) with MND **Interventions:** • MDT care alone • MDT care plus a coordinator • Usual care • Usual care plus coordinator **Comparison:** To be compared against each other **Outcomes:** Critical: • Survival (time to event)

	• Health related quality of life (continuous) • Number of unplanned hospital admissions (dichotomous) Important: • Reduction in crisis management interventions (dichotomous) • Hospital length of stay (continuous) • ALSFRS-R scale (continuous)
Search criteria	**Databases:** Medline, Embase, The Cochrane Library, CINAHL and PsycINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for cohort studies.
Review strategy	**Data analysis:** • The population will be stratified from the outset by people with cognitive impairment including frontotemporal dementia; • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. **Exclusion** • Study does not control for impact of confounders identified by the GDG

C.6 Frequency of assessment

Table 7: Review protocol: Frequency of assessment required to assess disease progression

Review question	What is the optimum frequency of assessment required to assess disease progression of MND?
Guideline condition and its definition	MND is a neurodegenerative condition which affects the brain and spinal cord and is primarily characterised by degeneration of the motor neurones and subsequent loss of motor neurone function.
Objectives	To identify the optimum frequency of assessment required to monitor disease progression in people with MND
Review population	Adults (aged 18 and over) with MND. People with cognitive impairment will be considered a separate subgroup.
	Adults (aged 18 and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Different time points; not relevant
Outcomes	**Critical:** • Health-related quality of life (continuous)

Review question	What is the optimum frequency of assessment required to assess disease progression of MND?
	• Patient/carer/healthcare professional satisfaction with the process (dichotomous)
Study design	Prospective cohort study Retrospective cohort study
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Sample size exclusion criteria	20< overall
Population stratification	People with cognitive impairment People without cognitive impairment People with frontotemporal dementia People without frontotemporal dementia
Reasons for stratification	People with cognitive impairment and frontal temporal dementia will have different care needs.
Subgroup analyses if there is heterogeneity	• Type of MND (ALS; primary lateral sclerosis); may differ in frequency requirement • Type of assessment (structured clinical interview; questionnaire; neuropsychological tests; routine clinical assessment); may differ in frequency requirement
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: None Language: Restricted to English

C.7 Psychological support

Table 8: Review protocol: Psychological support

Review question	What psychological support is needed for people with MND and their families and carers?
Objectives	To identify the psychological support needs of people with MND and their families and carers
Criteria	**Population:** Adults (aged ≥18 years) with MND **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND and their families and carers. For background information for the technical team, areas of relevance may include: • Coping with the diagnosis • Managing family relationships • Change in identity/roles • Sexuality • Psychological factors associated with employment (employment support to be covered in another review) • Management of anxiety and depression • Respite care **Setting** • Any setting where patients receive NHS care • International studies will be included
Search	**Databases:** Medline, Embase, CINAHL and PsychINFO.

criteria	**Date limit:** No date limit applied **Language:** English language only **Study designs:** • Qualitative studies (for example interviews, focus groups) • Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** ○ Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** • Stratify by people with/without frontotemporal dementia

C.8 Social care support

Table 9: Review protocol: Social care support

Review question	What are the social care support needs of people with MND and their families and carers?
Objectives	To identify the social care support needs of people with MND and their families and carers
Criteria	**Population:** Adults (aged ≥18 years) with MND Family and carers of adults with MND **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND and their families and carers. For background information for the technical team, areas of relevance may include: Financial support Employment support Transport Support with eating Support with dressing/washing Support to engage with social activities Adaptations at home Appropriate housing **Setting** Any setting where patients receive NHS care International studies will be included
Search criteria	**Databases:** Medline, Embase, CINAHL and PsychINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Qualitative studies (for example interviews, focus groups) Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** Studies with indirect populations will not be considered, for example patients with other

	neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** Stratify by people with/without frontotemporal dementia

C.9 Planning for end of life

Table 10: Review protocol: Anticipation and preparation for end of life

Review question	What are the most appropriate ways of communicating with and supporting people with MND and their families and carers to help them anticipate, and prepare for, end of life?
Objectives	To identify the best ways of communicating and supporting people with MND and their families and carers in preparation for, and anticipation of, end of life
Criteria	**Population:** • Adults (aged ≥18 years) with MND • Family and carers of adults with MND **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND and their families and carers. For background information for the technical team, areas of relevance may include: • Access to MND specialists (for example doctor, nurse, respiratory consultant, palliative care specialist) • Advance care planning • Advance refusal of treatment (including DNA CPR) • Timing of discussion about end of life • Discussion about end of life care (including withdrawal of treatments, for example NIV) • Information in appropriate format • Up-to-date information on informed choices (for example assisted dying) • Up-to-date information regarding expressed preferences • Specialist palliative care services, including access • Suitable environment for care and place of death • Point of contact for advice • Information regarding appointment of lasting power of attorney • Awareness and training of healthcare professionals and staff • Service provision according to stage of condition • Psychological support • Physical support • Social support • Urgent care • Care in the last days of life Bereavement support **Setting** • Any setting where patients receive NHS care • International studies will be included
Search	**Databases:** Medline, Embase, CINAHL and PsychINFO.

criteria	**Date limit:** No date limit applied **Language:** English language only **Study designs:** • Qualitative studies (for example interviews, focus groups) • Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** • Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** • Stratify by people with/without frontotemporal dementia

C.10 Pharmacological treatment for muscle problems

Table 11: Review protocol: Pharmacological treatments

Review question	**For adults with MND, what is the clinical- and cost-effectiveness of pharmacological treatments for:** **• Muscle cramps and fasciculations** **• Increased tone (including spasticity, muscle spasm or stiffness)** **• Muscle weakness, wasting or atrophy**
Objectives	To assess the clinical- and cost-effectiveness of pharmacological methods of managing muscle cramps, muscle stiffness and muscle weakness in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND who have muscle cramps and/or muscle stiffness and/or muscle weakness **Interventions:** • Baclofen (gamma-aminobutyric acid) • Diazepam, clonazepam, tetrazepam, midazolam (benzodiazepines) • Dantrolene sodium (muscle relaxant) • Tizanidine (Adrenergic agonist) • Memantine (Antipyretic/antimalarial/analgesic/anti-inflammatory) • Quinine sulphate • Gabapentin **Comparison:** To be compared against each other, with placebo, or no treatment. **Outcomes:** Critical: • Quality of life (EQ5D, SF36, SF12, SEQUOL)) continuous) • Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score) (continuous) • Reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) (continuous) • Reduction of muscle cramps (Ashworth scale, MRC score) (continuous) Important: • Mobility (functional independence measure, ALS functional rating score) (continuous; reasons: critical outcome for people at the end of life) • Patient/carer reported outcomes (pain (VAS), reduction of muscle stiffness, reduction of

	muscle cramps, reduction of fatigue) (continuous) • Adverse effects of treatment (drowsiness, treatment related reduction in mobility, treatment related reduction of functional ability) (dichotomous) **Setting:** All settings in which NHS care is provided
Search criteria	**Databases:** Medline, Embase, The Cochrane Library and CINAHL. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20
Review strategy	**Data analysis:** • The population will be stratified from the outset by people who are/are not at the end of life • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by: ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)

C.11 Non-pharmacological management of muscle problems

Table 12: Review protocol: Non-pharmacological management of muscle problems

Review question	**For adults with MND, what is the clinical- and cost-effectiveness of non-pharmacological treatments for:** **• muscle cramps and fasciculations** **• Increased tone (including spasticity, muscle spasm or stiffness)** **• Muscle stiffness, wasting or atrophy?**
Objectives	To assess the clinical- and cost-effectiveness of non-pharmacological methods of managing muscle cramps and muscle stiffness in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with muscle cramps and fasciculations, increased tone (including spasticity, muscle spasm or stiffness), and/or muscle weakness, wasting or atrophy **Interventions:** • Physical therapy (manual techniques, massage, exercise, stretching and positioning–range of movement exercises, endurance and strength training) • Electrotherapy adjuncts (TENS, ultrasound, intramuscular manual therapy-trigger point dry needling for relief of muscle spasms and contractions, functional electromedical stimulation, transcranial magnetic stimulation) • Orthoses, splinting and casting **Comparison:** To be compared against each other, with placebo, or usual care. **Outcomes:** Critical: • Health-related Quality of life (EQ5D, SF-36, SF12, SEQUOL)) (continuous) • Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score) (continuous) • Reduction of increased tone (Ashworth scale, MRC score or hand-held • dynamometry for muscle power) (continuous) • Reduction of muscle cramps (Ashworth scale, MRC score) (continuous)

	Important: • Mobility (functional independence measure, ALS functional rating score) (continuous; reasons: critical outcome for people at the end of life) • Patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) (continuous) • Adverse effects of treatment (drowsiness, treatment related increase in weakness, treatment related reduction of functional ability) (dichotomous) **Setting:** All settings in which NHS care is provided
Search criteria	**Databases:** Medline, Embase, The Cochrane Library and CINAHL. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20
Review strategy	**Data analysis:** • The population will be stratified from the outset by people who are/are not at the end of life • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by: ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis) ○ People with/without frontotemporal dementia ○ Self-management (self-management; healthcare professional management; multidisciplinary team management; mixed)

C.12 Saliva management

Table 13: Review protocol: Saliva management

Review question	What is the clinical- and cost-effectiveness of interventions for saliva management in people with MND?
Objectives	To assess the clinical- and cost-effectiveness of interventions for saliva management in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND with sialorrhoea or thick tenacious saliva **Interventions:** **Sialorrhoea:** • Atropine (sublingual) • Benztropine • Hyoscine (oral or sublingual or patch) • Glycopyrrolate (sublingual or syringe driver, orally or via PEG) • Amitriptyline (TCAs as oral solution or tablet) • Clonidine injection (antihypertensive, tablet or patch or via PEG) • Botulinum toxin injections • Suction pump • Postural advice • Destruction of salivary glands (radiotherapy, surgical procedures)

	• Behavioural approaches (that is, advice on swallowing) • Oral care **Thick tenacious saliva:** • Propranolol (beta-blocker) • Metoprolol (beta-blocker) • Carbocisteine (Mucolytic capsule or oral liquid) (non-NHS) • Bromelaine (non-prescription) • Bioxtra gel/spray • Dietary modification (avoiding dairy, recommend: pineapple juice, caffeine, papase) • Rehydration fluids (non-prescription) • Humidification and nebuliser • Suction • Postural advice • Oral care **Comparison:** Compared to each other and compared to no treatment, usual care **Outcomes:** Critical: • Health related quality of life (EQ5D, SF-36, SF-12) for patients and carers • Patient/carer reported outcomes (for example symptoms, satisfaction, pain [VAS]) • Aspiration pneumonia Important: • Function measured by disability scores (Ashworth scale) • Hospital admissions (and unplanned admissions) • Adverse effects of treatment (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)
Search criteria	**Databases:** Medline, Embase and The Cochrane Library. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20 If no cohort studies or abstracts of RCTs are found, we will look for RCTs including indirect populations (multiple system atrophy, Parkinson's disease, cerebral palsy, spinal muscular atrophy)

Review strategy	**Data analysis:**
	• The population will be stratified from the outset by:
	  ○ People with/without frontotemporal dementia
	  ○ People with sialorrhoea/people with tenacious, thick saliva
	• Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)
	• If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data.
	• If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by:
	  ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)
	  ○ Severity of swallowing difficulty (mild, moderate, severe swallowing difficulty) – scales can be used to assess severity of swallowing, for example dysphagia rating scale; ALSFRS has a

	swallowing subscale ○ Patient ability to cough (patients able to cough and clear secretions, people with significant inability to cough and clear secretions) If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed

C.13 Equipment and adaptations to aid activities of daily living and mobility

Table 14: Review protocol: Equipment needs

Review question	What are the equipment needs of people with MND for improving mobility and fulfilling activities of daily living due to muscle weakness?
Objectives	To thematically analyse the types of equipment people with MND require for improving their mobility and daily functioning
Criteria	**Population:** • Adults (aged ≥18 years) with MND **Context**: This is a qualitative review and themes included in the analysis will represent equipment identified by patients with MND feel are required to improve their mobility and to fulfil activities of daily living due to muscle weakness. For background information for the technical team, areas of relevance may include: • Wheelchair (basic manual wheelchair, electrically powered indoor and outdoor wheelchairs) • Head support or head rests/collar/back rests • Transfer/hoist/lifting equipment • Riser/recliner chair/bed, including mattresses/specialist postural support • Mobile arm support (Ergorest, powered mobile arm support) • Drinking/eating aids (for example, neater eater, other devices) • Braces or splints • Walking aid (stick or frame) • Assistive technology devises including environmental controls, communication aids, computer access devises, personal alarms, telecare/ health systems • Home adaptations including wheelchair access, access to all facilities **Setting** • Any setting where patients receive NHS care • International studies will be included
Search criteria	**Databases:** Medline, Embase and CINAHL. **Date limit:** No date limit applied **Language:** English language only **Study designs:** • Systematic reviews of qualitative studies • Qualitative studies (for example interviews, focus groups) • Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** • Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome.

	Data synthesis Thematic analysis of the data will be conducted and findings presented.

C.14 Nutrition

Table 15: Review protocol: Maintaining nutritional intake

Review question	What are the most clinically- and cost-effective methods for maintaining nutritional intake and managing weight in people with MND for whom a gastrostomy is not appropriate?
Objectives	Identify the most clinically- and cost-effective methods for maintenance of nutritional input and therefore maintenance of a healthy weight in people with MND for whom gastrostomy is not appropriate

Criteria	**Population:** Adults (aged ≥18 years) with MND
	Interventions:
	• Feeding assistance
	  ○ carer support
	  ○ altered utensils
	  ○ arm supports
	  ○ seating and posture
	• Altering food consistency (speech and language therapist advice, thickeners)
	• Oral nutritional support (dietary advice on food choices, food fortification, high calorie nutritional supplements)
	• Specialist assessment and advice on eating and swallowing (for example, from a speech and language therapist, fibreoptic endoscopic evaluation of swallowing, video fluoroscopy)
	Comparison: Compared to types of each other, each other and to no management strategy. Combinations of interventions will be considered.
	Outcomes:
	Critical:
	• Health-related quality of life (continuous)
	• Change in nutritional status (continuous)
	• Patient/carer reported outcomes (for example satisfaction) (continuous)
	• Change in weight/BMI (continuous)
	• Survival (time to event)
	Important:
	• Hospital admissions (dichotomous)

Search criteria	**Databases:** Medline, Embase, The Cochrane Library, CINAHL and PsycINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies

Review strategy	**Data analysis:**
	• The population will be stratified from the outset by:
	  ○ People with/without cognitive impairment, including frontotemporal dementia
	  ○ Swallowing and ability to feed
	  - People with normal swallowing and ability to feed themselves
	  - People with normal swallowing with self-feeding difficulties
	  - People with swallowing difficulties and no self-feeding difficulties
	  - People with swallowing and self-feeding difficulties
	The GDG felt that as different interventions will be needed to adapt for patients with swallowing difficulties and difficulties in feeding themselves, they should make separate

	recommendations for each of these groups. • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by: ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis) **Exclusion** • Study does not control for impact of confounders identified by the GDG

C.15 Gastrostomy

Table 16: Review protocol: Timing of gastrostomy

Review question	What is the clinically appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND?
Objectives	To identify the best time for placement of a gastrostomy tube for nutrition management in people with MND. Recommendations on the type of gastrostomy and the supplements given are provided within the NICE guideline on Enteral Feeding (CG32).
Criteria	**Population:** Adults (aged 18 years and over) with MND **Risk factors:** • Severity of dysphagia (continuous or dichotomous) (mild versus moderate/severe) • Weight loss (in order of preference; pre-/post- 10% weight loss, </> 18.5 BMI) • Respiratory function (in order of preference; ventilation versus no ventilation, </> 50% FVC, stable versus in decline) **Outcomes:** Critical: • Health related quality of life • Patients/carer reported outcomes (symptoms, satisfaction) • Hospital re-admissions and unplanned admissions • Time to death • Mortality related to procedure Important: • Nutritional status (malnutrition universal screening tool, % change in weight loss, change in BMI) • Hospital length of stay
Search	**Databases:** Medline, Embase, The Cochrane library, CINAHL and PsycINFO. **Date:** All years **Language:** Restrict to English only **Study designs:** Cohort studies
Review strategy	• Stratification: Adults with MND who need a gastrostomy; Adults with MND and cognitive dysfunction who need a gastrostomy • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • Use author's data. If there is a 10% differential or higher between groups or if missing data is higher than the event rate then downgrade on risk of bias. If authors use available case

	analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat analysis • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by: ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis) ○ Type of gastrostomy (PEG, RIG, PIG) ○ Skill/experience level of clinician • Some research has suggested that BMI is not a reliable indicator of nutritional status in MND. Therefore in paper where both are reported, % weight loss will be extracted preferentially • As each of the risk factors may act as confounders for each other if analysed separately, papers should use multivariate analysis to include all risk factors specified to be included in addition to accounting for the confounding effect of time since first symptom onset • If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed analysis

C.16 Communication

Table 17: Review protocol: Augmentative and alternative communication systems

Review question	What is the clinical- and cost-effectiveness of augmentative and alternative communication systems for supporting communication in people with MND?
Objectives	To assess the clinical- and cost-effectiveness of augmentative and alternative communication systems for supporting communication in people with MND with speech difficulties (dysarthia)?
Criteria	**Population** • Adults (aged 18 and over) with MND. **Interventions** Augmentative and alternative communication (aided and unaided systems), including electronic assistive technology, for example: • Alphabet boards • Pen and paper • Portable hardware ○ eye gaze systems ○ volume amplification ○ means of access (for example switches, infrared beams) • Software/applications for use on laptop, tablet devices etc. for those with no speech ○ Voice recognition software ○ Voice banking software • Complex speech/communication aids **Comparisons** Compared to types of each other. **Outcomes** Critical: • Health related quality of life (EQ5D, SF-36,SF-12) • Patient/carer reported outcomes (for example symptoms, satisfaction, pain (VAS) Important: • Function measured by disability scores, Speech and language scales)
Search	**Databases:** Medline, Embase, The Cochrane library, CINAHL and PsycINFO.

strategy	**Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20

Review strategy	**Data analysis**
	• The population will be stratified from the outset by:
	  ○ People with/without cognitive impairment including frontotemporal dementia
	  ○ With/without functional upper limbs
	  ○ With/without immobile upper limbs
	• Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)
	• Use author's data. If there is a 10% differential or higher between groups or if missing data is higher than the event rate then downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat analysis
	• If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by:
	  ○ Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)
	• If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed analysis

C.17 Cough effectiveness

Table 18: Review protocol: Cough augmentation techniques

Review question	What is the clinical- and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?
Objectives	To assess the clinical- and cost-effectiveness of cough augmentation techniques for people with MND
Criteria	**Population:** Adults (aged 18 and over) with MND who have reduced ability to cough **Interventions:** Basic cough augmentation techniques: • Active cycle of breathing techniques (ACBT) for example TEE, breathing control, huffing (breathing technique) • Postural drainage and manual techniques (shaking/percussion/vibration(s), GAP, positioning • Manual cough assisted coughing technique (quad coughing, assisted coughing) • Maximal insufflation capacity techniques (MIC) for example breath stacking (unassisted)/thoracic range of movement exercises, GPB • Respiratory muscle training (IMT) Devices (maximal insufflation capacity techniques/lung inflation capacity techniques): • Mechanical cough assist device (mechanical insufflation-exsufflation) • Intrapulmonary percussive ventilation • Lung volume recruitment techniques (for example LVR bags, NIV device to increase the inspiratory phase of cough to increase cough capacity rather than to treat respiratory failure) • Suction pump Devices will be reviewed singularly or in combination. **Comparisons:** • Compared with each other, or with nothing

Review question	What is the clinical- and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?
	Outcomes: Critical: • Survival • Health related quality of life (for example EQ5D, SF-36,SF-12, SRQ) • Patient/carer reported outcomes (ability to cough, ability to clear secretions, concordance, breathlessness [SOBAR/SOBOE], fatigue) Important: • Change in peak cough flow • Reduction of chest infection (pneumonia CAP or HAP and aspiration) • Hospital admissions (and unplanned admissions) and length of hospital stay [SRQ: St Georges Respiratory Questionnaire, for airways obstruction; SOBAR: shortness of breath at resting; SOBOE: shortness of breath on exertion]
Search strategy	**Databases:** Medline, Embase, The Cochrane library and CINAHL. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20 Where no RCTs or cohort studies in people with MND for either cough augmentation techniques or devices, we will consider RCTs in a population of patients with neuromuscular disease.

Review strategy	Data analysis
	• The population will be stratified from the outset by:
	  ○ People with/without cognitive impairment including frontotemporal dementia
	  ○ People with/without significant respiratory dysfunction
	  ○ People who are/are not at the end of life
	• Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)
	• Use authors data. If there is a 10% differential or higher between groups or if missing data is higher than the event rate then downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat analysis
	• If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be examined by:
	  ○ Types of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis)
	  ○ People who have a tracheostomy
	  ○ People who are obese
	  ○ People who are using NIV for respiratory failure
	• If heterogeneity cannot be explained, a random effects analysis will be performed in place of fixed analysis

C.18 Pharmacological management of breathing difficulties

Table 19: Review protocol: Breathing difficulties

Review question	What is the clinical- and cost-effectiveness of pharmacological treatments for managing breathing difficulties in people with MND?
Objectives	To assess the clinical and cost effectiveness of pharmacological treatment for managing

	breathing difficulties in people with MND
Criteria	**Population:** Adults (aged ≥18 years) with MND **Interventions:** Midazolam (benzodiazepine antiepileptic), Lorazepam (benzodiazepine anxiolytic), Diazepam (benzodiazepine anxiolytic), Clonazepam (benzodiazepine anxiolytic), Morphine (opioid analgesic), Diamorphine (opioid analgesic), Oxycodone (opioid analgesic), Fentanyl (opioid analgesic) **Comparison:** To be compared against each other, with placebo, or with usual care. **Outcomes:** Critical: • Health related quality of life (EQ-5D, SF-36, SF-12) • Patient reported outcomes (tolerance, improvement in breathing difficulties, improvement in cough, improvement in mobility, anxiety, pain [VAS]) Important: • Hospital admissions (and unplanned admissions) • Adverse events of treatment (sleepiness, nausea and vomiting) • Mortality **Setting:** All settings in which NHS care is provided
Search criteria	**Databases:** Medline, Embase and The Cochrane Library. **Date limit:** No date limit applied **Language:** English language only **Study designs:** RCTs or systematic reviews of RCTs; if no RCTs are retrieved, we will search for abstracts of RCTs or cohort studies with a sample size >20; if no cohorts are available we will look for RCTs and systematic reviews of RCTs including patients with multiple system atrophy, Parkinson's disease, progressive supranuclear palsy and spinal muscular atrophy.
Review strategy	**Data analysis:** • The population will be stratified from the outset by people with cognitive impairment including frontal temporal dementia; people who are at the end of life; people with swallowing difficulties (with or without gastronomy) • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) • If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data. • If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by: o Type of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis) o Mode of administration (tablet, liquid, transdermal patch, injection)

C.19 Experience of discontinuation of NIV

Table 20: Review protocol: Experience of discontinuation of NIV

Review question	What factors influenced the experience of discontinuation, at a patient's request, of NIV for relatives/carers/healthcare/social care professionals?
Objectives	To establish how the discontinuation of NIV was managed from the point of view of the relatives/carers/health and social care professionals.
Criteria	**Population:** • Family and carers of adults with MND

	• Health and social care professionals who support patients with MND **Context**: This is a qualitative review and themes included in the analysis will represent those identified by patients with MND and their families and carers. For background information for the technical team, areas of relevance may include timeliness in: • Preparation for discontinuation • Who removes NIV • Who needs to be there when NIV is discontinued • How discontinuation is done, for example weaning, immediate discontinuation • The use of medication including use of oxygen (rather than which medication should be used) • Carer/family support • Where it is done (hospital, hospice and home) • Time to death **Setting** • Any setting where patients receive NHS care • The review will include only papers from the UK because we consider this relevant to the UK health service.
Search criteria	**Databases:** Medline, Embase, CINAHL and PsychINFO. **Date limit:** No date limit applied **Language:** English language only **Study designs:** • Qualitative studies (for example interviews, focus groups) • Surveys if no qualitative studies are retrieved
Review strategy	**Population size and directness** • Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders **Appraisal of methodological quality** The methodological quality of each study will be assessed using NCGC modified NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome. **Data synthesis** Thematic analysis of the data will be conducted and findings presented. **Stratification/subgrouping** • Stratify by people who are dependent / not dependent on NIV

C.20 Management of discontinuation of NIV

Table 21: Review protocol: Management of discontinuation of NIV

Review question	What is the most appropriate management of discontinuation, at a patient's request, of NIV? (cohort review)
Objectives	To establish how the process of discontinuation of NIV can be managed effectively and sensitively in people with MND
Criteria	**Population:** Adults (aged ≥18 years) who request discontinuation of non-invasive ventilation **Interventions:** • Immediate discontinuation • Gradual discontinuation **Comparison:** To be compared against each other **Outcomes:**

	Critical: • Pain • Distress of the person with MND • Respiratory symptoms including rapid breathing • Time to death
Search criteria	**Databases:** Medline, Embase, CINAHL and PsycInfo. **Date limit:** No date limit applied **Language:** English language only **Study designs:** Cohort studies

Review strategy	**Data analysis:**
	• The population will be stratified from the outset by:
	  ○ People with/without frontotemporal dementia
	  ○ Discontinuation by a specialist with knowledge and experience of MND / discontinuation by a non-specialist without knowledge and experience of MND
	  ○ Dependent users of NIV (>22 hours per day) / non-dependent users of NIV (<22 hours per day)
	• Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)
	• If there is a 10% or higher differential between groups or if missing data is higher than the event rate then we will downgrade on risk of bias. If authors use available case analysis and intention to treat analysis, then available case analysis will be preferred over intention to treat data.
	• If heterogeneity is found, it will be explored by performing a sensitivity analysis and eliminating papers that have high risk of bias. If heterogeneity is still present, the influence of subgroups will be identified by:
	  ○ Use of drugs (analgesia, anaesthesia, sedative
	  ○ Place of discontinuation (home; hospital; hospice)
	• Key confounders: oxygen, sedation used

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C.21 Economic review protocol

Table 22: Health economic review protocol – all review questions

Review question	All questions – health economic evidence
Objectives	To identify economic evaluations relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of 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. • Studies must not be published before 1999.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G [in the Full guideline].
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[421] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the 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 an economic evidence table will not be completed and it will not be included in the 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 GDG if required. The ultimate aim is to include 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 GDG 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 economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example, USA, Switzerland)

	• non-OECD settings (always 'Not applicable'). *Economic study type:* • cost–utility analysis • 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 (always 'Not applicable'). *Year of analysis:* • The more recent the study, the more applicable it is. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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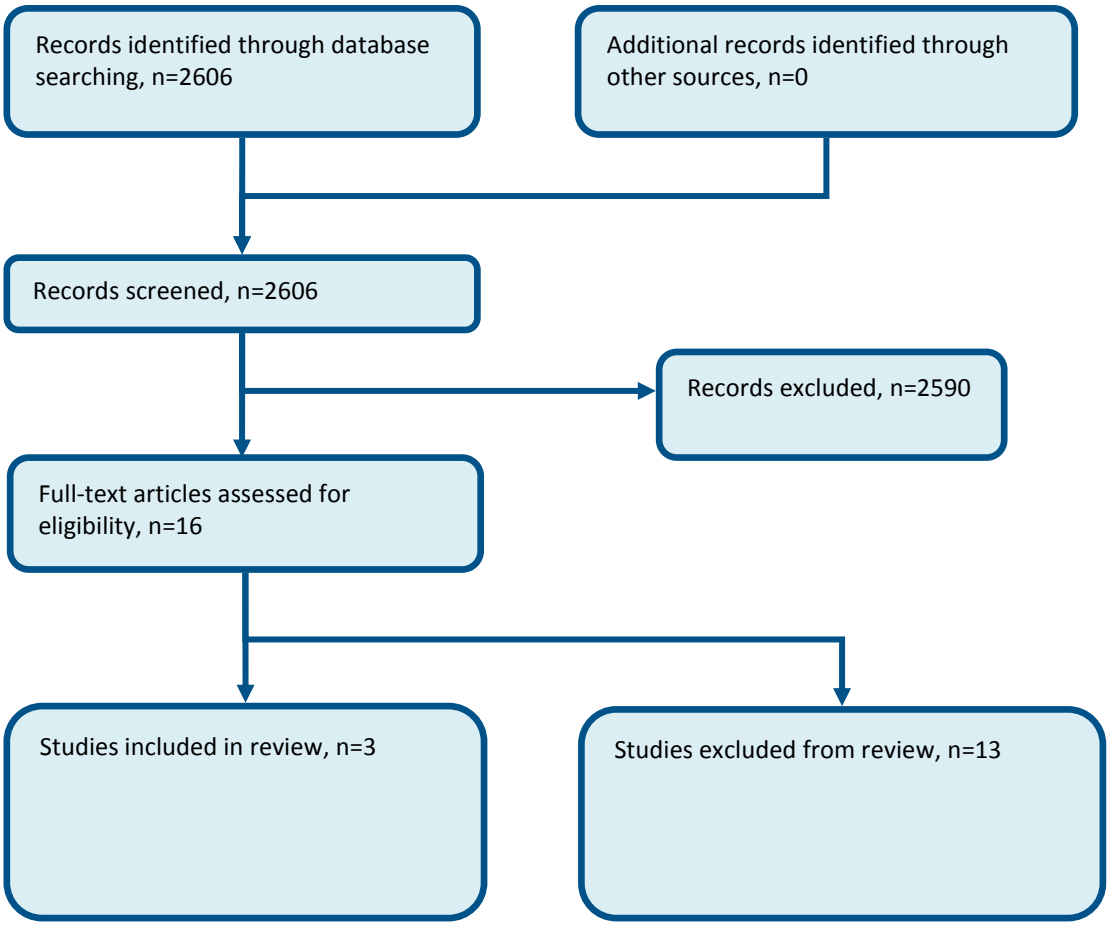
Appendix D: Clinical article selection

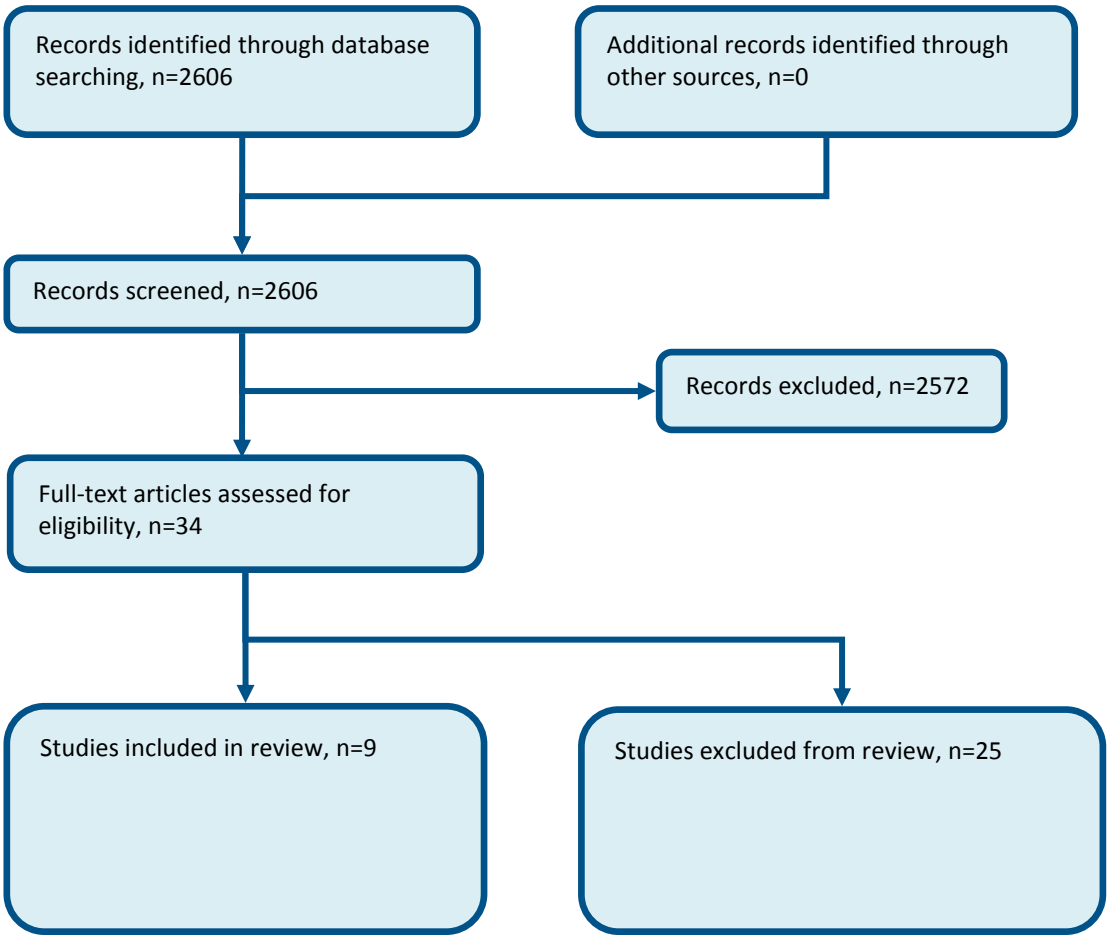
D.1 Recognition and referral

Figure 1: Flow chart of clinical article selection for the review of: Timeliness of diagnosis



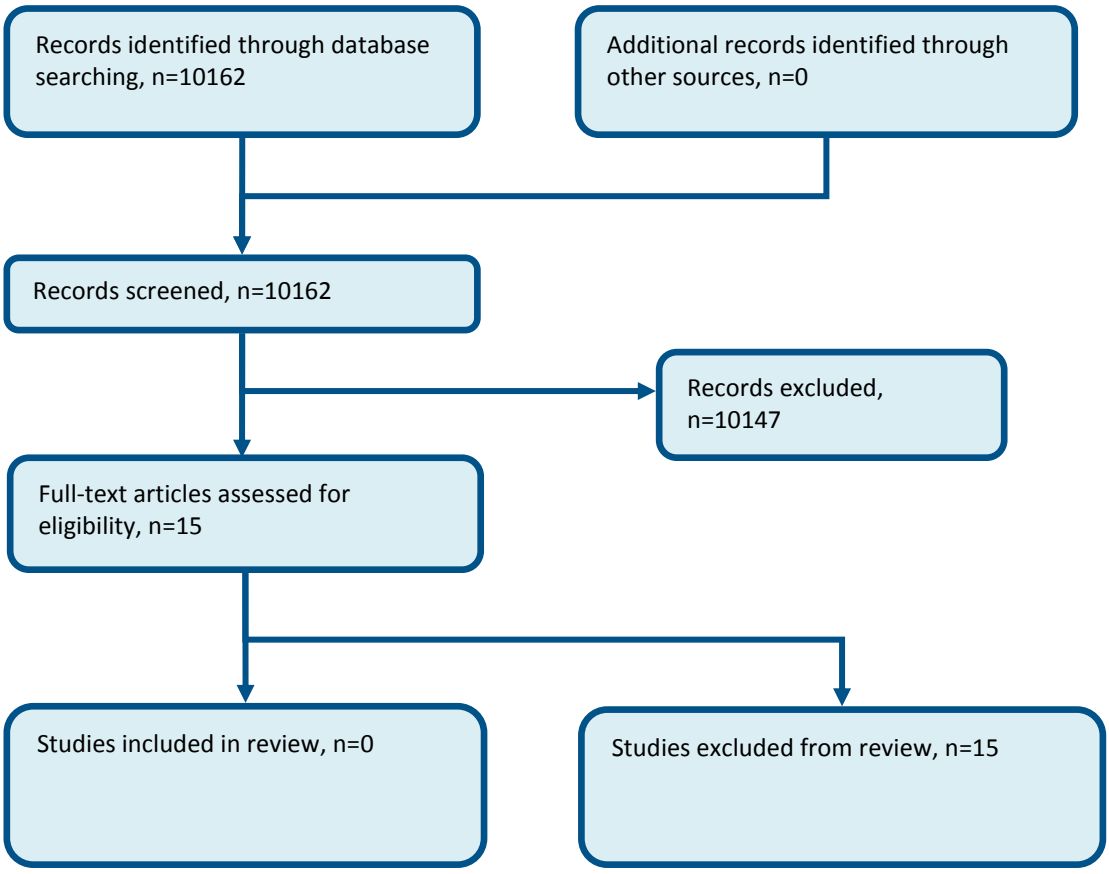
D.2 Information and support at diagnosis

Figure 2: Flow chart of clinical article selection for the review of: Knowledge to communicate diagnosis and prognosis



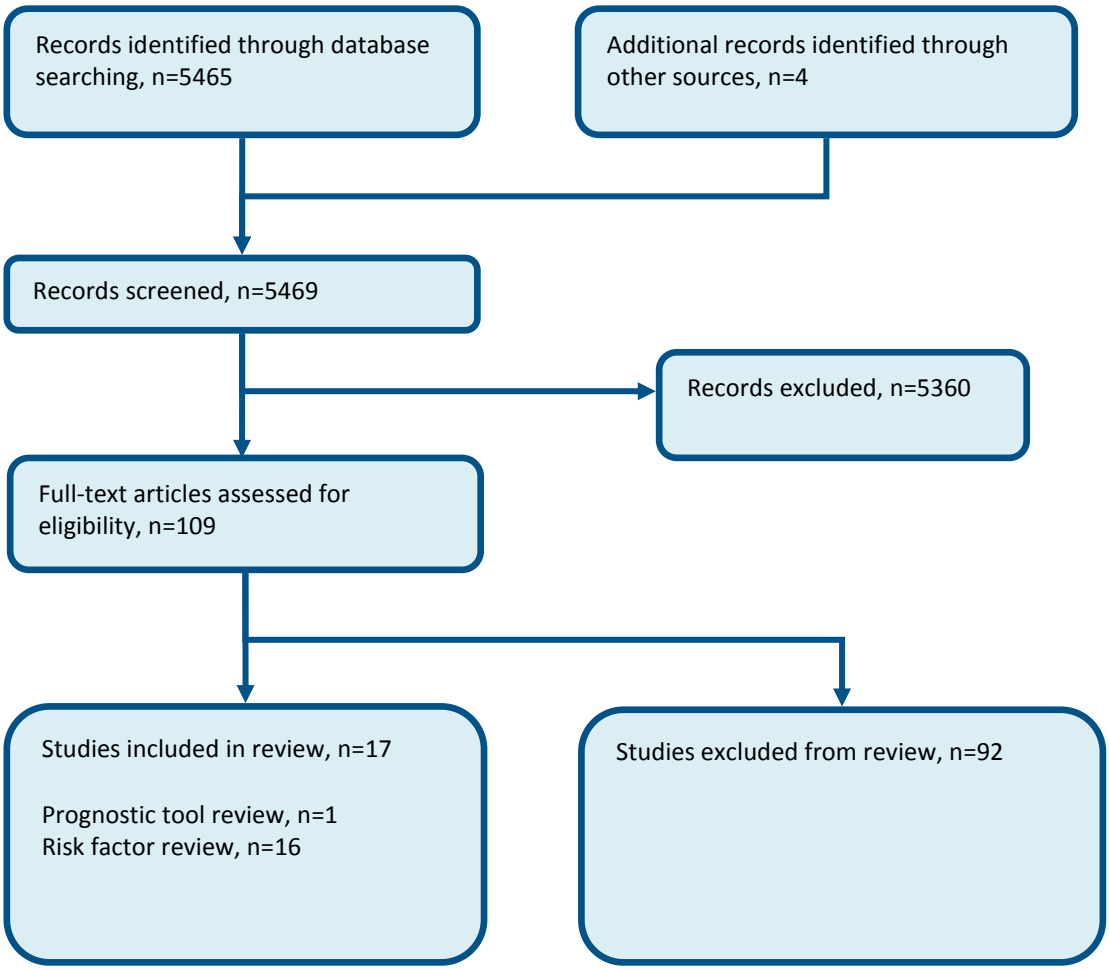
D.3 Cognitive assessments

Figure 3: Flow chart of clinical article selection for the review of: Frequency of cognitive assessments



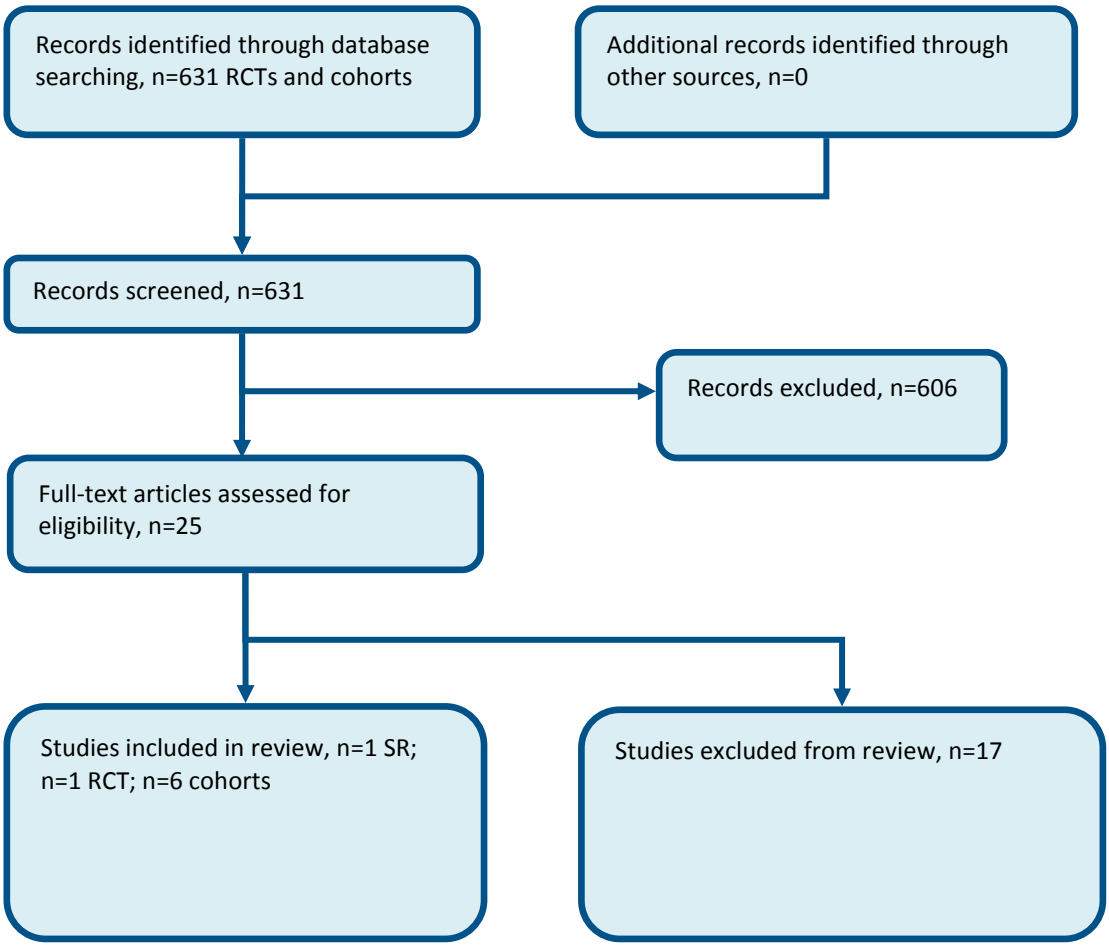
D.4 Prognostic factors

Figure 4: Flow diagram of article selection for: Prognostic tools for estimating survival



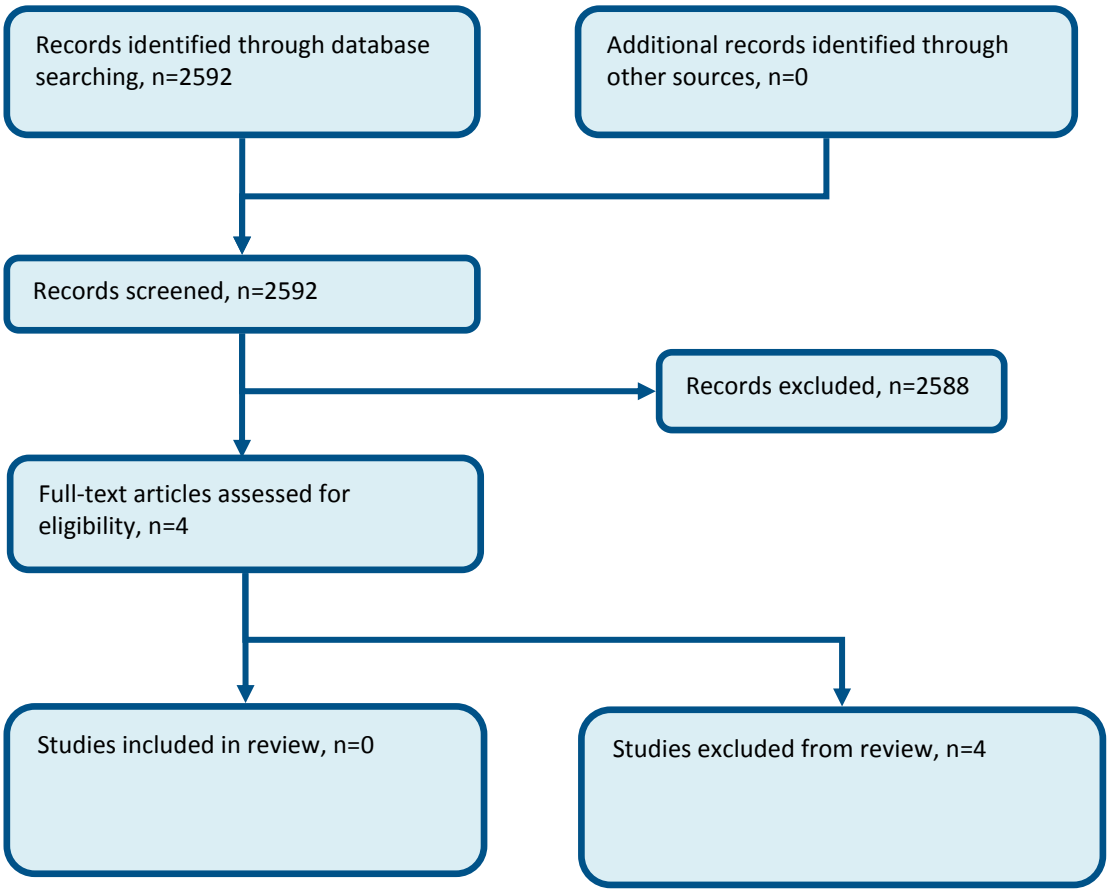
D.5 Organisation of care

Figure 5: Flow chart of clinical article selection for: Organisation of care



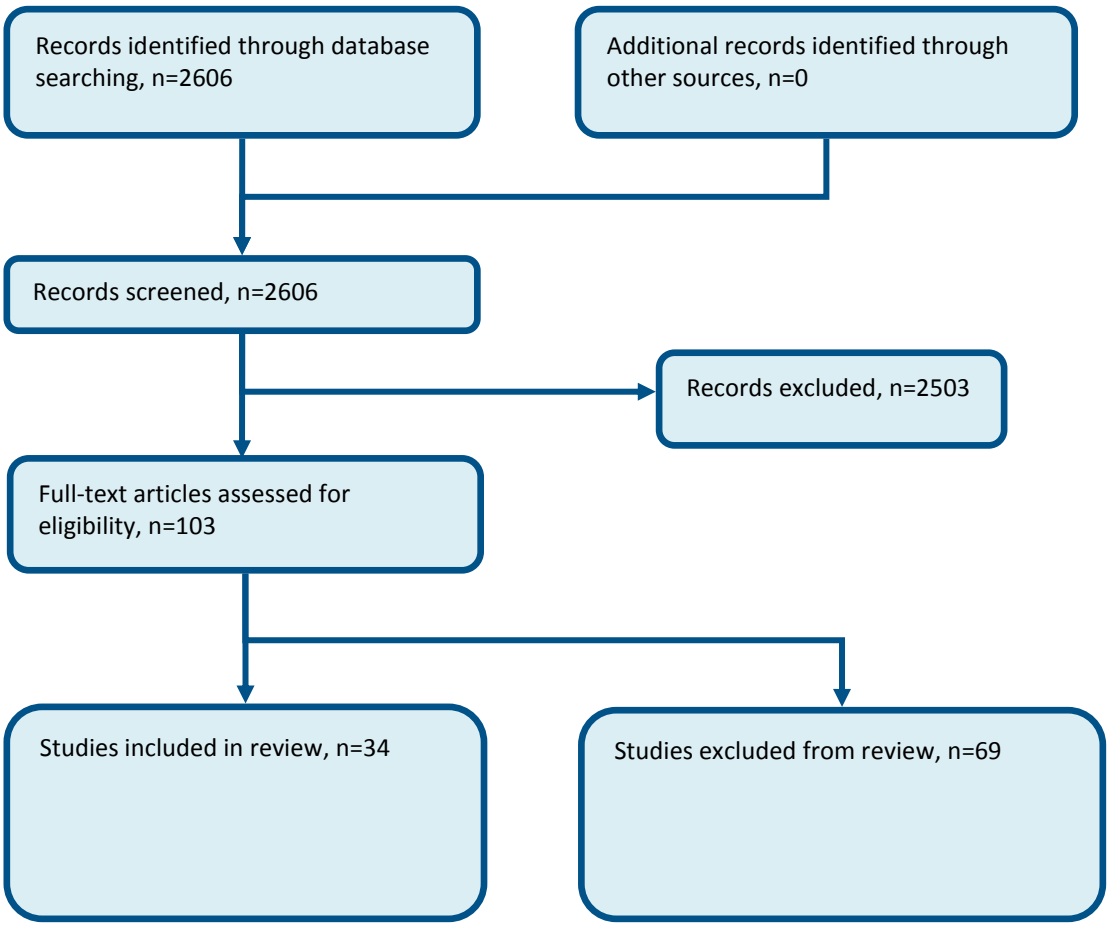
D.6 Frequency of assessment

Figure 6: Flow chart of clinical article selection for: Frequency of assessment



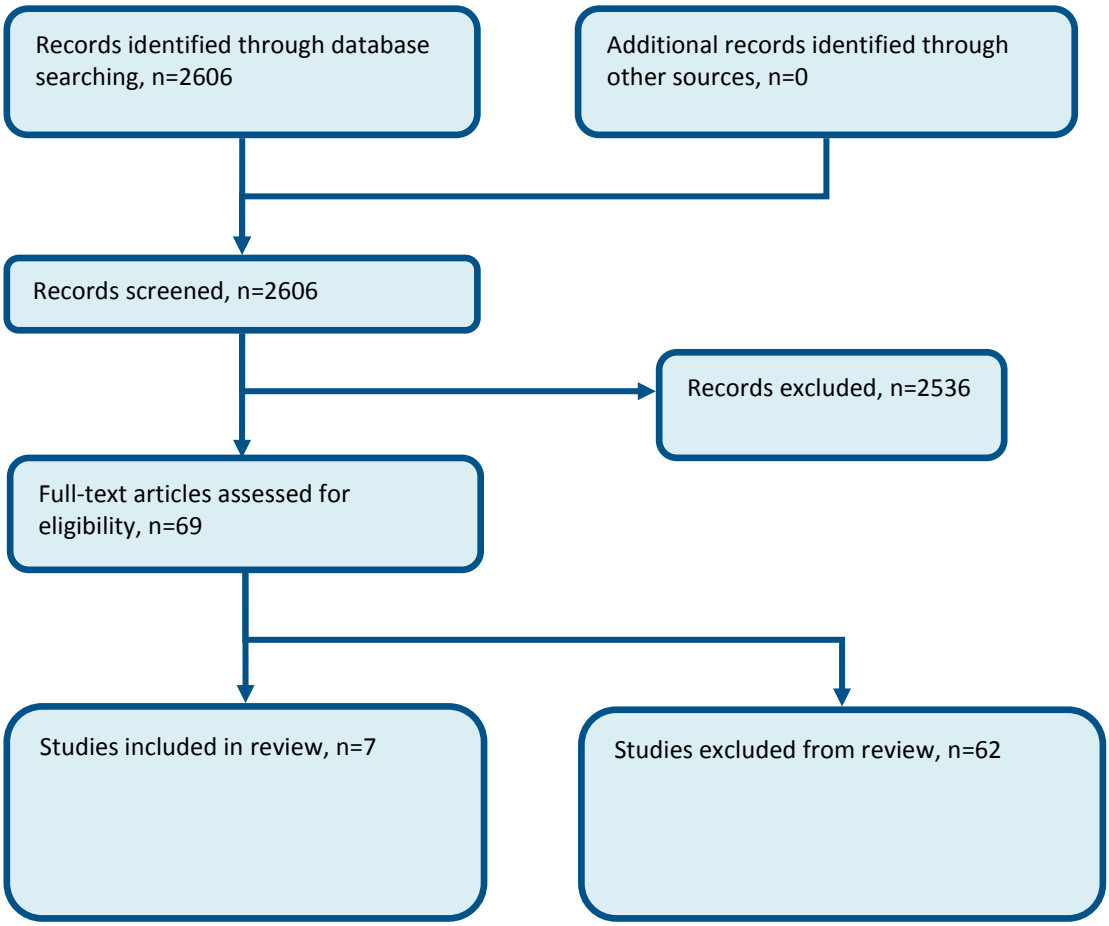
D.7 Psychological support

Figure 7: Flow chart of clinical article selection for: Psychological support



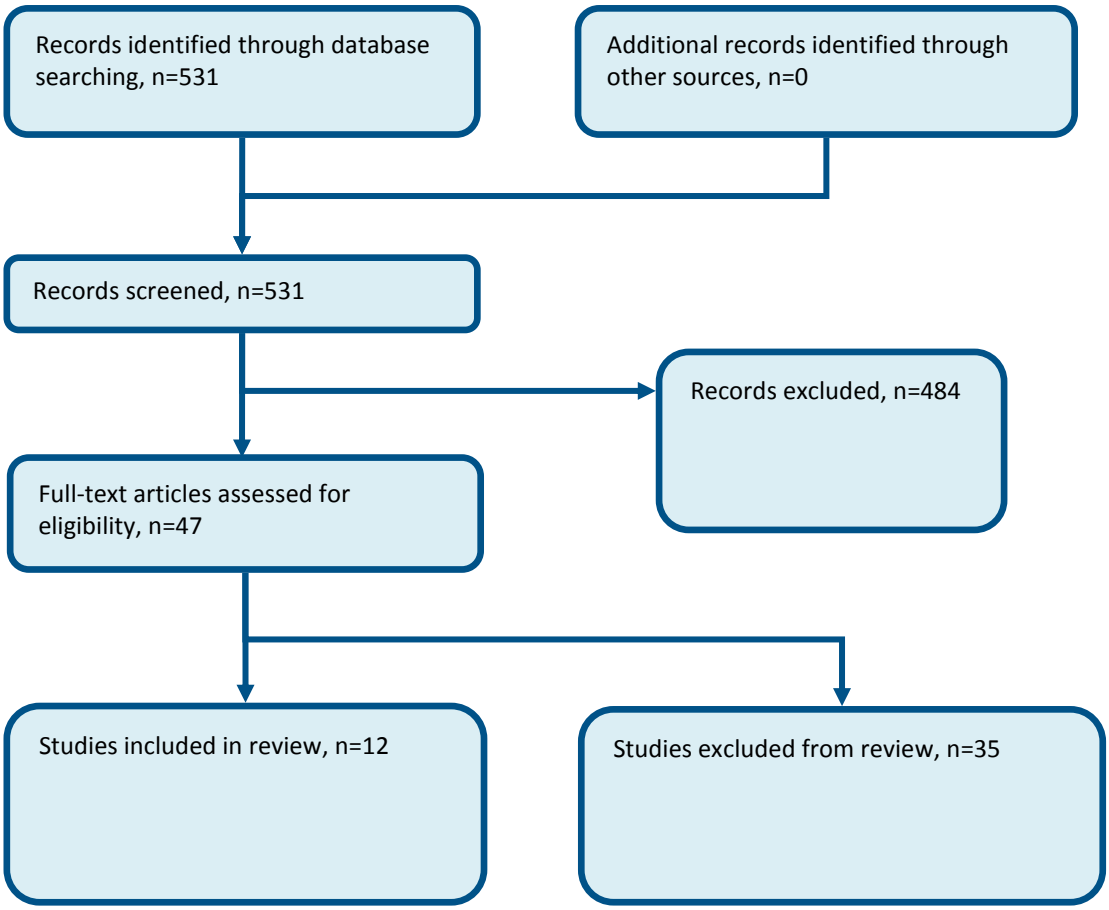
D.8 Social care support

Figure 8: Flow chart of clinical article selection for: Social care support



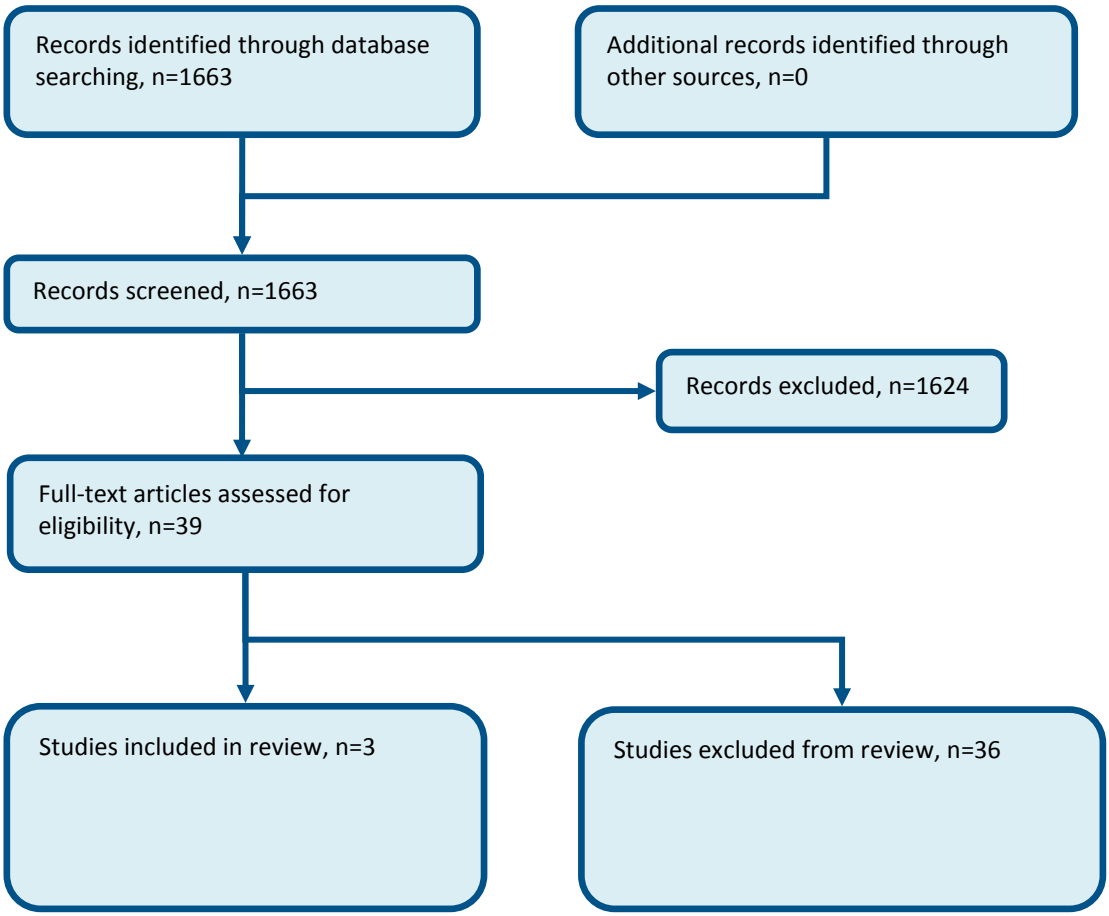
D.9 Planning for end of life

Figure 9: Flow chart of clinical article selection for: Anticipation of and preparation for end of life



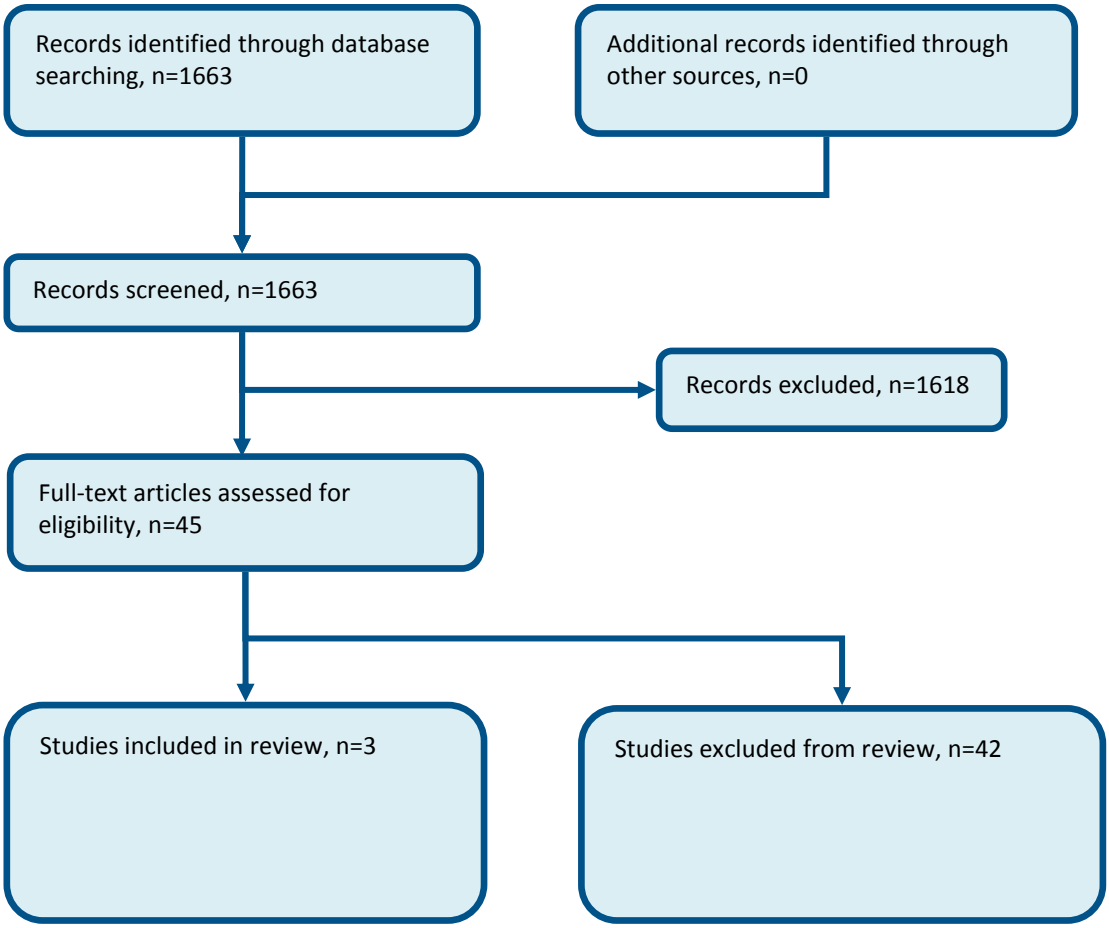
D.10 Pharmacological treatment for muscle problems

Figure 10: Flow chart of clinical article selection for: Pharmacological treatment for muscle problems



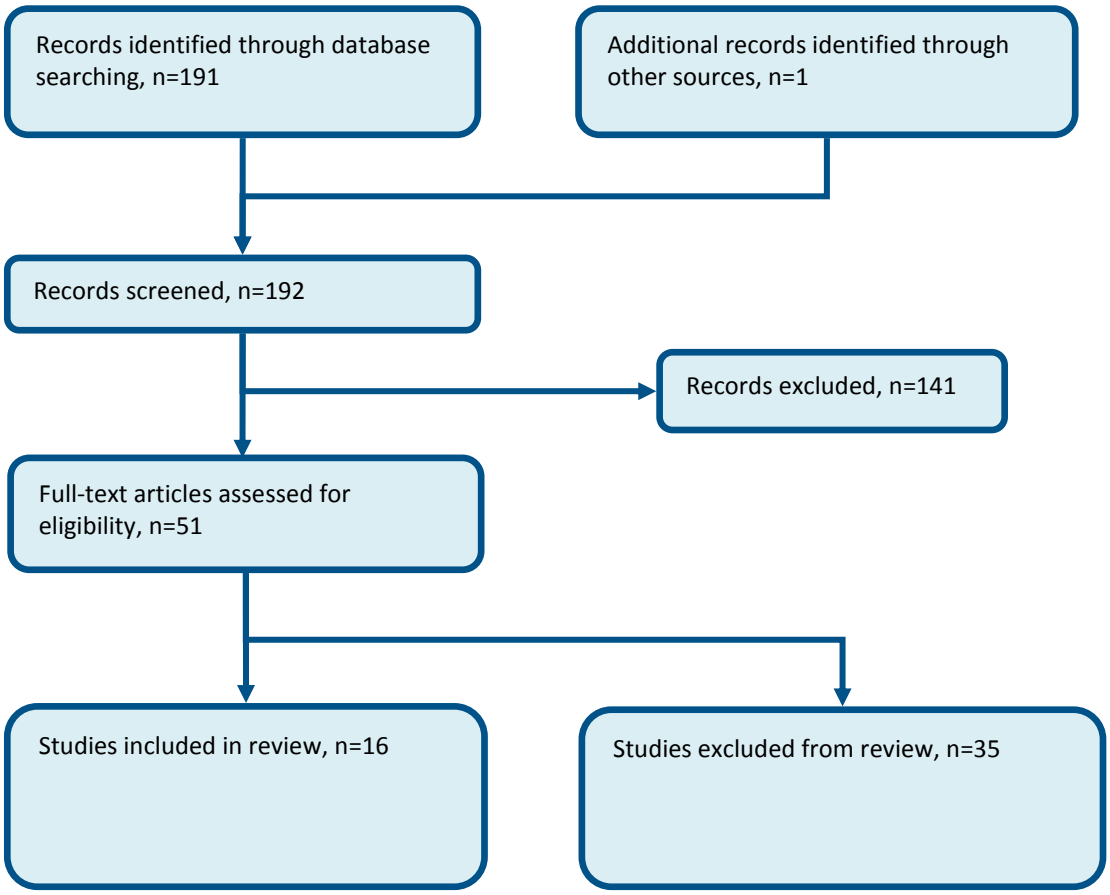
D.11 Non-pharmacological management of muscle problems

Figure 11: Flow chart of clinical article selection for: Non-pharmacological management of muscle problems



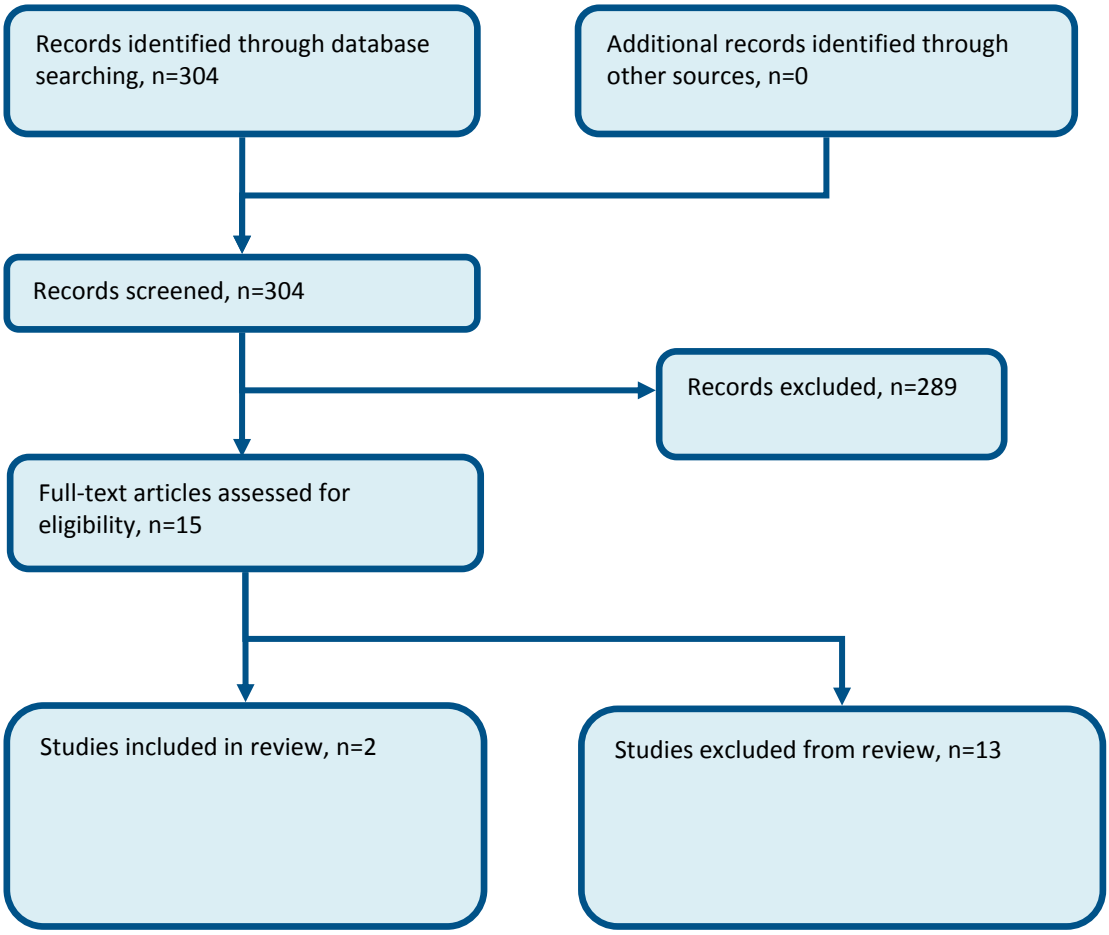
D.12 Saliva management

Figure 12: Flow chart of clinical article selection for: Saliva management



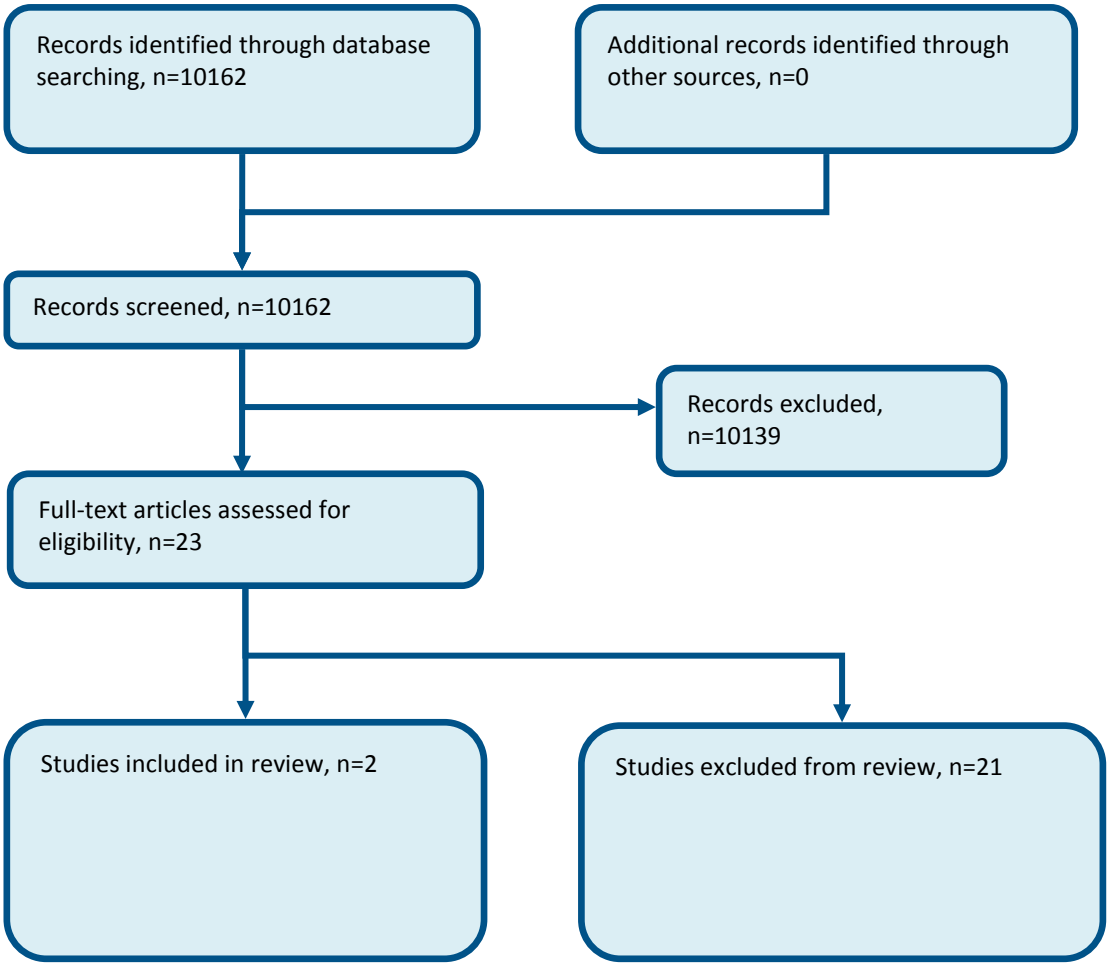
D.13 Equipment and adaptations to aid activities of daily living and mobility

Figure 13: Flow chart of clinical article selection for: Equipment needs



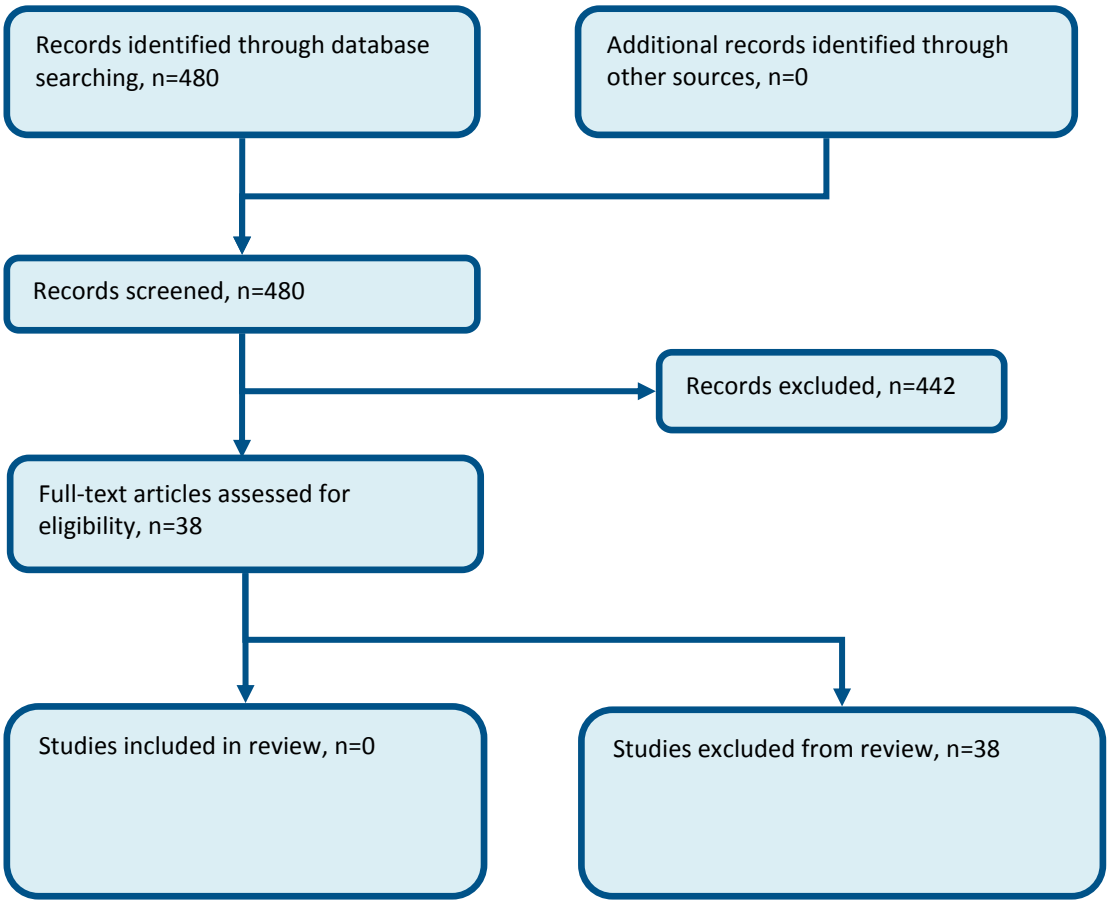
D.14 Nutrition

Figure 14: Flow chart of clinical article selection for: Nutritional intake



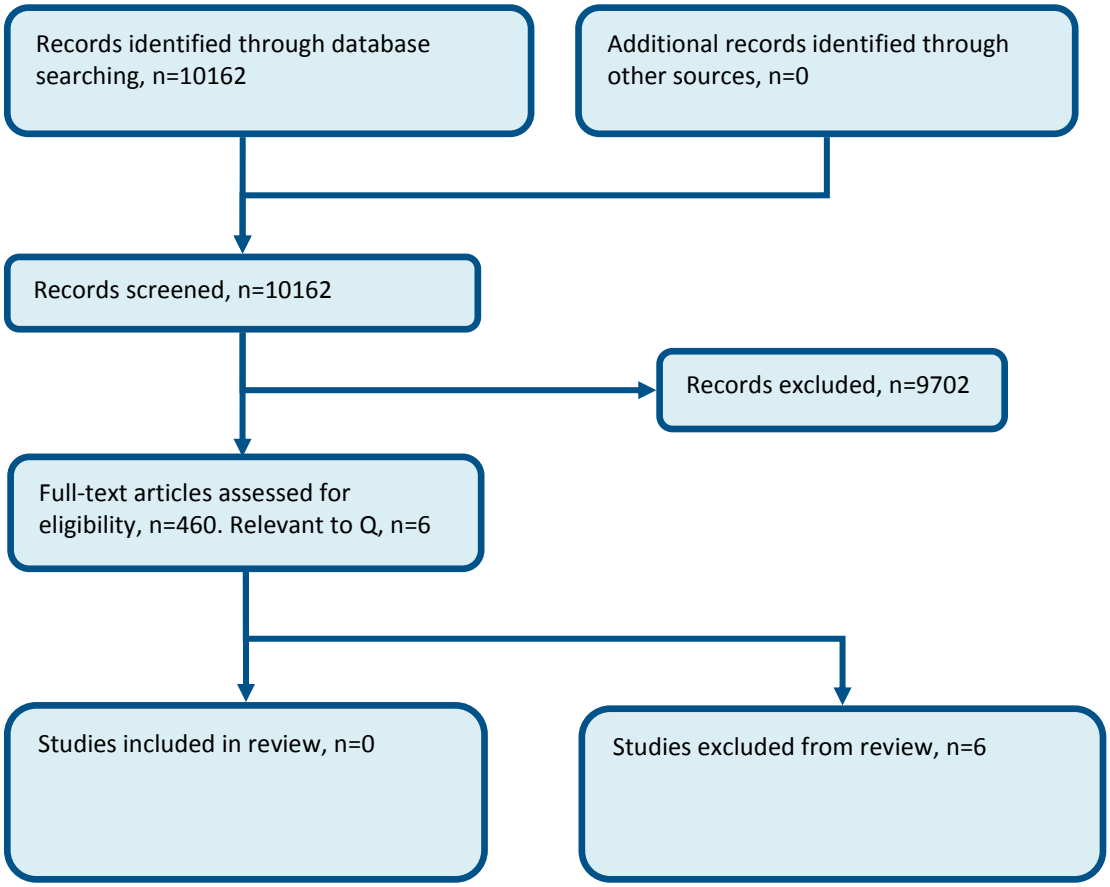
D.15 Gastrostomy

Figure 15: Flow chart of clinical article selection for: Timing of gastrostomy



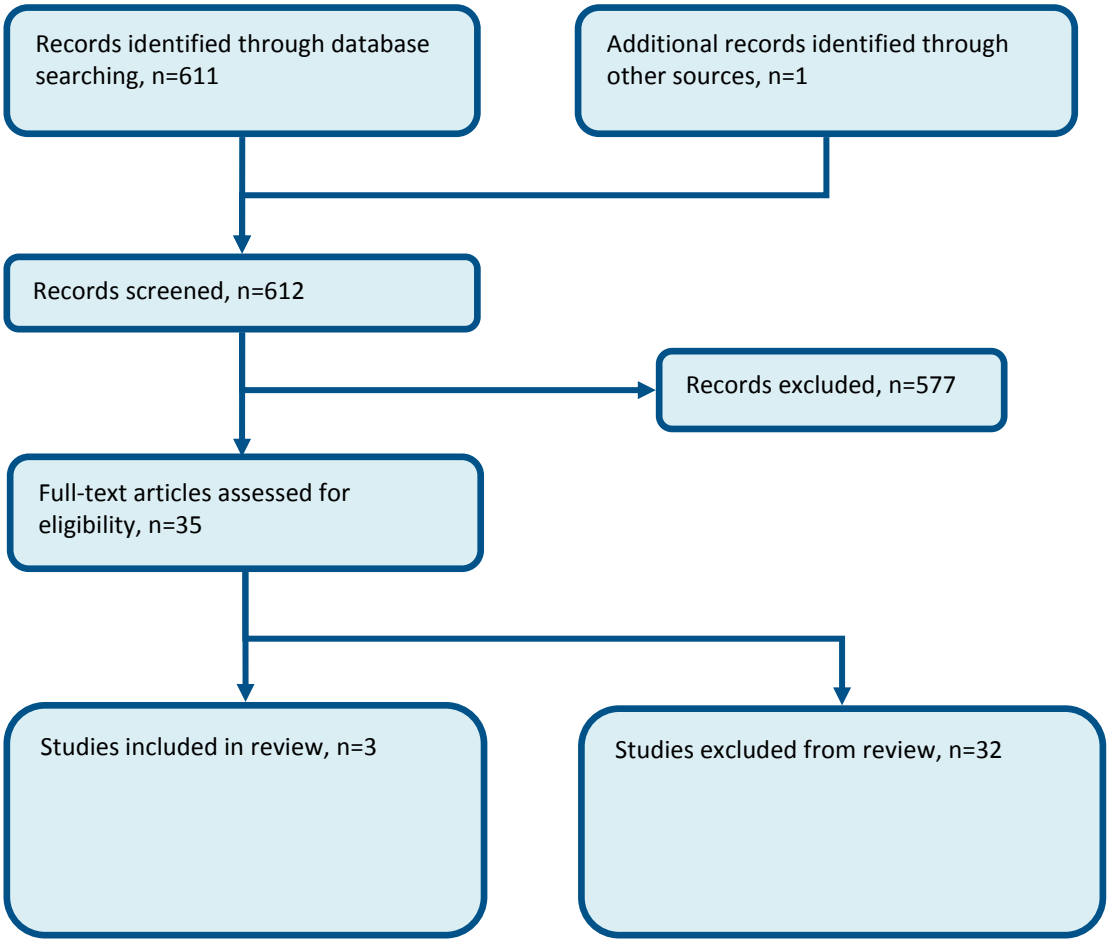
D.16 Communication

Figure 16: Flow chart of clinical article selection for: Augmentative and alternative communication



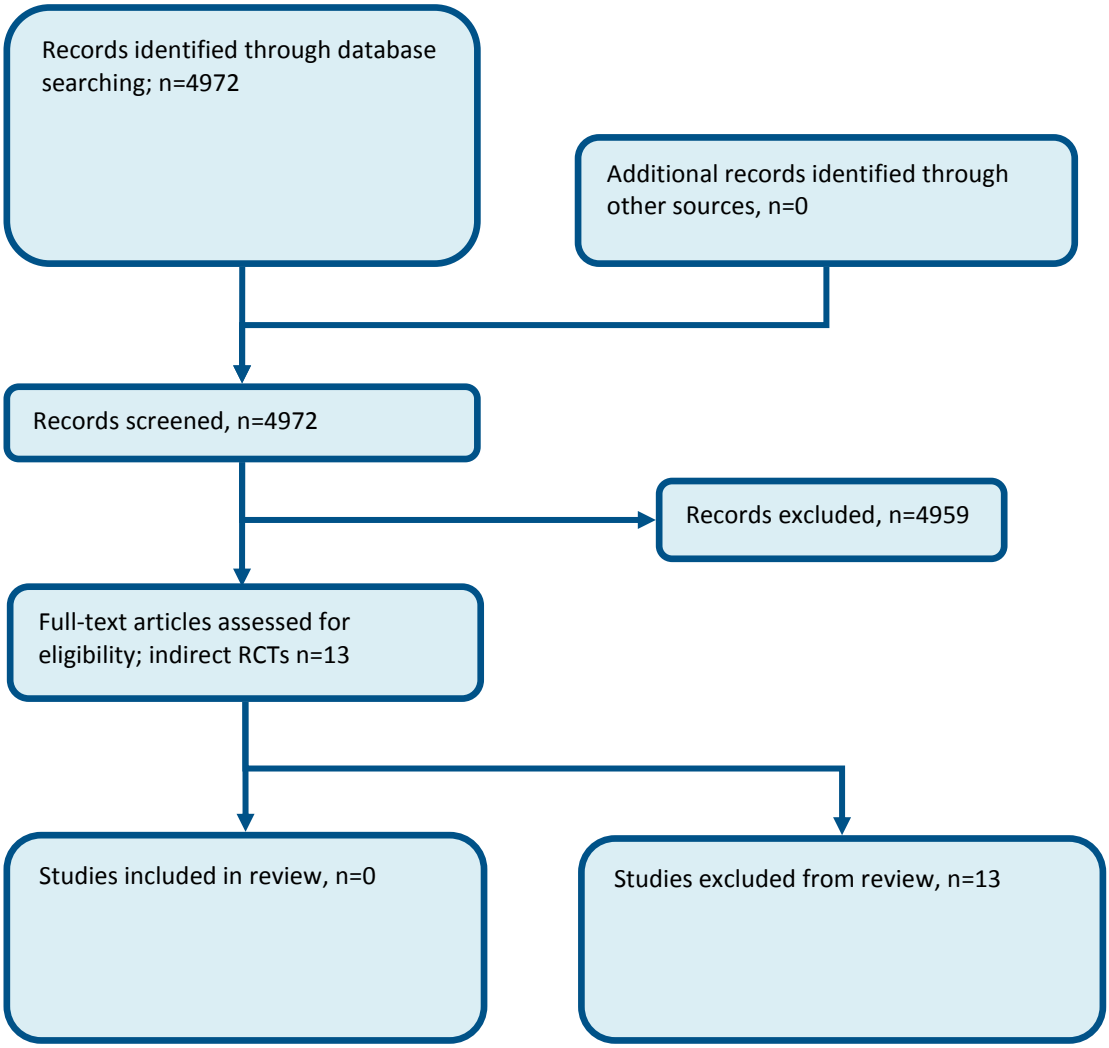
D.17 Cough effectiveness

Figure 17: Flow chart of clinical article selection for: Cough augmentation techniques



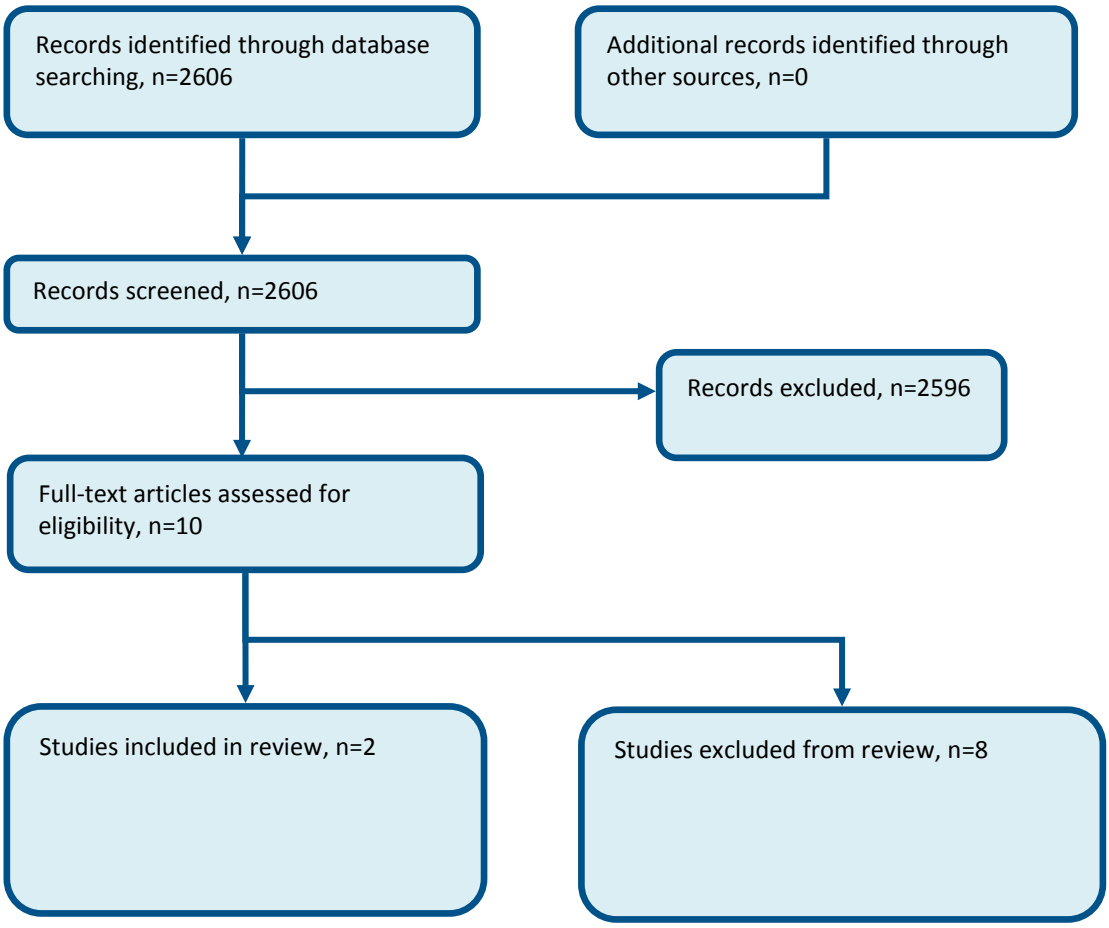
D.18 Pharmacological management of breathing difficulties

Figure 18: Flow chart of clinical article selection for: Pharmacological management of breathing difficulties



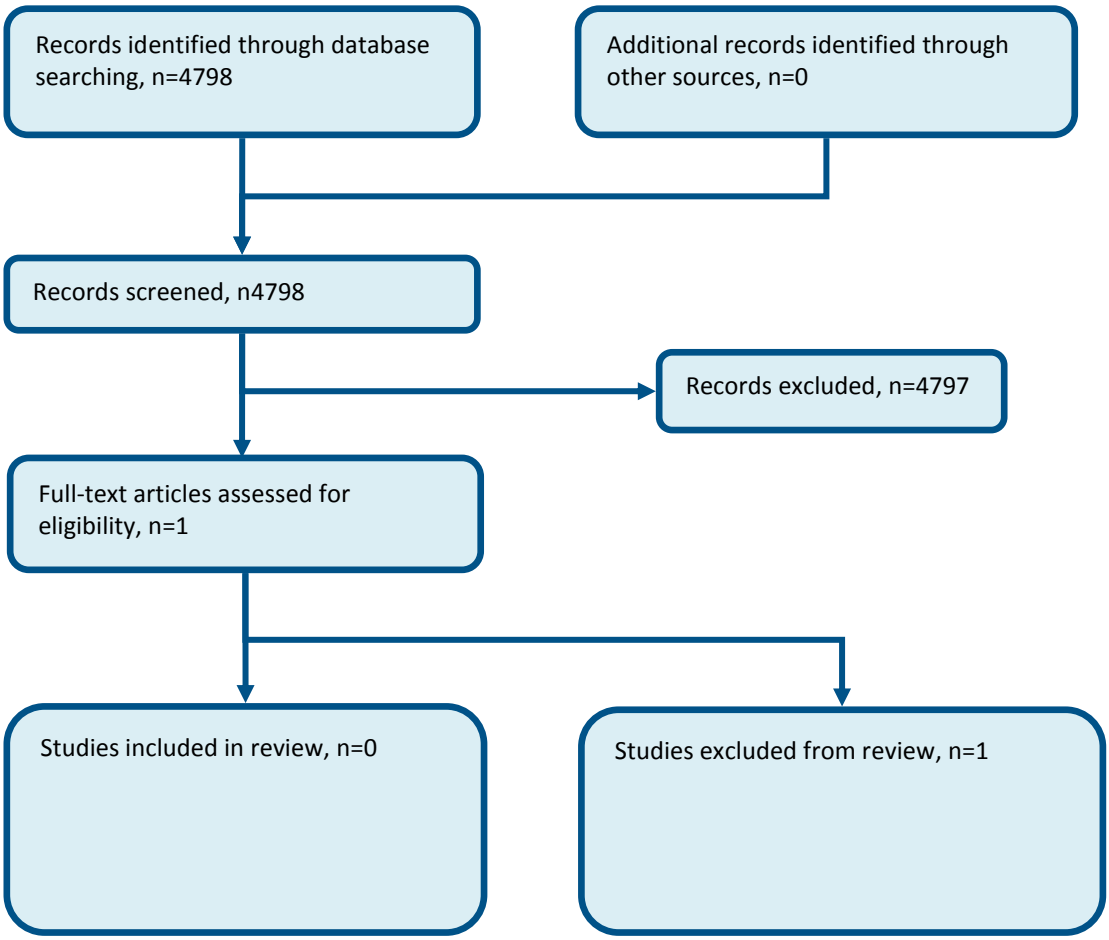
D.19 Experience of discontinuation of NIV

Figure 19: Flow chart of clinical article selection for: Experience of discontinuation of NIV



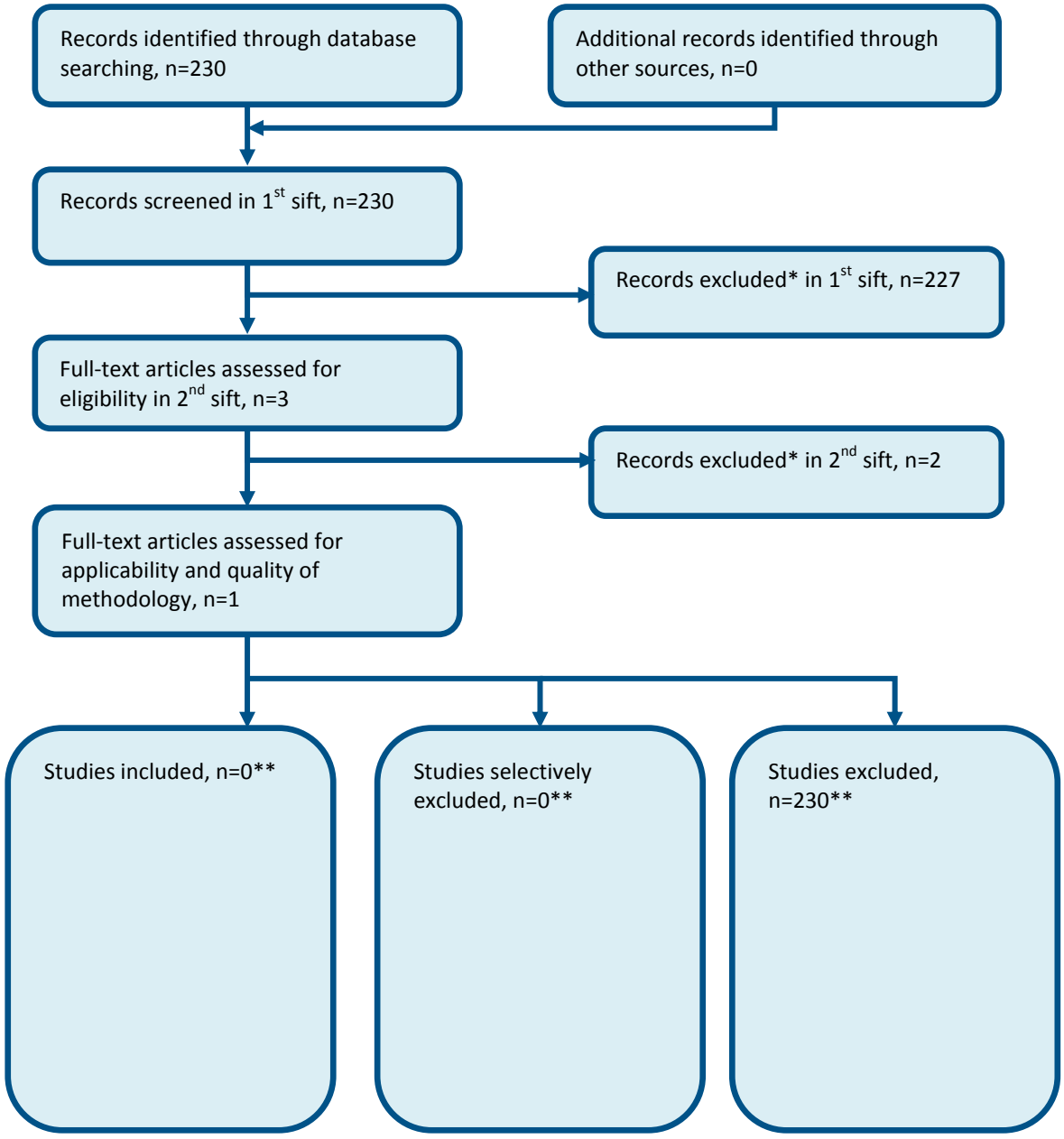
D.20 Management of discontinuation of NIV

Figure 20: Flow chart of clinical article selection for: Management of discontinuation of NIV



Appendix E: Economic article selection

Figure 21: Flow chart of economic article selection for the guideline



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

**Pending decision after assessment

1 Appendix F: Literature search strategies

2 F.1 Contents

Introduction	Search methodology
F.5.2	Quality of life reviews
F.5.3	Breathlessness
F.5.4	Saliva

Search strategies used for the motor neurone disease guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2012.[421] All searches were run up to **18 May 2015** unless otherwise stated. Any studies added to the databases after this date (even if they were published prior to this date) were not included unless specifically stated in the text. We do not routinely search for electronic, ahead of print or 'online early' publications. Where possible searches were limited to retrieve material published in English.

Table 23: Database date parameters

Database	Dates searched
Medline	1946 – 18th May 2015
Embase	1974 – 18th May 2015
The Cochrane Library	Cochrane Reviews to 2015 Issue 5 of 12 CENTRAL to 2015 Issue 4 of 12 DARE, HTA and NHSEED to 2015 Issue 2 of 4
CINAHL	1960-18th May 2015
PsycINFO (OVID)	1967-31st March 2015
PsycINFO (ProQuest)	2014-18th May 2015

Searches for the **clinical reviews** were run in Medline (OVID) and Embase (OVID). Additional searches were run in the Cochrane Library, CINAHL (EBSCO) and PsycInfo (OVID and ProQuest) for some questions. See Table 2.

Table 2: Databases searched in addition to Medline and Embase

Question	Question number	Databases
AAC	F.4.3	Cochrane, CINAHL, PsycINFO
Breathlessness	F.4.4	Cochrane
Cognitive assessment	F.4.5	Cochrane, CINAHL, PsycINFO
Co-ordination of care	F.4.6	Cochrane, CINAHL, PsycINFO
Cough	F.4.7	Cochrane, CINAHL
Discontinuation of NIV	F.4.8	CINAHL, PsycINFO
End of life	F.4.9	CINAHL, PsycINFO
Equipment for muscle weakness	F.4.10	CINAHL
Frequency of assessment	F.4.11	Cochrane
Knowledge for communicating diagnosis	F.4.13	CINAHL, PsycINFO
Muscle weakness	F.4.14	Cochrane, CINAHL
Nutrition	F.4.15	Cochrane, CINAHL, PsycINFO
Population only search 1	F.4.1	Cochrane, CINAHL, PsycINFO
Population only search 2	F.4.2	Cochrane, CINAHL
Psychological support	F.4.16	CINAHL, PsycINFO
Risk factors	F.4.17	None
Saliva	F.4.18	Cochrane
Social care	F.4.19	CINAHL, PsycINFO

Question	Question number	Databases
Timeliness of diagnosis	F.4.20	CINAHL, PsycINFO
Timing of gastrostomy	F.4.12	Cochrane, CINAHL, PsycINFO

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where Population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). NHS EED and HTA databases were hosted by the Centre for Research and Dissemination (CRD). The Health Economic Evaluation Database (HEED) ceased production in 2014 with access ceasing in January 2015. For the final dates of HEED searches, please see individual economic questions.

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

F.2 Population search strategies

F.2.1 Standard population

This search was used in all clinical questions except questions F.4.4 and F.4.18.

Medline search term

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

18.	or/1-17

1 **Embase search terms**

1.	exp *motor neuron disease/
2.	*bulbar paralysis/
3.	*motoneuron/
4.	(motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*).ti,ab.
5.	((primary or amyotrophic) adj lateral scleros*).ti,ab.
6.	(progressive adj (muscular atroph* or bulbar pals*)).ti,ab.
7.	(pseudopolyneur* or pseudo-polyneur* or psuedo polyneur*).ti,ab.
8.	((pseudobulbar or pseudo-bulbar or pseudo bulbar) adj pals*).ti,ab.
9.	((bulbar or respirat* or limb) adj onset*).ti,ab.
10.	lou gehrig*.ti,ab.
11.	((anterior or ventral) adj (horn or column) adj3 (disease* or disorder*)).ti,ab.
12.	(flail* adj (arm* or leg*) adj (syndrome* or disorder*)).ti,ab.
13.	(guam adj (disease* or disorder* or syndrome*)).ti,ab.
14.	monomelic amyotroph*.ti,ab.
15.	exp *frontotemporal dementia/
16.	((frontotemporal or fronto temporal or fronto-temporal) adj dement*).ti,ab.
17.	or/1-16

2 **Cochrane search terms**

#1.	MeSH descriptor: [motor neuron disease] explode all trees
#2.	MeSH descriptor: [motor neurons] explode all trees
#3.	(motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*):ti,ab
#4.	lateral next scleros*:ti,ab
#5.	(progressive muscular atroph*) or (progressive bulbar pals*):ti,ab
#6.	(pseudopolyneur* or pseudo-polyneur* or psuedo polyneur*) .ti,ab.
#7.	(pseudobulbar or pseudo-bulbar or pseudo bulbar):ti,ab
#8.	((bulbar or respirat* or limb) next onset*):ti,ab
#9.	lou gehrig*:ti,ab
#10.	(anterior next (horn or column)):ti,ab
#11.	(ventral next (horn or column)):ti,ab
#12.	(flail* arm*) or flail* leg*:ti,ab
#13.	(guam and (disease* or disorder* or syndrome*)):ti,ab
#14.	monomelic amyotroph*:ti,ab
#15.	MeSH descriptor: [frontotemporal dementia] explode all trees
#16.	((frontotemporal or fronto temporal or fronto-temporal) and dement*):ti,ab
#17.	{or #1-#16}

3 **CINAHL search terms**

S1.	(MH "motor neuron diseases+")
S2.	(MH "amyotrophic lateral sclerosis")
S3.	(MH "bulbar palsy, progressive+")
S4.	(mm "motor neurons+")

S5.	motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*
S6.	primary n1 lateral scleros* or amyotrophic n1 lateral scleros*
S7.	progressive n1 muscular atroph* or progressive n1 bulbar pals*
S8.	pseudopolyneur* or pseudo-polyneur* or psuedo polyneur
S9.	pseudobulbar n1 pals* or pseudo-bulbar n1 pals* or pseudo bulbar n1 pals*
S10.	bulbar n1 onset* or respirat* n1 onset* or limb n1 onset*
S11.	lou gehrig*
S12.	anterior horn n3 disease* or anterior horn n3 disorder* or anterior column n3 disease* or anterior column n3 disorder* or ventral horn n3 disease* or ventral horn n3 disorder* or ventral column n3 disease* or ventral column n3 disorder*
S13.	flail* arm* syndrome* or flail* arm* disorder* or flail* leg* syndrome* or flail* leg* disorder*
S14.	guam disease* or guam disorder* or guam syndrome*
S15.	monomelic amyotroph*
S16.	frontotemporal dement* and fronto temporal dement* and fronto-temporal dement*
S17.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16

PsycINFO (Ovid) search terms

1.	exp motor neurons/ or exp amyotrophic lateral sclerosis/
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*.ti,ab.
9.	((anterior or ventral) adj (horn or column) adj3 (disease* or disorder*)).ti,ab.
10.	(flail* adj (arm* or leg*) adj (syndrome* or disorder*)).ti,ab.
11.	(guam adj (disease* or disorder* or syndrome*)).ti,ab.
12.	monomelic amyotroph*.ti,ab.
13.	((frontotemporal or fronto temporal or fronto-temporal) adj dement*).ti,ab.
14.	or/1-13

PsycINFO (ProQuest) search terms

1.	((su.exact.explode("motor neurons") or su.exact.explode("amyotrophic lateral sclerosis") or ti,ab(motoneuron* or motorneuron* or moto-neuron* or motor-neuron*) or ti,ab((primary or amyotrophic) near/1 lateral scleros*) or ti,ab(pseudopolyneur* or pseudo-polyneur*) or ti,ab((pseudobulbar or pseudo-bulbar) near/1 pals*) or ti,ab((bulbar or respirat* or limb) near/1 onset*) or ti,ab((anterior or ventral) near/1 (horn or column) near/3 (disease* or disorder*)) or ti,ab(flail* near/1 (arm* or leg*) near/1 (syndrome* or disorder*)) or ti,ab(guam near/1 (disease* or disorder* or syndrome*)) or ti,ab(monomelic amyotroph*) or ti,ab((frontotemporal or fronto-temporal) near/1 dement*) or ti,ab((muscular-atroph*) or (bulbar-pals*) near/1 progressive) or ti,ab(lou-gehrig*))

F.2.2 Neuromuscular disease

This search was used in question F.4.7 in conjunction with the standard population.

Medline search term

1.	exp neuromuscular diseases/
2.	randomized controlled trial.pt.
3.	controlled clinical trial.pt.
4.	randomi#ed.ab.
5.	placebo.ab.
6.	randomly.ab.
7.	clinical trials as topic.sh.
8.	trial.ti.
9.	or/2-8
10.	1 and 9

Embase search term

1.	exp neuromuscular diseases/
2.	random*.ti,ab.
3.	factorial*.ti,ab.
4.	(crossover* or cross over*).ti,ab.
5.	((doubl* or singl*) adj blind*).ti,ab.
6.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
7.	crossover procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	double blind procedure/
11.	or/2-10
12.	1 and 11

Cochrane search term

1.	MeSH descriptor: [neuromuscular diseases] explode all trees

CINAHL search term

1.	(MH "neuromuscular diseases+")

F.3 Study filter search terms

F.3.1 Systematic reviews (SR) search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.

10.	or/1-9

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10.	cochrane.jw.
11.	or/1-10

PsycInfo (Ovid) search terms

1.	"review"/ or review.pt. or review.ti. or literature review.md.
2.	(systematic or evidence* or methodol* or quantitativ*).ti,ab.
3.	1 and 2
4.	meta-analysis/
5.	(meta-analys* or metanalys* or metaanalys* or meta analys*).ti,ab.
6.	((systematic or evidence* or methodol* or quantitativ*) adj3 (review* or overview*)).ti,ab.
7.	((pool* or combined or combining) adj2 (data or trials or studies or results)).ti,ab.
8.	(systematic or meta*).pt. or (meta analysis or systematic review).md.
9.	or/3-8

PsycInfo (ProQuest) search terms

1.	((SU.EXACT("Literature Review") or RTYPE(review) or ti(review) or me(literature review)) AND (ti,ab(systematic or evidence or methodol* or quantitative*))) or (SU.EXACT("Meta Analysis") or ti,ab(meta-analys* or metanalys* or metaanalys* or meta analys*) or ti,ab((systematic or evidence* or methodol* or quantitative*) near/3 (review* or overview*)) or ti,ab((pool* or combined or combining) near/2 (data or trials or studies or results)) or RTYPE(systematic or meta*) or ME(meta analysis or systematic review))

F.3.2 Randomised controlled trials (RCT) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.

2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

PsycInfo (Ovid) search terms

1.	exp clinical trial/
2.	randomi*.ti,ab.
3.	((clinical or control*) adj3 trial*).ti,ab.
4.	((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).ti,ab.
5.	(volunteer* or control group or controls).ti,ab.
6.	placebo/ or placebo*.ti,ab.
7.	or/1-6

PsycInfo (ProQuest) search terms

1.	(su.exact.explode("clinical trials") or ti,ab((clinical or control*) near/3 trial*) or ti,ab((singl* or doubl* or trebl* or tripl*) near/5 (blind* or mask*)) or ti,ab(volunteer* or control-group or controls) or su.exact("placebo") or ti,ab(placebo*))

F.3.3 Observational studies (OBS) search terms

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 or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

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

PsycInfo (Ovid) search terms

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

PsycInfo (ProQuest) search terms

1.	(su.exact.explode("longitudinal studies") or su.exact.explode("followup studies") or ti,ab(cohort near/1 (study or studies or analys*)) or ti,ab((follow-up or observational or uncontrolled or non-randomi?ed or nonrandomi?ed or epidemiologic*) near/1 (study or studies)) or ti,ab((longitudinal or retrospective or prospective or cross-section) and (study or studies or review or analys* or cohort*)))

F.3.4 Qualitative reviews (QUAL) search terms

Medline search terms

1.	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

Embase search terms

1.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

CINAHL search terms

1.	(MH "qualitative studies+")
2.	(MH "qualitative validity+")
3.	(MH "interviews+") or (MH "focus groups") or (MH "surveys") or (MH "questionnaires+")
4.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
5.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
6.	S1 or S2 or S3 or S4 or S5

PsycINFO (Ovid) search terms

1.	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

PsycINFO (Ovid) search terms

1.	((su.exact.explode("qualitative research") or su.exact("narratives") or su.exact.explode("questionnaires") or su.exact.explode("interviews") or su.exact.explode("health care services") or ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)))

F.3.5 Health economics (HE) search terms

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

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

F.3.6 Quality of life (QOL) search terms

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/

3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

F.3.7 Health economic modelling (MOD) search terms

Medline search terms

1.	exp models, economic/
2.	*models, theoretical/
3.	*models, organizational/
4.	markov chains/
5.	monte carlo method/
6.	exp decision theory/
7.	(markov* or monte carlo).ti,ab.
8.	econom* model*.ti,ab.
9.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
10.	or/1-9

Embase search terms

1.	statistical model/
2.	exp economic aspect/
3.	1 and 2
4.	*theoretical model/
5.	*nonbiological model/
6.	stochastic model/
7.	decision theory/
8.	decision tree/
9.	monte carlo method/
10.	(markov* or monte carlo).ti,ab.

11.	econom* model*.ti,ab.
12.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13.	or/3-12

F.3.8 Excluded study designs and publication types

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

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

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

PsycINFO (Ovid) search terms

1.	animals/ not humans/
2.	exp rodents/ or exp mice/
3.	(rat or rats or mouse or mice).ti.
4.	or/1-3

PsycINFO (Ovid) search terms

1.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

F.4 Searches for specific questions

F.4.1 Population only search 1

Searches for the following three questions were run as one search:

1. What is the clinical and cost-effectiveness of augmentative and alternative communication systems for supporting communication in people with MND?
2. What is the optimum frequency of assessing cognitive function in patients with MND?
3. What are the most clinically and cost-effective methods for maintaining nutritional intake and managing weight in people with MND for whom a gastrostomy is not appropriate?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)			The following filters were used in Medline, Embase and PsycINFO only: OBS, RCT, SR	See Table 23 English only Exclusion filter applied in Medline, Embase and PsycINFO

F.4.2 Population only search 2

Searches for the following four questions were run as one search:

4. What specific MND knowledge do patients, their carers and health professionals consider is required in order to communicate diagnosis of MND, its prognosis, and choices of ongoing care appropriately?
5. What psychological support is needed for people with MND and their families and carers?
6. What are the social care support needs of people with MND and their families and carers?
7. What factors impact upon timeliness of diagnosis in people with MND in the UK?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)			The following filters were used in Medline, Embase, CINAHL and PsycINFO only: QUAL	See Table 23 English only Exclusion filter applied in Medline, Embase

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
				and PsycINFO

F.4.3 Augmentative and alternative communication (AAC)

See F.4.1

F.4.4 Breathlessness

8. What is the clinical and cost-effectiveness of pharmacological treatments for managing breathing difficulties in people with MND?

Search constructed by combining the columns in the following table using the AND Boolean operator and by combining the rows using the OR Boolean operator. Exclusion filter applied using NOT Boolean operator.

Search	Population	Intervention or exposure	Study design filter	Date parameters and other limits
A		Pharmacological treatments for managing breathing difficulties	The following filters were used in Medline and Embase only: RCT, SR	See Table 23 English only Exclusion filter applied in Medline and Embase
B	Adults (aged 18 and over) with motor neurone disease (A.2.1)		The following filters were used in Medline and Embase only: OBS	Same as search A

Medline search terms

1.	exp diazepam/ or lorazepam/ or midazolam/ or clonazepam/
2.	heroin/ or morphine/
3.	oxycodone/
4.	exp fentanyl/
5.	(diazepam or lorazepam or midazolam or rimapan or tensium or dialar of diazemuls).ti,ab.
6.	(morphine or diamorphine or oxycodone or fentanyl or oramorph or sevredol or filnarine or morphgesic or mst continus or zomorph or mxl or cyclimorph or oxynorm or dolocodon or longtec or oxycontin or targinact or abstral or effentora or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mezolar or osmanil or tilofyl or victanyl or durogesic or clonazepam or rivotil).ti,ab.
7.	or/1-6
8.	*dyspnea/
9.	dyspn?ea.ti,ab.
10.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
11.	breathlessness.ti,ab.
12.	or/8-11
13.	7 and 12

Embase search terms

1.	*diazepam/ or *lorazepam/ or *midazolam/ or *clonazepam/
2.	*diamorphine/ or *morphine/ or *oxycodone/ or *fentanyl/
3.	(diazepam or lorazepam or midazolam or rimapan or tensium or dialar of diazemuls).ti,ab.

4.	(morphine or diamorphine or oxycodone or fentanyl or oramorph or sevredol or filnarine or morphgesic or mst continus or zomorph or mxl or cyclimorph or oxynorm or dolocodon or longtec or oxycontin or targinact or abstral or effentora or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mezolar or osmanil or tilofyl or victanyl or durogesic or clonazepam or rivotil).ti,ab.
5.	or/1-4
6.	exp *dyspnea/
7.	dyspn?ea.ti,ab.
8.	((difficult* or labo?r* or short*) adj2 breath*).ti,ab.
9.	breathlessness.ti,ab.
10.	or/6-9
11.	5 and10

Cochrane search terms

#1.	MeSH descriptor: [diazepam] explode all trees
#2.	MeSH descriptor: [lorazepam] explode all trees
#3.	MeSH descriptor: [midazolam] explode all trees
#4.	MeSH descriptor: [clonazepam] explode all trees
#5.	MeSH descriptor: [heroin] explode all trees
#6.	MeSH descriptor: [morphine] explode all trees
#7.	MeSH descriptor: [oxycodone] explode all trees
#8.	MeSH descriptor: [fentanyl] explode all trees
#9.	(diazepam or lorazepam or midazolam or rimapan or tensium or dialar of diazemuls):ti,ab
#10.	(morphine or diamorphine or oxycodone or fentanyl or oramorph or sevredol or filnarine or morphgesic or mst continus or zomorph or mxl or cyclimorph or oxynorm or dolocodon or longtec or oxycontin or targinact or abstral or effentora or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mezolar or osmanil or tilofyl or victanyl or durogesic or clonazepam or rivotil)
#11.	{or #1-#10}
#12.	MeSH descriptor: [dyspnea] explode all trees
#13.	(dyspnea or dyspnoea):ti,ab
#14.	((difficult* or labo?r* or short*) near/2 breath*):ti,ab
#15.	breathlessness:ti,ab
#16.	{or #12-#15}
#17.	#11 and #16

F.4.5 Cognitive assessment

See F.4.1

F.4.6 Co-ordination of care

9. What is the most clinically and cost-effective approach for coordinating care and support across health and social care for people with MND and their families and carers?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with	Co-ordination of			See Table 23

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
motor neurone disease (F.2.1)	care			English only Exclusion filter applied in Medline, Embase and PsycINFO

1 **Medline search terms**

1.	exp patient care team/ or exp nursing, team/
2.	interdisciplinary communication/
3.	"continuity of patient care"/
4.	"delivery of health care, integrated"/
5.	exp *interprofessional relations/
6.	patient care planning/ or critical pathways/
7.	case management/
8.	(interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT).ti,ab.
9.	(key-worker* or key worker* or keyworker*).ti,ab.
10.	((continuity or continuum or co-ordinat* or plan* or pathway*) adj2 (care or service*)).ti,ab.
11.	((integrated or collaborative or manage*) adj2 (healthcare or service* or care or team*)).ti,ab.
12.	case management.ti,ab.
13.	or/1-12

2 **Embase search terms**

1.	exp *patient care/
2.	exp *team nursing/
3.	*interdisciplinary communication/
4.	*integrated health care system/
5.	*teamwork/
6.	*patient care planning/
7.	*clinical pathway/
8.	*case management/
9.	(interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT).ti,ab.
10.	(key-worker* or key worker* or keyworker*).ti,ab.
11.	((continuity or continuum or co-ordinat* or plan* or pathway*) adj2 (care or service*)).ti,ab.
12.	((integrated or collaborative or manage*) adj2 (healthcare or service* or care or team*)).ti,ab.
13.	case management.ti,ab.
14.	or/1-13

3 **Cochrane search terms**

#1.	MeSH descriptor: [Patient Care Team] explode all trees
#2.	MeSH descriptor: [Nursing, Team] explode all trees
#3.	MeSH descriptor: [Interdisciplinary Communication] explode all trees
#4.	MeSH descriptor: [continuity of patient care] explode all trees
#5.	MeSH descriptor: [delivery of health care, integrated] explode all trees
#6.	MeSH descriptor: [interprofessional relations] explode all trees

#7.	MeSH descriptor: [patient care planning] explode all trees
#8.	MeSH descriptor: [critical pathways] explode all trees
#9.	MeSH descriptor: [case management] explode all trees
#10.	(interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT):ti,ab
#11.	(key-worker* or key worker* or keyworker*):ti,ab
#12.	((continuity or continuum or co-ordinat* or plan* or pathway*) near/2 (care or service*)):ti,ab
#13.	((integrated or collaborative or manage*) near/2 (healthcare or service* or care or team*)):ti,ab
#14.	case management.ti,ab.
#15.	{or #1-#14}

1 **CINAHL search terms**

S1.	(MH "multidisciplinary care team+")
S2.	(MH "team nursing")
S3.	(MH "continuity of patient care+")
S4.	(MH "health care delivery, integrated")
S5.	(MH "interprofessional relations+")
S6.	(MH "patient care plans+")
S7.	(MH "critical path")
S8.	(MH "case management")
S9.	interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT
S10.	key-worker* or key worker* or keyworker*
S11.	continuity n/2 care or continuity n2 service* or continuum n2 care or continuum n2 service* or co-ordinat* n2 care or co-ordinat* n2 service* or plan* n2 care or plan* n2 service* or pathway* n2 care or pathway* n2 service*
S12.	integrated n2 healthcare or integrated n2 service* or integrated n2 care or integrated n2 team*
S13.	collaborative n2 healthcare or collaborative n2 service* or collaborative n2 care or collaborative n2 team*
S14.	manage* n2 healthcare or manage* n2 service* or manage* n2 care or manage* n2 team*
S15.	case management
S16.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15

2 **PsycINFO (Ovid) search terms**

1.	exp health care delivery/
2.	exp teams/ or exp work teams/
3.	exp interdisciplinary treatment approach/
4.	exp integrated services/
5.	exp treatment planning/
6.	exp case management/
7.	(interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT).ti,ab.
8.	(key-worker* or key worker* or keyworker*).ti,ab.
9.	((continuity or continuum or co-ordinat* or plan* or pathway*) adj2 (care or service*)).ti,ab.
10.	((integrated or collaborative or manage*) adj2 (healthcare or service* or care or team*)).ti,ab.
11.	case management.ti,ab.

12.	or/1-11

PsycINFO (ProQuest) search terms

1.	(su.exact.explode("health care delivery") or su.exact.explode("teams") or su.exact.explode("work teams") or su.exact.explode("interdisciplinary treatment approach") or su.exact("integrated services") or su.exact("treatment planning") or ti,ab(interdisciplinary or inter-disciplinary or multidisciplinary or multi-disciplinary or multi-professional or multiprofessional or MDC or MDT or IDT) or ti,ab(key-worker* or keyworker*) or ti,ab((continuity or continuum or co-ordinat* or plan* or pathway*) near/2 (care or service*)) or ti,ab((integrated or collaborative or manage*) near/2 (healthcare or service* or care or team*)) or ti,ab(case management)))

F.4.7 Cough

10. What is the clinical and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1) OR Neuromuscular disease (F.2.2)	Cough augmentation techniques			See Table 23 English only Exclusion filter applied in Medline, Embase and PsycINFO

Medline search terms

1.	cough/
2.	cough*.ti,ab.
3.	*respiratory therapy/ or *drainage, postural/
4.	(insufflat* or exsufflat*).ti,ab.
5.	postural drain*.ti,ab.
6.	((inhaling or inhalation or inhale or respiratory) adj2 therap*).ti,ab.
7.	percussion/
8.	((chest or lung) adj2 (percussion or resonance)).ti,ab.
9.	(lung adj2 volume).ti,ab.
10.	((breath* or air*) adj2 (stack* or technique*)).ti,ab.
11.	((air* or chest*) adj2 clear*).ti,ab.
12.	(inspiratory adj2 (exercise* or exercising)).ti,ab.
13.	or/1-12

Embase search terms

1.	exp *coughing/
2.	cough*.ti,ab.
3.	exp *artificial ventilation/
4.	exp *postural drainage/
5.	(insufflat* or exsufflat*).ti,ab.
6.	postural drain*.ti,ab.

7.	((inhaling or inhalation or inhale or respiratory) adj2 therap*).ti,ab.
8.	exp *percussion/
9.	((chest or lung) adj2 (percussion or resonance)).ti,ab.
10.	(lung adj2 volume).ti,ab.
11.	((breath* or air*) adj2 (stack* or technique*)).ti,ab.
12.	((air* or chest*) adj2 clear*).ti,ab.
13.	(inspiratory adj2 (exercise* or exercising)).ti,ab.
14.	or/1-13

Cochrane search terms

#1.	MeSH descriptor: [cough] explode all trees
#2.	cough*:ti,ab
#3.	MeSH descriptor: [respiratory therapy] explode all trees
#4.	MeSH descriptor: [drainage, postural] explode all trees
#5.	(insufflat* or exsufflat*):ti,ab
#6.	postural drain*:ti,ab
#7.	((inhaling or inhalation or inhale or respiratory) near/2 therap*):ti,ab
#8.	MeSH descriptor: [percussion] explode all trees
#9.	((chest or lung) near/2 (percussion or resonance)):ti,ab
#10.	(lung near/2 volume):ti,ab
#11.	((breath* or air*) near/2 (stack* or technique*)):ti,ab
#12.	((air* or chest*) near/2 clear*):ti,ab
#13.	(inspiratory near/2 (exercise* or exercising)):ti,ab
#14.	{or #1-#13}

CINAHL search terms

S1.	(MH "cough")
S2.	cough*
S3.	(MH "respiratory therapy+")
S4.	(MH "drainage, postural")
S5.	insufflat* or exsufflat*
S6.	postural drain*
S7.	inhaling n2 therap* or inhalation n2 therap* or inhale n2 therap* or respiratory n2 therap*
S8.	(MH "percussion")
S9.	chest n2 percussion or lung n2 percussion or lung n2 resonance or chest n2 resonance
S10.	breath* n2 stack* or breath* n2 technique or air* n2 stack* or air* n2 technique
S11.	air* n2 clear* or chest* n2 clear*
S12.	inspiratory n2 exercis*
S13.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12

F.4.8 Discontinuation of non-invasive ventilation (NIV)

11. What is the most appropriate management of discontinuation, at a patient's request, of NIV?
12. What factors influenced the experience of discontinuation, at a patient's request, of NIV for relatives/carers/healthcare/social care professionals?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)			Question 11 The following filter was used in Medline, Embase and PsycINFO only: OBS Question 12 The following filter was used in Medline, Embase, CINAHL and PsycINFO QUAL	See Table 23 English only Exclusion filter applied in Medline, Embase and PsycINFO

F.4.9 End of life

13. What are the most appropriate ways of communicating with and supporting people with MND and their families and carers to help them anticipate, and prepare for, end of life?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	End of life		The following filters were used in Medline and Embase, CINAHL and PsycINFO only: QUAL	See Table 23 English only Exclusion filter applied in Medline, Embase and PsycINFO

Medline search terms

1.	death/
2.	(dying or die or dies or died or death).ti,ab.
3.	terminally ill/ or terminal care/ or palliative care/
4.	((terminal or palliati*) adj1 care).ti,ab.
5.	"terminally ill".ti,ab.
6.	"terminal illness".ti,ab.
7.	(palliati* adj1 stage*).ti,ab.
8.	("end of life" adj2 (stage or stages)).ti,ab.
9.	"end of life".ti,ab.
10.	((last or final) adj1 (hour* or day* or minute* or stage*)).ti,ab.
11.	((dying or terminal) adj1 phase*).ti,ab.
12.	((dying or terminal or end) adj1 stage*).ti,ab.
13.	(dying adj2 (actively or begin* or begun)).ti,ab.
14.	((death adj2 imminent*) or impending).ti,ab.
15.	(body adj2 (shut down or shutting down or deteriorat*)).ti,ab.
16.	deathbed.ti,ab.
17.	or/1-16

Embase search terms

1.	death/
2.	(dying or die or dies or died or death).ti,ab.
3.	terminally ill patient/ or terminal care/ or palliative therapy/
4.	((terminal or palliati*) adj1 care).ti,ab.
5.	"terminally ill".ti,ab.
6.	"terminal illness".ti,ab.
7.	(palliati* adj1 stage*).ti,ab.
8.	("end of life" adj2 (stage or stages)).ti,ab.
9.	"end of life".ti,ab.
10.	((last or final) adj1 (hour* or day* or minute* or stage*)).ti,ab.
11.	((dying or terminal) adj1 phase*).ti,ab.
12.	((dying or terminal or end) adj1 stage*).ti,ab.
13.	(dying adj2 (actively or begin* or begun)).ti,ab.
14.	((death adj2 imminent*) or impending).ti,ab.
15.	(body adj2 (shut down or shutting down or deteriorat*)).ti,ab.
16.	deathbed.ti,ab.
17.	or/1-16

1 **CINAHL search terms**

S1.	(MH "death+")
S2.	dying or die or dies or died or death
S3.	(MH "terminally ill patients+")
S4.	(MH "terminal care+")
S5.	(MH "palliative care")
S6.	terminal n1 care or palliati* n1 care
S7.	terminally ill or terminal illness
S8.	palliati* n1 stage*
S9.	end of life n2 stage or end of life n2 stages
S10.	end of life
S11.	last n1 hour* or last n1 day* or last n1 minute* or last n1 stage*
S12.	final n1 hour* or final n1 day* or final n1 minute* or final n1 stage*
S13.	dying n1 phase* or terminal n1 phase*
S14.	dying n1 stage* or terminal n1 stage* or end n1 stage*
S15.	dying n2 actively or dying n1 begin* or dying n1 begun
S16.	death n2 imminent* or death n2 impending*
S17.	body n2 shut down or body n2 shutting down or body n2 deteriorat*
S18.	deathbed
S19.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18

2 **PsycINFO (OVID) search terms**

1.	exp "death and dying"/
2.	(dying or die or dies or died or death).ti,ab.
3.	exp terminally ill patients/
4.	exp palliative care/
5.	((terminal or palliati*) adj1 care).ti,ab.

6.	"terminally ill".ti,ab.
7.	"terminal illness".ti,ab.
8.	(palliati* adj1 stage*).ti,ab.
9.	("end of life" adj2 (stage or stages)).ti,ab.
10.	"end of life".ti,ab.
11.	((last or final) adj1 (hour* or days* or minute* or stage*)).ti,ab.
12.	((dying or terminal) adj1 phase*).ti,ab.
13.	((dying or terminal or end) adj1 stage*).ti,ab.
14.	(dying adj2 (actively or begin* or begun)).ti,ab.
15.	((death adj2 imminent*) or impending).ti,ab.
16.	(body adj2 (shut down or shutting down or deteriorat*)).ti,ab.
17.	deathbed.ti,ab.
18.	or/1-17

PsycINFO (ProQuest) search terms

1.	su.exact.explode("death and dying") or ti,ab(dying or die or dies or died or death) or su.exact.explode("terminally ill patients") or su.exact.explode("palliative care") or ti,ab((terminal or palliati*) near/1 care) or ti,ab("terminally ill") or ti,ab("terminal illness") or ti,ab(palliati* near/1 stage*) or ti,ab("end of life" near/2 (stage or stages)) or ti,ab("end of life") or ti,ab((last or final) near/1 (hour* or days* or minute* or stage*)) or ti,ab((dying or terminal) near/1 phase*) or ti,ab((dying or terminal or end) near/1 stage*) or ti,ab(dying near/2 (actively or begin* or begun)) or ti,ab((death near/2 imminent*) or impending) or ti,ab(body near/2 (shut-down or shutting-down or deteriorat*)) or ti,ab(deathbed)

F.4.10 Equipment for muscle weakness

14. What are the equipment needs of people with MND for improving mobility and fulfilling activities of daily living due to muscle weakness?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	Equipment aids for muscle weakness Terms not used in CINAHL search		The following filters were used in Medline, Embase and CINAHL only: QUAL	See Table 23 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	(mobil* adj4 (equip* or aid* or device*)).ti,ab.
2.	wheelchairs/
3.	(wheelchair* or wheel chair* or wheel-chair*).ti,ab.
4.	(mobil* adj3 scooter*).ti,ab.
5.	((head or neck or cervical or back) adj3 (collar* or support*)).ti,ab.
6.	patient lifting/
7.	(hoist* or lift*).ti,ab.
8.	exp posture/
9.	beds/
10.	(postur* adj3 support*).ti,ab.

11.	(bed* or mattress* or cushion* or seat* or chair* or pillow*).ti,ab.
12.	(riser* or reclin*).ti,ab.
13.	((arm* or shoulder*) adj3 support*).ti,ab.
14.	((eat* or drink*) adj3 (aid* or device* or equip*)).ti,ab.
15.	braces/ or splints/
16.	exp orthotic devices/
17.	(orthos#s or orthoti* or splint* or AFO or DAFO or brace*).ti,ab.
18.	walkers/ or canes/ or crutches/
19.	(walk* adj3 (stick* or frame* or troll*)).ti,ab.
20.	(cane* or crutch*).ti,ab.
21.	exp self-help devices/
22.	telemedicine/
23.	environmental control*.ti,ab.
24.	((assist* or communicat*) adj3 (technolog* or aid* or device* or equip*)).ti,ab.
25.	(ramp* or access* or adapt*).ti,ab.
26.	personal alarm*.ti,ab.
27.	or/1-26

1 **Embase search terms**

1.	(mobil* adj4 (equip* or aid* or device*)).ti,ab.
2.	exp *wheelchair/
3.	(wheelchair* or wheel chair* or wheel-chair*).ti,ab.
4.	(mobil* adj3 scooter*).ti,ab.
5.	((head or neck or cervical or back) adj3 (collar* or support*)).ti,ab.
6.	*patient lifting/
7.	(hoist* or lift*).ti,ab.
8.	*body posture/
9.	exp *bed/
10.	(postur* adj3 support*).ti,ab.
11.	(bed* or mattress* or cushion* or seat* or chair* or pillow*).ti,ab.
12.	(riser* or reclin*).ti,ab.
13.	((arm* or shoulder*) adj3 support*).ti,ab.
14.	((eat* or drink*) adj3 (aid* or device* or equip*)).ti,ab.
15.	exp *splint/
16.	exp *orthosis/
17.	(orthos#s or orthoti* or splint* or AFO or DAFO or brace*).ti,ab.
18.	exp *walking aid/
19.	(walk* adj3 (stick* or frame* or troll*)).ti,ab.
20.	(cane* or crutch*).ti,ab.
21.	*self help/
22.	*assistive technology/
23.	*communication aid/
24.	exp *telemedicine/
25.	((assist* or communicat*) adj3 (technolog* or aid* or device* or equip*)).ti,ab.
26.	(ramp* or access* or adapt*).ti,ab.

27.	environmental control*.ti,ab.
28.	personal alarm*.ti,ab.
29.	or/1-28

F.4.11 Frequency of assessment

15.What is the optimum frequency of assessment required to assess disease progression of MND?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	Frequency of assessment		The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 23 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	time factors/
2.	"appointments and schedules"/
3.	(visit* adj5 clinic*).ti,ab.
4.	(optimal or routine* or regular or periodic* or review* or frequent* or time* or timing or week* or month* or year* or day* or recall*).ti,ab.
5.	(assess* or interval* or visit* or inspect* or examin* or attend* or check-up* or recall* or appointment*).ti,ab.
6.	4 and 5
7.	or/1-3,6

Embase search terms

1.	*time/
2.	*hospital management/
3.	(visit* adj5 clinic*).ti,ab.
4.	(optimal or routine* or regular or periodic* or review* or frequent* or time* or timing or week* or month* or year* or day* or recall*).ti,ab.
5.	(assess* or interval* or visit* or inspect* or examin* or attend* or check-up* or recall* or appointment*).ti,ab.
6.	4 and 5
7.	or/1-3,6

Cochrane search terms

#1.	MeSH descriptor: [time factors] explode all trees
#2.	MeSH descriptor: [appointments and schedules] explode all trees
#3.	(visit* near/5 clinic*):ti,ab
#4.	(optimal or routine* or regular or periodic* or review* or frequent* or time* or timing or week* or month* or year* or day* or recall*):ti,ab
#5.	(assess* or interval* or visit* or inspect* or examin* or attend* or check-up* or recall* or appointment*):ti,ab
#6.	#4 and #5
#7.	#1 or #2 or #3 or #6

F.4.12 Timing of gastronomy

16. What is the clinically appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	Timing of gastronomy			See Table 23 English only Exclusion filter applied in Medline, Embase and PsycINFO

Medline search terms

1.	enteral nutrition/
2.	((enteral or enteric) adj2 (nutrition* or feed*)).ti,ab.
3.	gastrostomy/
4.	gastrostom*.ti,ab.
5.	((tube or tubes) adj2 (nutrition* or feed*)).ti,ab.
6.	(PEG or PIG or RIG).ti,ab.
7.	(gavage adj2 feed*).ti,ab.
8.	(tubing adj2 (nutrition* or feed*)).ti,ab.
9.	"g tube".ti,ab.
10.	(artificial adj2 feed*).ti,ab.
11.	or/1-10

Embase search terms

1.	enteric feeding/
2.	gastrostomy/
3.	((enteral or enteric) adj2 (nutrition* or feed*)).ti,ab.
4.	gastrostom*.ti,ab.
5.	((tube or tubes) adj2 (nutrition* or feed*)).ti,ab.
6.	(tubing adj2 (nutrition* or feed*)).ti,ab.
7.	(artificial adj2 feed*).ti,ab.
8.	(gavage adj2 feed*).ti,ab.
9.	(PEG or PIG or RIG).ti,ab.
10.	"g tube".ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [enteral nutrition] explode all trees
#2.	MeSH descriptor: [gastrostomy] explode all trees
#3.	((enteral or enteric) near/2 (nutrition* or feed*)):ti,ab
#4.	((tube or tubes or tubing) near/2 (nutrition* or feed*)):ti,ab
#5.	(gavage near/2 feed*):ti,ab
#6.	(artificial near/2 feed*) .ti,ab
#7.	gastrostom*:ti,ab

#8.	(PEG or PIG or RIG):ti,ab
#9.	g tube:ti,ab
#10.	{or #1-#9}

CINAHL search terms

S1.	(MM "enteral nutrition")
S2.	(MM "gastrostomy")
S3.	gastrostom*
S4.	PEG or PIG or RIG
S5.	g tube
S6.	enteral n2 nutrition* or enteral n2 feed* or enteric n2 nutrition* or enteric n2 feed*
S7.	tube n2 nutrition* or tube n2 feed* or tubes n2 nutrition* or tubes n2 feed* or tubing n2 nutrition* or tubing n2 feed*
S8.	gavage n2 feed* or artifical n2 feed*
S9.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

PsycINFO (OVID) search terms

1.	exp nutrition/ or exp food intake/
2.	gastrostom*.ti,ab.
3.	(PEG or PIG or RIG).ti,ab.
4.	"g tube".ti,ab.
5.	((enteral or enteric) adj2 (nutrition* or feed*)).ti,ab.
6.	((tube or tubes or tubing) adj2 (nutrition* or feed*)).ti,ab.
7.	(gavage adj2 feed*).ti,ab.
8.	(artificial adj2 feed*).ti,ab.
9.	or/1-8

PsycINFO (ProQuest) search terms

1.	su.exact.explode("nutrition") or su.exact.explode("food intake") or ti,ab(gastrostom*.ti,ab) or ti,ab(peg or pig or rig) or ti,ab("g tube") or ti,ab((enteral or enteric) near/2 (nutrition* or feed*)) or ti,ab((tube or tubes or tubing) near/2 (nutrition* or feed*)) or ti,ab(gavage near/2 feed*) or ti,ab(artificial adj2 feed*)

F.4.13 Knowledge for the communication of diagnosis

See F.4.2

F.4.14 Muscle weakness

Searches for the following two questions were run as one search:

17. For adults with MND, what is the clinical and cost-effectiveness of non-pharmacological treatments for muscle cramps and fasciculations, increased tone (including spasticity, muscle spasm or stiffness), muscle stiffness, wasting or atrophy?
18. For adults with MND, what is the clinical and cost-effectiveness of pharmacological treatments for muscle cramps and fasciculations, increased tone, muscle weakness, wasting or atrophy?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	Pharmacological and non-pharmacological treatments for muscle weakness		The following filters were used in Medline and Embase only: OBS, RCT, SR	See Table 23 English only Exclusion filter applied in Medline and Embase

1 **Medline search terms**

1.	baclofen/ or diazepam/ or clonazepam/ or dantrolene/ or memantine/
2.	(baclofen* or baclophen or lioresal or diazepam or rimapan or tensium or dialar or diazemuls or clonazepam or rivotil or dantrolene or dantrium or tizanidine or zanaflex or tetrazepam or memantine or ebixa).ti,ab.
3.	exp botulinum toxins/
4.	(botulinum adj3 (a or b or toxin*)).ti,ab.
5.	(dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc).ti,ab.
6.	transcutaneous electric nerve stimulation/
7.	((function* or neuromuscul* or peripheral* or transcutan* or electric*) adj4 stimulat*).ti,ab.
8.	TENS.ti,ab.
9.	ultrasonography/
10.	(sonograph* or ultrasound* or ultrason*).ti,ab.
11.	exp physical therapy modalities/
12.	exp exercise/
13.	(physiotherap* or exercis* or stretch* or resist* or position*).ti,ab.
14.	(physical adj2 therap*).ti,ab.
15.	muscle cramp/ or muscle rigidity/ or muscle spasticity/ or muscle weakness/
16.	((muscle* or muscular) adj2 (cramp* or rigid* or spast* or weak* or tight* or stiff* or twitch* or spasm*)).ti,ab.
17.	(fasciculat* or contract*).ti,ab.
18.	transcranial magnetic stimulation/
19.	((transcran* or intramusc*) adj4 stimulat*).ti,ab.
20.	(gabapentin or neurontin).ti,ab.
21.	or/1-20

2 **Embase search terms**

1.	*baclofen/ or *diazepam/ or *clonazepam/ or *dantrolene/ or *memantine/ or *tizanidine/ or *tetrazepam/
2.	(baclofen* or baclophen or lioresal or diazepam or rimapan or tensium or dialar or diazemuls or clonazepam or rivotil or dantrolene or dantrium or tizanidine or zanaflex or tetrazepam or memantine or ebixa).ti,ab.
3.	*botulinum toxin/ or *botulinum toxin e/ or *botulinum toxin f/
4.	*botulinum toxin b/ or *botulinum toxin a/
5.	(botulinum adj3 (a or b or toxin*)).ti,ab.
6.	(dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc).ti,ab.
7.	*transcutaneous nerve stimulation/
8.	((function* or neuromuscul* or peripheral* or transcutan* or electric*) adj4 stimulat*).ti,ab.

9.	TENS.ti,ab.
10.	*echography/
11.	(sonograph* or ultrasound* or ultrason*).ti,ab.
12.	exp *physiotherapy/
13.	exp *exercise/
14.	(physiotherap* or exercis* or stretch* or resist* or position*).ti,ab.
15.	(physical adj2 therap*).ti,ab.
16.	transcranial magnetic stimulation/
17.	((transcran* or intramusc*) adj4 stimulat*).ti,ab.
18.	(gabapentin or neurontin).ti,ab.
19.	*muscle cramp/ or *muscle rigidity/ or *muscle weakness/ or *spasticity/
20.	((muscle* or muscular) adj2 (cramp* or rigid* or spast* or weak* or tight* or stiff* or twitch* or spasm*)).ti,ab.
21.	(fasciculat* or contract*).ti,ab.
22.	or/1-21

1 **Cochrane search terms**

#1.	MeSH descriptor: [baclofen] explode all trees
#2.	MeSH descriptor: [diazepam] explode all trees
#3.	MeSH descriptor: [clonazepam] explode all trees
#4.	MeSH descriptor: [dantrolene] explode all trees
#5.	MeSH descriptor: [memantine] explode all trees
#6.	(baclofen* or baclophen or lioresal or diazepam or rimapan or tensium or dialar or diazemuls or clonazepam or rivotil or dantrolene or dantrium or tizanidine or zanaflex or tetrazepam or memantine or ebixa):ti,ab
#7.	MeSH descriptor: [botulinum toxins] explode all trees
#8.	(botulinum near/3 (a or b or toxin*)):ti,ab
#9.	(dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc):ti,ab
#10.	MeSH descriptor: [transcutaneous electric nerve stimulation] explode all trees
#11.	((function* or neuromuscul* or peripheral* or transcutan* or electric*) near/4 stimulat*):ti,ab
#12.	TENS:ti,ab
#13.	MeSH descriptor: [ultrasonography] explode all trees
#14.	(sonograph* or ultrasound* or ultrason*):ti,ab
#15.	MeSH descriptor: [physical therapy modalities] explode all trees
#16.	MeSH descriptor: [exercise] explode all trees
#17.	(physiotherap* or exercis* or stretch* or resist* or position*):ti,ab
#18.	(physical near/2 therap*):ti,ab
#19.	MeSH descriptor: [muscle cramp] explode all trees
#20.	MeSH descriptor: [muscle rigidity] explode all trees
#21.	MeSH descriptor: [muscle spasticity] explode all trees
#22.	MeSH descriptor: [muscle weakness] explode all trees
#23.	((muscle* or muscular) near/2 (cramp* or rigid* or spast* or weak* or tight* or stiff* or twitch* or spasm*)):ti,ab
#24.	(fasciculat* or contract*):ti,ab
#25.	MeSH descriptor: [transcranial magnetic stimulation] explode all trees
#26.	((transcran* or intramusc*) near/4 stimulat*):ti,ab

#27.	(gabapentin or neurontin):ti,ab
#28.	#1-#27

CINAHL search terms

S1.	baclofen* or baclophen or lioresal or diazepam or rimapan or tensium or dialar or diazemuls or clonazepam or rivotil or dantrolene or dantrium or tizanidine or zanaflex or tetrazepam or memantine or ebixa
S2.	(MH "botulinum toxins")
S3.	botulinum n3 a OR botulinum n3 b OR botulinum n3 toxin*
S4.	dysport or botox or btx or oculinum or xeomin or reloxin or prosigne or purtox or nt201 or mybloc or neurobloc
S5.	(MH "transcutaneous electric nerve stimulation")
S6.	function* n4 stimulat* or neuromuscul* n4 stimulat* or peripheral* n4 stimulat* or transcutan* n4 stimulat* or electric* n4 stimulat*
S7.	tens
S8.	(MH "ultrasonography+")
S9.	sonograph* or ultrasound* or ultrason*
S10.	(MH "physical therapy+")
S11.	(MH "exercise+")
S12.	physiotherap* or exercis* or stretch* or resist* or position*
S13.	physical n2 therap*
S14.	(MH "muscle cramp")
S15.	(MH "muscle weakness")
S16.	(MH "muscle spasticity")
S17.	musc* n2 cramp* or musc* adj2 rigid* or musc* adj2 spast* or musc* adj2 weak* or musc* adj2 tight* or musc* adj2 stiff* or musc* adj twitch* or musc* adj2 spasm*
S18.	fasciculat* or contract*
S19.	transcran* n4 stimulat* or intramusc* n4 stimulat*
S20.	(MH "gabapentin")
S21.	gabapentin or neurontin
S22.	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21

F.4.15 Nutrition

See F.4.1

F.4.16 Psychological support

See F.4.2

F.4.17 Risk factors

Searches for the following two questions were run as one search:

19.What are the most accurate prognostic tools for estimating survival in people with MND?

20.What risk factors predict survival in people with MND?

Search constructed by combining the columns in the following table using the AND Boolean operator and by combining the rows using the OR Boolean operator. Exclusion filter applied using NOT Boolean operator.

Search	Population	Intervention or exposure	Study design filter	Date parameters and other limits
A	Adults (aged 18 and over) with motor neurone disease (F.2.1)	Risk factors		See Table 23 English only Exclusion filter applied in Medline and Embase
B	Same as search A		The following filters were used in Medline and Embase only: OBS	Same as search A

1 **Medline search terms**

1.	exp risk/
2.	disease progression/
3.	"amyotrophic lateral sclerosis functional rating scale".ti,ab.
4.	alsfrs*.ti,ab.
5.	(measur* adj2 scale*).ti,ab.
6.	body weight changes/ or exp weight loss/ or body mass index/
7.	(weight adj2 (los* or reduc*)).ti,ab.
8.	(body mass index or bmi).ti,ab.
9.	exp respiratory function tests/
10.	((respiratory or pulmonary or lung) adj3 test*).ti,ab.
11.	exp vital capacity/
12.	exp forced expiratory flow rates/ or forced expiratory volume/
13.	(("sniff nasal inspiratory pressure" or "maximal inspiratory pressure" or "maximal expiratory pressure" or "forced vital capacity" or "forced expiratory volume") adj6 test*).ti,ab.
14.	(peak expiratory flow* or peak flow*).ti,ab.
15.	peak expiratory flow rate/
16.	((force* or time*) adj vital capacit*).ti,ab.
17.	(forced expiratory adj3 (flow* or rat* or vol*)).ti,ab.
18.	exp cough/
19.	cough*.ti,ab.
20.	or/1-19
21.	(death* or dying or died or deceas* or mortalit* or surviv*).ti,ab.
22.	mortality/ or survival rate/
23.	survival analysis/ or survival/
24.	mo.fs.
25.	or/21-24
26.	20 and 25

2 **Embase search terms**

1.	exp *disease course/
2.	"amyotrophic lateral sclerosis functional rating scale".ti,ab.
3.	alsfrs*.ti,ab.
4.	(measur* adj2 scale*).ti,ab.
5.	*body mass/
6.	*weight change/

7.	exp *weight reduction/
8.	(weight adj2 (los* or reduc*)).ti,ab.
9.	(body mass index or bmi).ti,ab.
10.	exp *lung function test/
11.	((respiratory or pulmonary or lung) adj3 test*).ti,ab.
12.	*vital capacity/
13.	*forced expiratory volume/
14.	*expiratory flow rate/ or *peak expiratory flow/
15.	(("sniff nasal inspiratory pressure" or "maximal inspiratory pressure" or "maximal expiratory pressure" or "forced vital capacity" or "forced expiratory volume") adj6 test*).ti,ab.
16.	(peak expiratory flow* or peak flow*).ti,ab.
17.	((force* or time*) adj vital capacit*).ti,ab.
18.	(forced expiratory adj3 (flow* or rat* or vol*)).ti,ab.
19.	exp coughing/
20.	cough.ti,ab.
21.	exp *risk/
22.	or/1-21
23.	(death* or dying or died or deceas* or mortalit* or surviv*).ti,ab.
24.	*mortality/
25.	*survival/ or *survival time/ or *survival prediction/ or *survival factor/
26.	or/23-25
27.	22 and 26

F.4.18 Saliva

21. What is the clinical and cost-effectiveness of interventions for saliva management in people with MND?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator.

Population	Intervention or exposure	Comparison	Study design filter	Date parameters and other limits
Adults (aged 18 and over) with swallowing problems caused by neurological disorders	Saliva management		The following filters were used in Medline and Embase only: RCT, SR	See Table 23 English only Exclusion filter applied in Medline and Embase

Medline search terms

1.	cerebral palsy/
2.	parkinson disease/
3.	exp multiple system atrophy/
4.	supranuclear palsy, progressive/
5.	little* disease*.ti,ab.
6.	((cerebral or brain or central) adj2 (pals* or paralysis)).ti,ab.
7.	spastic diplegi*.ti,ab.
8.	parkinson* disease*.ti,ab.

9.	hypokinetic rigid syndrome*.ti,ab.
10.	paralysis agitans.ti,ab.
11.	primary parkinsonism.ti,ab.
12.	multiple system atroph*.ti,ab.
13.	olivopontocerebellar atroph*.ti,ab.
14.	shy-drager* syndrome*.ti,ab.
15.	striatonigral degeneration.ti,ab.
16.	((multi-system* or multisystem*) adj atroph*).ti,ab.
17.	((corticobasal or cortico-basal) adj2 (syndrome* or degeneration*)).ti,ab.
18.	(progressive supranuclear adj2 (pals* or ophthalmoplegi*)).ti,ab.
19.	(richardson* adj2 (syndrome* or disease*)).ti,ab.
20.	or/1-19
21.	saliva/
22.	salivation/
23.	salivary glands/
24.	sialorrhea/
25.	saliva*.ti,ab.
26.	sialorrhea*.ti,ab.
27.	ptyalis*.ti,ab.
28.	(hypersaliva* or hyper-saliva*).ti,ab.
29.	drool*.ti,ab.
30.	phlegm.ti,ab.
31.	mucus.ti,ab.
32.	dribbl*.ti,ab.
33.	sialorrhoea*.ti,ab.
34.	or/21-33
35.	20 and 34

1 **Embase search terms**

1.	cerebral palsy/
2.	exp parkinson disease/
3.	shy drager syndrome/
4.	progressive supranuclear palsy/
5.	corticobasal degeneration/
6.	little* disease*.ti,ab.
7.	((cerebral or brain or central) adj2 (pals* or paralysis)).ti,ab.
8.	spastic diplegi*.ti,ab.
9.	parkinson* disease*.ti,ab.
10.	hypokinetic rigid syndrome*.ti,ab.
11.	paralysis agitans.ti,ab.
12.	primary parkinsonism.ti,ab.
13.	multiple system atroph*.ti,ab.
14.	olivopontocerebellar atroph*.ti,ab.
15.	shy-drager* syndrome*.ti,ab.
16.	striatonigral degeneration.ti,ab.

17.	((multi-system* or multisystem*) adj atroph*).ti,ab.
18.	((corticobasal or cortico-basal) adj2 (syndrome* or degeneration*)).ti,ab.
19.	(progressive supranuclear adj2 (pals* or ophthalmoplegi*)).ti,ab.
20.	(richardson* adj2 (syndrome* or disease*)).ti,ab.
21.	or/1-20
22.	*saliva/
23.	*salivation/
24.	exp *hypersalivation/
25.	exp *salivary gland/
26.	saliva*.ti,ab.
27.	sialorrhea*.ti,ab.
28.	ptyalis*.ti,ab.
29.	(hypersaliva* or hyper-saliva*).ti,ab.
30.	drool*.ti,ab.
31.	phlegm.ti,ab.
32.	mucus.ti,ab.
33.	dribbl*.ti,ab.
34.	sialorrhoea*.ti,ab.
35.	or/22-34
36.	21 and 35

1 **Cochrane search terms**

#1.	[MeSH "cerebral palsy"]
#2.	[MeSH "parkinson disease"]
#3.	[MeSH "multiple system atrophy"]
#4.	[MeSH "supranuclear palsy, progressive"]
#5.	little* disease*:ti,ab
#6.	((cerebral or brain or central) near/2 (pals* or paralysis)):ti,ab
#7.	spastic diplegi*:ti,ab
#8.	parkinson* disease*:ti,ab
#9.	hypokinetic rigid syndrome*:ti,ab
#10.	paralysis agitans:ti,ab
#11.	primary parkinsonism:ti,ab
#12.	multiple system atroph*:ti,ab
#13.	olivopontocerebellar atroph*:ti,ab
#14.	shy-drager* syndrome*:ti,ab
#15.	striatonigral degeneration:ti,ab
#16.	((multi-system* or multisystem*) near atroph*):ti,ab
#17.	((corticobasal or cortico-basal) near/2 (syndrome* or degeneration*)):ti,ab
#18.	(progressive supranuclear) near/2 (pals* or ophthalmoplegi*):ti,ab
#19.	(richardson* near/2 (syndrome* or disease*)):ti,ab
#20.	{or #1-#19}
#21.	[MeSH saliva]
#22.	[MeSH salivation]
#23.	[MeSH "salivary glands"]

#24.	[MeSH sialorrhea]
#25.	saliva*:ti,ab
#26.	sialorrhea*:ti,ab
#27.	sialorrhoea*:ti,ab
#28.	ptyalis*:ti,ab
#29.	(hypersaliva* or hyper-saliva*):ti,ab
#30.	drool*:ti,ab
#31.	phlegm:ti,ab
#32.	mucus:ti,ab
#33.	dribbl*:ti,ab
#34.	{or #21-#33}
#35.	#20 and #34

F.4.19 Social care

See F.4.2

F.4.20 Timeliness of diagnosis

See F.4.2

F.5 Health economics search

The standard populations (F.2.1) for Medline and Embase were used unless stated otherwise.

F.5.1 Health economic reviews

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	n/a	n/a	The following filters were used in Medline and Embase only: HE	Medline and Embase 2012–18/05/2015 CRD EED and HTA Inception–18/05/2015 HEED Inception-19/08/2013 English only

CRD search terms

#1.	MeSH descriptor motor neuron disease explode all trees
#2.	MeSH descriptor amyotrophic lateral sclerosis explode all trees
#3.	MeSH descriptor bulbar palsy, progressive explode all trees
#4.	(motor neuron*) or (motorneuron*) or (moto neuron*) or (motoneuron*) or (moto-neuron*) or (motor-neuron*)
#5.	(pseudopolyneur*) or (pseudo-polyneur*) or (psuedo polyneur*)
#6.	(lateral adj scleros*) or (muscular adj atroph*) or (bulbar adj pals*)
#7.	(((bulbar or respirat* or limb) adj onset*))

#8.	(gehrig*)
#9.	(anterior adj (horn* or column)) or (ventral adj (horn or column))
#10.	((flail* adj (arm* or leg*)))
#11.	(guam adj disease*) or (guam adj disorder*) or (guam adj syndrome*)
#12.	(monomelic and amyotroph*)
#13.	MeSH descriptor frontotemporal dementia explode all trees
#14.	(frontotemporal adj dement*) or (fronto temporal adj dement*) or (fronto-temporal adj dement*)
#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

HEED search terms

1.	AX=motor and neuron*
2.	AX=motor neuron* or moto neuron* or motoneuron* or motorneuron* or moto-neuron* or motor-neuron*
3.	AX=lateral and scleros*
4.	AX=muscular and atroph*
5.	AX=bulbar and pals*
6.	AX=pseudopolyneur* or pseudo-polyneur* or psuedo polyneur*
7.	AX=gehrig*
8.	AX='bulbar onset' within 3
9.	AX='respiratory onset' within 3
10.	AX='limb onset' within 3
11.	AX=anterior and horn
12.	AX=anterior and column
13.	AX=ventral and horn
14.	AX=ventral and column
15.	AX=flail* and arm*
16.	AX=flail* and leg*
17.	AX=guam and disease
18.	AX=monomelic and amyotroph*
19.	AX=frontotemporal or fronto temporal or fronto-temporal
20.	CS=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

F.5.2 Quality of life reviews

Quality of life searches were conducted in Medline and Embase only

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Adults (aged 18 and over) with motor neurone disease (F.2.1)	n/a	n/a	The following filters were used in Medline and Embase only: QOL	Medline 1948-18/05/2015 Embase 1980–18/05/2015 English only

F.5.3 Breathlessness

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
	Pharmacological treatments for managing breathing difficulties	n/a	The following filters were used in Medline and Embase only: HE. MOD	Medline and Embase Inception - 18/05/2015 CRD EED and HTA Inception– 18/05/2015 HEED Inception- 22/05/2015 English only

1 **Medline & Embase search terms**

2 See F.4.4

3 **CRD search terms**

#1.	MeSH descriptor diazepam explode all trees
#2.	MeSH descriptor lorazepam explode all trees
#3.	MeSH descriptor midazolam explode all trees
#4.	MeSH descriptor clonazepam explode all trees
#5.	MeSH descriptor heroin explode all trees
#6.	MeSH descriptor morphine explode all trees
#7.	MeSH descriptor oxycodone explode all trees
#8.	MeSH descriptor fentanyl explode all trees
#9.	(diazepam or lorazepam or midazolam or rimapan or tensium or dialar of diazemuls)
#10.	(morphine or diamorphine or oxycodone or fentanyl or oramorph or sevredol or filnarine or morphgesic or mst continus or zomorph or mxl or cyclimorph or oxynorm or dolocodon or longtec or oxycontin or targinact or abstral or effentora or actiq or instanyl or pecfent or fencino or fentalis or matrifen or mezolar or osmanil or tilofyl or victanyl or durogesic or clonazepam or rivotil)
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	MeSH descriptor dyspnea explode all trees
#13.	(dyspnea or dyspnoea)
#14.	(breathlessness)
#15.	(((difficult* or labor* or labour or short*) adj2 breath*))
#16.	#12 or #13 or #14 or #15
#17.	#11 and #16

4 **HEED search terms**

1.	AX=diazepam or lorazepam or midazolam or rimapan or tensium or dialar of diazemuls
2.	AX=morphine or diamorphine or oxycodone or fentanyl or oramorph or sevredol or filnarine or morphgesic or mst continus
3.	AX=zomorph or mxl or cyclimorph or oxynorm or dolocodon or longtec or oxycontin or targinact or abstral or effentora
4.	AX=actiq or instanyl or pecfent or fencino or fentalis or matrifen or mezolar or osmanil or tilofyl or victanyl
5.	AX=durogesic or clonazepam or rivotil

6.	CS=1 or 2 or 3 or 4 or 5
7.	AX=dyspnea or dyspnoea
8.	AX=breathlessness
9.	AX=shortage and breath
10.	AX=difficulty and breathing
11.	AX=difficulties and breathing
12.	AX=laboured and breathing
13.	AX=labored and breathing
14.	CS=7 or 8 or 9 or 10 or 11 or 12 or 13
15.	CS=6 and 14

F.5.4 Saliva

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Adults (aged 18 and over) with swallowing problems caused by neurological disorders	Saliva management	n/a	The following filters were used in Medline and Embase only: HE	Medline and Embase All years-18/05/2015 CRD EED and HTA Inception–18/05/2015 HEED Inception-09/07/2015 English only

Medline & Embase search terms

See F.4.18

CRD search terms

#1.	MeSH descriptor cerebral palsy explode all trees
#2.	MeSH descriptor parkinson disease explode all trees
#3.	MeSH descriptor multiple system atrophy explode all trees
#4.	MeSH descriptor supranuclear palsy, progressive explode all trees
#5.	(little* disease*)
#6.	(((cerebral or brain or central) adj2 (pals* or paralysis)))
#7.	(spastic diplegi*)
#8.	(parkinson* disease*)
#9.	(hypokinetic rigid syndrome*)
#10.	(paralysis agitans)
#11.	(primary parkinsonism)
#12.	(multiple system atroph*)
#13.	(olivopontocerebellar atroph*)
#14.	(shy-drager* syndrome*)
#15.	(striatonigral degeneration)
#16.	(((multi-system* or multisystem*) adj atroph*))
#17.	(((corticobasal or cortico-basal) adj2 (syndrome* or degeneration*)))

#18.	((progressive supranuclear adj2 (pals* or ophthalmoplegi*)))
#19.	((richardson* adj2 (syndrome* or disease*)))
#20.	#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
#21.	MeSH descriptor saliva explode all trees
#22.	MeSH descriptor salivation explode all trees
#23.	MeSH descriptor salivary glands explode all trees
#24.	MeSH descriptor sialorrhea explode all trees
#25.	(saliva*)
#26.	(sialorrhea*)
#27.	(ptyalis*)
#28.	((hypersaliva* or hyper-saliva*))
#29.	(drool*)
#30.	(phlegm)
#31.	(mucus)
#32.	(dribbl*)
#33.	(sialorrhoea*)
#34.	#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
#35.	#20 and #34

1 **HEED search terms**

1.	AX=palsy or palsies
2.	AX=parkinson*
3.	AX=atroph*
4.	AX=little's and disease*
5.	AX=cerebral and paralysis
6.	AX=brain and paralysis
7.	AX=central and paralysis
8.	AX=spastic and diplegi*
9.	AX=hypokinetic rigid syndrome
10.	AX=paralysis agitans
11.	AX=olivopontocerebellar
12.	AX=shy-drager
13.	AX=striatonigral degeneration
14.	AX=corticobasal or cortico-basal
15.	AX=progressive supranuclear
16.	AX=richardson
17.	CS=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
18.	AX=saliva*
19.	AX=sialorrhea
20.	AX=ptyalis*
21.	AX=hypersaliva* or hyper-saliva*
22.	AX=drool*
23.	AX=phlegm*
24.	AX=mucus*
25.	AX=dribbl*

26.	CS=18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27.	CS=17 and 26

1

2

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Appendix G: Clinical evidence tables

G.1 Recognition and referral

Study	Hugel 2006
Aim	To explore patients' experiences regarding their recent diagnosis of MND
Population	n=13 people with MND in UK. 9 male/4 female. Mean age=64 years (SD=14, range 33–79 years). El Escorial criteria: 8=clinically definite, 3= clinically probable, 1= laboratory probable and 1 possible MND.
Study design	Qualitative: semi-structured interviews
Methods and analysis	Interpretative Phenomenological Analysis (IPA) was used. The results were part of a currently ongoing (2006) longitudinal study of quality of life in patients with MND under the influence of current care practice.
Themes with findings	**The time before the diagnosis** Causes of delay in diagnosis: healthcare professionals' unawareness of symptoms suggesting MND. Patients also had prolonged the process by delaying seeking medical attention as they were unaware of the seriousness of their symptoms.
	Communication of the diagnosis Giving the diagnosis in a private atmosphere with a relative or carer present was important. Pacing the discussion empathically according to patients' needs and being led by the patient as much as possible. There may be problems of distance between the specialist centre and patients' homes, and this may affect whether relatives are able to be present. Forewarning the patient that relatives could be present sometimes increased anxiety. Sometimes communication could be piecemeal and partly delegated to another clinician.
	Reaction to diagnosis Many felt a sense of shock in the immediate phase after diagnosis. Feelings of frustration were expressed over the inability to pinpoint reasons for their illness as the cause is still not understood. Some felt self-blame. It was important for healthcare professionals to be aware of prominent cases of MND in the media as these may influence patients' reactions to their diagnosis. After initial shock, reactions varied widely from despair to fatalism and even relief (from knowing what was wrong).
	Information

Study	Hugel 2006
	5/10 who raised questions wanted little or no information about the disease, and left it to their relatives to seek information. **Formal support** Participants were generally appreciative of the services they received. The overriding issue was the sharp increase in the number of services involved in the patients' care after formal diagnosis of MND. This may be associated with a risk of patients feeling overwhelmed by the sudden surge in support, which may aggravate rather than improve feelings of losing control. Coordination of services was not always felt to be optimal.
Limitations	No details of the researcher but interviews were conducted by people not involved in care. No details if patient-validated. Rational not given for sampling, data collection or data analysis techniques used. Only one interviewer.
Applicability of evidence	Applicable

Study	Mistry 2013[398]
Aim	To explore how each participant's individual understanding of MND, their feelings, and how their sense of self and identity were affected after their diagnosis. Also to explore the movement from receiving a diagnosis through to coping strategies.
Population	n=7 people with MND who had received a diagnosis of MND in the previous 6 months; recruited from a specialist MND service in north-west England.
Study design	Qualitative study using interviews, IPA approach.
Methods and analysis	Interviews were conducted in the person's own home. A semi-structured interview schedule was used to guide and prompt interview topics and additional questions for additional information and clarification. The schedule included questions on the diagnostic process, subsequent hospital visits, and the participants' emotions, attitudes, behaviours and thoughts about the diagnosis up to the point of interview. They were given a lot of freedom to discuss and reflect on topics they thought important, in line with the IPA approach.
Themes with findings	**'Then they dropped the bomb shell': receiving a diagnosis of MND** The participants' feelings of shock and devastation were apparent as they realised they had been diagnosed with a life-threatening condition. The physicality of the shock is emphasised. After diagnosis, most tried to make sense of it and to understand how or why they had MND. Some felt they were being punished and their life had been 'robbed' from them when they had not harmed anyone. They felt that there was unfairness and questioned what they had done to deserve their diagnosis, typical of a 'search for meaning' (for example Janoff-Bulman, 1989). They said they were unable to take in any other information that was given to them after the MND diagnosis, describing themselves as 'shell-

Study	Mistry 2013[398]
	shocked', as they were struggling to make sense of their diagnosis and the possible future implications. Feelings of falling, or being in a dream-like state. The experience of the 'bombshell' of the diagnosis contrasted with their expectations at the start of the medical investigations. When they first had physical/functional changes, they had not thought them significant, thinking them part of the ageing process or work hazards. They only sought medical attention when the changes were becoming more significant, although this differed by person. People experienced different symptoms, therefore were referred into different medical specialties related to the initial symptoms they experienced. This was a time of uncertainty where they felt frustrated, worried, confused and angry as they did not know what was causing them to lose control over their bodies and whether they would get treatment to stop or slow down the symptoms. People were thought of as a 'puzzle' to their clinicians which evoked feelings of fear, confusion and worry for all participants in the study. Thoughts participants had before they received the MND diagnosis suggested that although potentially serious, it would be treatable. Yet any hopes of this were destroyed by the 'bomb shell' diagnosis.
	'Got to get to grips with it': learning to live with MND People felt a sense of urgency to get to grips with the diagnosis in order to make the most of the time left. Each had their own way to think about their diagnosis and how it would affect them as it progressed, and how to manage the changes. They acknowledged and accepted that they were unable to do anything to change or slow down the progression of their MND and it was not their fault that they had the condition. By maintaining control and reaching a causal understanding they could move on to practical concerns. Some had difficulties adjusting to the diagnosis. One participant was frustrated from not knowing what causes MND. Not being able to plan meant a change in perspective on life from being meaningful and predictable. She had to change the way she approached stressful situations. Other participants were able to make changes by focusing on the implications of the life-limiting disease and unpredictability that were not under their control to help them acknowledge and adjust to their diagnosis. Those who were able to adjust to their diagnosis seemed to very quickly start the process of re-assessing their goals and aims. As MND symptoms progressed, they had to make a series of modifications to the tasks and activities in which they used to engage, for example using physical aids or embracing modern technology. Adaptations included using the internet to continue with employment and the use of a mobility scooter to maintain independent movement. There was a positive psychological effect of these as they maintained valued aspects of their lives, indicating that whilst the level of impairment was important, the functional changes impacted more seriously on their psychological well-being. However, functional adaptations are only possible up to a certain point. One participant could not change her view of life and death as she did not have the information necessary to do so – the cause of the disease. This may have hindered her ability to find appropriate coping mechanisms and start the dynamic process of belief modification, coping and adaption.
	'A lot of normal life is lost': experiencing progressive loss Many noticed that their 'normal' previous life was being eroded. Type and frequency of social interactions had changed and the sense of control and autonomy they had over their bodies also altered as they could not complete or engage in specific tasks or activities.

Study	Mistry 2013[398]
	One participant found that the communication device impeded the normal flow of conversation with his wife, friends and family, which he felt affected his personality as he was unable to express himself. Other participants found social interactions reduced as they became self-conscious in public settings. One participant felt that although she had lots of support from family and friends, she didn't like that she couldn't do things without their support, reminding her that she had MND. Another participant found that explicitly informing people of his condition meant that they made accommodations for him when they conversed, which made him feel accepted. Freedom and control over bodies dwindled as MND progressed, and participants felt that this took away their freedom to make choices. One participant felt that as MND progresses he will be alive but not 'living'. As social situations made them uncomfortable they would less likely go out on their own. This increased the reliance on others.
Limitations	Findings not validated by participants. Themes needed further refinement. Role of the researcher not clearly defined. Not enough details on data analysis. Small sample size n=7.
Applicability of evidence	Applicable

Study	O'Brien 2011[434]
Aim	To explore the personal perspectives of the diagnostic experience for people with ALS/MND and their family and carers, identifying issues that could impact positively or negatively on these experiences.
Population	Individuals with MND/ALS (n =24/25) [contradictory in report]; 16 female/9 male), current carers (n =18; 7 female/11 male) and former carers (n =10; 7 female/3 male) of family members with MND/ALS. Patients' mean disease duration =22.8 months (range =1–156 months). Current carers were caring for family member diagnosed with MND between 1 months and 7.5 years prior to the interview; former carers had been bereaved between 2 months and 7 years at the time of their interview.
Study design	Qualitative interviews
Methods and analysis	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND care and research centre in north-west England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only 1 carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the 3 members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and

Study	O'Brien 2011[434]
	similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	**Symptom onset** Symptoms went unnoticed by those with MND and their family. Often acquaintances pointed it out. No immediate cause for concern; it was assumed that symptoms were due to other things such as the stress of a new job. Did not associate even troublesome symptoms with a potentially serious condition. Sought medical advice when they noticed their condition worsening or experienced additional difficulties. Assumed that muscle weakness was due to poor fitness so many took up exercise.
	Experiences within primary care Some patients were not taken seriously. Failure of GPs to recognise symptoms or the significance of progressive symptoms. Concurrent health problems confused matters, so new symptoms not noticed.
	Diagnosis delays Delays in referral in primary care due to a lack of urgency. Delays when directed to specialities other than neurology. Some took a proactive stance to get a neurologist opinion, some paid for private care for initial consultation or investigative test for a speedier diagnosis. Long periods of uncertainty surrounding assessments added to their distress.
	Communication of diagnosis Mixed experiences; for some the process was handled sensitively with appropriate explanation and sympathy. Yet many described interaction as blunt and unsatisfactory, revealing poor communication skills and a lack of consideration of the impact of the diagnosis on the patient and their family. Patients were afforded little privacy or time despite the devastating nature of the diagnosis. The people present and the location where the diagnosis was delivered were commented on. Immediate post-diagnosis support was important for coping. Sympathy for doctors who have to deliver a diagnosis, however there was anger about the poor circumstances under which some individuals received their diagnosis. A number were told they had anterior horn cell disease, but as all were unaware of such a diagnosis, they sought clarity about it without adequate support.
	Responding to the diagnosis Although traumatic, there was relief at having a name for and understanding their symptoms.

Study	O'Brien 2011[434]
	Some were left to cope, with inadequate support, immediately post-diagnosis. Patients should know their follow-up arrangements and have a point of contact for when they got home. Difficult telling the family. Information needs varied, but insufficient explanation was sometimes given. As ALS/MND is variable, generic information about prognosis had implications for those with atypical progression. Comparisons made with care routinely provided for people with cancer (cancer support). Despite the availability of specialist MND support, there was a feeling that provision was better in this group.
Limitations	Themes needed further refinement. Not much detail about the researcher.
Applicability of evidence	Applicable.

G.2 Information and support at diagnosis

Study	Hocking 2006A[275] Hocking 2006[274] Brott 2007[87]
Aim	To explore the experience of living with MND
Population	N=7 (4 women and 3 men) in New Zealand. Participants were at different stages of MND, with varying mobility. They were diagnosed between 8 months and 4 years previously. One of the participants used an assistive device to communicate.
Study design	Semi-structured and interviews
Methods and analysis	Interviews were focused on actual events and situations participants had experienced. Participants were interviewed in their own homes. Interviews were transcribed verbatim and drawn into stories under themes. The analysis was informed by van Manen's 1990 description of the 6 activities or stages in the research process.
Themes with findings	**The wobbly body** Experience of living with a body that was changing and that they were losing control over. Bodies felt different and moved differently, which affected activities. Deteriorating performance on familiar activities became the benchmark for progression of the disease. Embarrassment of falls or reliance on others for daily care and activities, such as toileting, showering, cleaning teeth and grooming. Participants searched for explanations as to why they had this wobble, seeing different specialists. For example, 1 participant saw a podiatrist as he thought he had a drop foot, and subsequently saw 2 locums GPs, a doctor who referred them to an orthopaedic specialist, 2 neurologists, and a

Study	Hocking 2006A[275] Hocking 2006[274] Brott 2007[87]
	3rd neurologist who finally made diagnosis when they had seen the participant 3 times. In order to cope, participants looked for information (often from the internet).
	Doing and being
	Changed world – changed future As participants' lives changed so did their families'. Patients had to tell their families about their diagnosis, which was very difficult. Changed relationships and worries of being a burden due to assistance with showering, dressing and toileting. Relief of 'getting into the health care system' as participants then expected help to be at hand, however they had to open up their home to people they didn't know, to assist with highly intimate care. The numbers of people involved in care could be overwhelming, and participants wished to be left alone at times. Barely time or energy to see friends. It was important to participants to plan ahead so they gained a sense of control. Knowing who to trust regarding seeking, receiving and following advice was important, but participants were often given conflicting information.
Limitations	The MNDA of Australia field workers approached prospective participants. The role of the researcher was not clearly explained. The authors did not explain the process of analysis in-depth, so we do not know if there was triangulation of data to arrive at the themes. Stories were sent to participants to check but the themes were not. Particular emphasis was given to the 1st and 3rd theme but not the 2nd theme as the other 2 themes had 'particular relevance to working as a member of a multidisciplinary team to support people with MND who are living in their own home'. Small sample size n=7.
Applicability of evidence	Applicable

Study	Hogden 2012A[276]
Aim	To explore clinicians' perspectives on patient decision-making in multidisciplinary care for ALS, to identify factors influencing decision-making
Population	N=32 health professionals from 2 specialised multidisciplinary ALS clinics and regional advisors from the Motor Neuron Disease Association in New South Wales, Australia. They included medical, nursing and allied health professionals. Working primarily in acute inpatient, community-based rehabilitation, or palliative care services and attended the monthly ALS clinics in addition to their usual clinical load.
Study design	Qualitative: semi-structured interviews.

Study	Hogden 2012A[276]
Methods and analysis	Convenience sampling was used. Structured interview guide developed through a 3-stage process. 12 open-ended interview questions about participant experience with decision-making, barriers, facilitators and improvements to decision-making processes in multidisciplinary care. In-depth interviews were audio recorded and lasted approximately 60 minutes. Two group interviews were held with a palliative care nursing team and members of a multidisciplinary ALS clinic team. Transcripts were analysed using thematic analysis.
Themes with findings	**Influences on decision-making** Clinicians reported that their aim was to guide the patient and carer through upcoming decisions, in a timely manner, with the provision of evidence-based information on the available options regularly discussed. They saw it as a cyclical process, responding to recurrent change as the person's condition deteriorated. Their definition of the objective of collaborative decision-making was facilitating patient-centred decisions to suit the inevitable changes to patient health and lifestyle.
	Patient factors The clinicians perceived 3 main barriers to decision making: patient acceptance of the diagnosis, the types of information patients sourced, and the patient-carer relationship. They found that poor family dynamics and problems with acceptance or insight impacted on their relationship with the patient. Health professionals reported little control over these issues, but aimed to respond to the changing needs of patients as best they could.
	Ability to accept the diagnosis The majority raised concerns with patients who had difficulties coming to terms with the diagnosis of ALS and adjusting to deterioration as the disease progressed. Limited clinical understanding impeded acceptance of the diagnosis by patients and family members. Limited public awareness of ALS meant patients delayed seeking a diagnosis and the shock of receiving a terminal prognosis for an unfamiliar condition delayed the patient's and family's ability to take in information. Those who used denial as a coping strategy delayed discussion of planning and decision-making. Cognitive and behavioural changes impacted on patients' health care decision-making. Patients had the capacity to make decisions but the quality and timing of their decisions appeared compromised by lack of motivation and limited insight into their condition and the needs of their families. Many patients were described as being 'difficult' and having rigid personalities, particularly in the palliative phase. Because cognitive and behavioural change was not routinely assessed in the clinics, identification of patients at risk of impaired decision-making skills was neither systematic nor standardised. More specific and detailed knowledge of these changes could improve their approach with the patient and carer. Patients who struggled to accept their condition responded passively to physical deterioration, and sought assistance only when their condition was unmanageable. Decisions were made at last moment, or after critical timing windows were lost. Crisis management strategies were seen as a

Study	Hogden 2012A[276]
	last resort for those who were unable to come to terms with the changes to their life.
	Types of information patients sourced Credible sources of information were mainstream health services and associations based on empirical evidence, such as ALS patient association information kits and health research-based websites. Non-credible sources lacked an evidence base, but were easily accessed via the internet. There was concern over the patient's ability to distinguish between non-credible and credible sources. Clinicians reported a sense of responsibility to monitor the quality of information accessed by patients, and to provide guidance on the range of evidence-base information available. Practitioners were wary of crushing patients' sense of hope, but thought that poor-quality information compounded their difficulty in accepting the inevitable nature of MND. Some information gave unrealistic expectations of services that could be offered. Patients' wish for a cure led them to collect misleading information and develop false hopes which were counterproductive to accepting and adjusting to MND, and making effective decisions.
	Patient-carer relationship Decisions about employment, artificial nutrition and hydration, home modifications and accommodation had considerable influence on carers' quality of life. Decision-making was disrupted if the patient and carer could not reach agreement, or when the patient's poor decision-making put the well-being of the carer at risk. Respondents reported instances where carers had a negative influence on decision-making discussions, such as a gate-keeping role blocking access to the health professional and the patient.
	Health system factors [note that this study is conducted in Australia] Timing of diagnosis and symptom management: Participants from diagnosis, management and end-of-life services expressed concern about the time lag between patients reporting symptoms and receiving a diagnosis of ALS. The heterogeneity and subtlety of ALS symptoms created delays in making the diagnosis and in decision-making to optimise symptom management. Limited awareness of ALS by non-specialist health care providers hindered timely referrals to ALS services. Once symptoms were recognised as ALS, access to specialised services became the next challenge for patients and their primary health care providers. Access to health services was difficult for those outside of a clinic catchment area, with long waiting lists for services which impacted on the ability to make decisions.

Study	Hogden 2012A[276]
	Even when accessing specialised services, physical resource constraints compromised care options. Participants reported frustration with long waiting times for equipment. Extended delays rendered the equipment obsolete for patients who had deteriorated. Respondents thought that well-timed information was crucial for patients' decision-making. Patients and family should be informed as early as possible about the diagnosis, prognosis, and expected course of disease progression. Knowing when to do so without overwhelming patient and carer was a difficult decision, and specific to each case. Judging optimal timing for provision of information challenged health professionals both as individuals and as a team. It depended on the patient's readiness to hear it. **Access to ALS-specific resources** Health professionals stated that the wider health system created barriers to collaborative and patient-centred decision-making. Health service funding was frequently mentioned as blocking the delivery of specialised ALS multidisciplinary clinic services. Health professionals reported frustration with constraints imposed by these factors largely outside of their control. **Inter-professional communication** Communication difficulties between health professionals were a barrier to decision-making in multidisciplinary ALS practice. Breakdowns in inter-professional communication disrupted information exchange and implementation of collaborative, patient-centred decisions. Communication with external health providers was also problematic with a lot of time spent trying to contact external practitioners.
	Decision-making facilitators An MDT model of care enhanced their role in decision-making, when supported by access to ALS research information and clinician education websites. Collaborative teamwork, effective communication systems which underpinned that teamwork and evidence-based clinical information promoted meeting the patient at their point of need and improving decision-making. Guidelines were useful for decision making in the MDT ALS team to: assist provision of clear information to health professionals, patients and families; to provide structure and timeframes to facilitate planning with patients; and to give clarification of roles and responsibilities for decision-making within the MDT. Guidelines also reduced specific gaps in services, including the use of routine screening for cognitive and behavioural change and the completion of advance care plans with patients.
Limitations	The role of the researcher was not clearly explained, but the questions were developed by 2 clinicians with extensive experience in ALS. Themes needed further refinement.
Applicability of evidence	Applicable

Study	Hugel 2006
Aim	To explore patients' experiences regarding their recent diagnosis of MND
Population	N=13 people with MND in UK. 9 male/4 female. Mean age 64 years (SD 14, range 33-79 years). El Escorial criteria 8 had clinically definite, 3 clinically probable, 1 laboratory probable and 1 possible MND.
Study design	Qualitative: semi-structured interviews
Methods and analysis	Interpretative Phenomenological Analysis (IPA) was used. The results were part of a currently ongoing (2006) longitudinal study of quality of life in patients with MND under the influence of current care practice.
Themes with findings	**Communication of the diagnosis** Giving the diagnosis in a private atmosphere with a relative or carer present was important. Pacing the discussion empathically according to patients' needs and being led by the patient as much as possible. There may be problems of distance between the specialist centre and the patients' home, and this may affect whether relatives are able to be present. Forewarning the patient that relatives could be present sometimes increased anxiety. Sometimes communication could be piecemeal and partly delegated to another clinician.
	Reaction to diagnosis Many had a sense of shock in the immediate phase after diagnosis. Feelings of frustrated were expressed over the inability to pinpoint reasons for their illness as the cause is still not understood. Some felt self-blame. It was important for health professionals to be aware of prominent cases of MND in media as these may influence patients' reactions to their diagnosis. After initial shock, reactions varied widely from despair to fatalism and even relief (from knowing what was wrong).
	Information 5/10 who raised questions wanted little or no information about the disease, and left it to their relatives to seek information.
	Formal support Participants were generally appreciative of the services they received. The overriding issue was the sharp increase in the number of services involved in the patients' care after formal diagnosis of MND. This may be associated with a risk of patients feeling overwhelmed by the sudden surge in support, which may aggravate rather than improve feelings of losing control. Coordination of services was not always felt to be optimal.
Limitations	No details of the researcher but interviews were conducted by people not involved in care. No details if patient-validated. Rational not given for

Study	Hugel 2006
	sampling, data collection or data analysis techniques used. Only one interviewer.
Applicability of evidence	Applicable

Study	Hughes 2005[284]
Aim	To look at the lives, experiences of services and suggestions for change of people living with MND
Population	People with MND (N=9) and their carers (N=5), and professionals (N=15) with front-line or strategic interests in MND working within 3 boroughs in London, UK: Lambeth, Southwark and Lewisham (among the most socially and economically deprived areas in the UK, covered by King's College Hospital MND Care and Research Centre). People with MND and their families were recruited by a database at the MND Care and Research Centre.
Study design	Qualitative, semi-structured interviews from a topic guide based on existing literature: living with MND and its impact, experiences of services and suggestions for service changes.
Methods and analysis	The authors excluded anyone with mental health problems, involved in other research or who did not have good command of English. A 'snowball' technique was used to sample families and professionals. A letter was written to invite participants to an interview. Research questions included: living with MND and its impact; experiences of services; and suggestions for service changes.
Themes with findings	**Impact of MND on people's lives** As MND progresses, it has a debilitating physical effects on the body. MND can limit travel, the pursuit of hobbies and pastimes. Many of the participants were older so disentangling the difficulties of age with that of MND was difficult. One younger participant kept doing what he used to do, including socialising, but got fatigued a bit earlier. As people 'get used to' living with MND, changes can become routine and 'natural' adjustments were made. The increased dependency on spouse and family altered relationship roles and left them feeling bad that it had been reversed. One participant tried to conceal the impact of the illness from his spouse. His spouse also worried as their partner had always dealt with practical matters such as finance. Although they felt uncertainty about the future, people at all stages of MND and of all ages discussed the importance of illness acceptance. Some people ignored their illness as much as they could. This in some cases led to reticent information-seeking. Sometimes carers would restrict the information available to people with MND to protect their loved ones from distress and upset. Professionals recognised that individuals – like everyone - had many different emotions and coping strategies. Professionals were also aware of the effects of MND on people's lives and their struggle to have a quality of life. People with MND felt that there was an overall lack of understanding of MND which impacts on their experience of services.

Study	Hughes 2005[284]
	Experiences of services Many people felt unsure about the services they were entitled to, especially when first diagnosed, and were also unsure of where to obtain information from. Professionals recognised that people with MND would be exposed to a number of forms of information from different sources, which could potentially be confusing. Some professionals attached priority to MND care. Some people with MND discussed lengthy procedures in referrals and in obtaining an accurate diagnosis. Some people with MND felt that the approach of professionals was distant and divorced. Some people with MND were concerned about professionals' lack of knowledge and understanding of MND and its impact on people's lives. They thought some professionals had incomplete knowledge of MND, and that its rareness was an explanation. Lack of understanding of the illness led to problems in accessing service entitlements, such as social security benefits. Some professionals' apparent lack of understanding and knowledge about MND, or their attitudes and approach to users, made people with MND reluctant to approach them with questions. Such situations made them feel dissatisfied with the information and services they were receiving. Problems of receiving the right kinds of information at appropriate times led some to seek information for themselves, for example, books and leaflets, MND stories in the media, the internet. People with MND did appreciate the complexities and challenges for professionals giving information. One respondent questioned whether it could be presented any better. Different people have different information-seeking requirements.
	Suggestions for service change Some people with MND felt that there needed to be improved information and communication between professionals and users. Others wanted information on what to expect in the future, especially if newly diagnosed, desiring practical information about MND and their entitlements to services immediately. One carer found that there was need for more efficient social service responses. Those who had been living with MND longer also wanted information on treatments, therapies and research. Some wanted specific information but realised that they needed to work through their own needs. Professionals identified a need for increased knowledge about MND, through improved education and training for their colleagues. They also thought there should be better coordination and information exchange between professional teams, especially between those in hospitals and those in the community. Some professionals felt that services should be restructured to reduce demarcation between providers so that professionals could follow-up their caseload between hospitals and the community. These changes were understood to improve coordination and consistency of care. **Improvements to services** There was a need for support from people with an understanding of MND, not necessarily professionals.
Limitations	Themes not explicit, more descriptive. Findings not validated by participants. No details of researcher's role.

Study	Hughes 2005[284]
Applicability of evidence	Applicable

Study	McConigley 2014[383]
Aim	To determine the experiences of, and need for, education of health professionals who may be required to provide care for people with MND.
Population	N=31 health professionals with some experience in providing palliative care for people with MND in Australia; mean time since graduation =24.3 years (SD 13.1, range 0-42); health professional type: registered nurse n=8, occupational therapist n=4, case coordinator/care advisor n=5, medical specialist n=3, physiotherapist n=3, speech pathologist n=3, complementary therapist n=1, counsellor n=1, dietician n=1, prosthetist n=1, chaplain n=1.
Study design	Interviews and focus groups
Methods and analysis	Descriptive, exploratory qualitative design to understand the experiences of providing MND care in the community. 250 health professionals who were signed up for the National MND conference were invited. N=11 attended the focus group. For additional health professionals, a snowball sampling technique was used to find a purposive sample of 20 health professionals, who were interviewed face-to-face or on the phone. Sampling continued until saturation reached. Interviews and focus groups conducted by health professionals with experience in this methodology. The interviews and focus groups were audiotaped and transcribed verbatim. Thematic analysis was used to identify common themes.
Themes with findings	**Just one step ahead** The health professionals felt they needed to stay one step ahead of the patient by being aware of what was likely to happen next, anticipating their needs and problems arising, and implementing immediate solutions expectantly but not too soon. Predict changes in care needs, rather than waiting for a crisis. If changes were not predicted or there was a sudden change in the condition then a quick response to that change was needed. Needed to be aware of potential changes as there were many possible manifestations and disease trajectories. Important to be one step ahead but not too far ahead. Careful negotiations needed with patients and families. Staging of information and timing of support was important so patients could cope with new information and changes being made before giving more information. Too much information too soon could be detrimental. Connecting the person to a palliative care service was considered one way that MND care providers could stay one step ahead, by providing a framework for planning proactive care, tailored to an individual's care needs.
	Expertise in MND It was necessary to have the required knowledge of the disease and an understanding of each patient's version of the disease in order to plan, advise, support and anticipate the patients' and carers' needs.

Study	McConigley 2014[383]
	Knowledgeable and credible health professionals were essential to meet peoples' needs, however generalist providers of care to people with MND are not MND specialists. Poorly prepared staff could undermine the efforts of the care team. They generally suggested a need to provide education about the diseases aetiology, progression and management. Understanding that what people with MND required was distinct from other life-limiting conditions, and recognising their unique care needs was paramount. Keeping up to date with current knowledge and services related to MND was difficult for participants who provided care infrequently. Need for health professional training and non-professional staff education on the disease and its progression.
	Bespoke communication ***Communication with patients*** Needed to communicate carefully to ensure that they adequately prepared patients for next stage of illness. The negotiation required skilled communication in order for people to make informed choices. There may be communication problems related to disease process, and so knowledge of devices to assist communication and how to use them effectively to communicate was an important skill. Staying one step ahead required the introduction of communication aids early in disease trajectory, so that they were ready for when they were required. ***Communication with patients*** Needed to develop good relationship with families, as often they were the go-between for those with communication difficulties and the health professional. ***Communication within the care team*** As so many team members were involved, communication was crucial between team members to ensure that care was coordinated and seamless. Difficulties in communication between specialities were described. Informing and involving all care team members in care was important but difficult, due to location and few face-to-face meetings. ***Communication about end-of-life issues*** Careful, empathic communication was required to assist families in accepting the changes that led to the requirement for a palliative approach to care.
Limitations	No details of the researcher. More details could be given on how themes were arrived at and themes could have been drilled down more. No details if participant-validated.
Applicability of evidence	Applicable. Note that this is exploring the educational needs of clinicians in Australia, however it is asking health professionals what educational needs are required and therefore matches the protocol.

Study	O'Brien 2011[434]
Aim	To explore the personal perspectives of the diagnostic experience for people with ALS/MND and their family and carers, identifying issues that could impact positively or negatively on these experiences
Population	Individuals with MND/ALS (n = 24/25) (contradictory in report); 16 female/9 male), current carers (N = 18; 7 female/11 male) and former carers (N = 10; 7 female/3 male) of family members with MND/ALS. Patients' mean disease duration = 22.8 months (range = 1 – 156 months). Current carers were caring for family member diagnosed with MND between 1 months and 7.5 years prior to the interview; former carers had been bereaved between 2 months and 7 years at the time of their interview.
Study design	Qualitative interviews
Methods and analysis	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND care and research centre in NW England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only 1 carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the 3 members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	**Symptom onset** Symptoms went unnoticed by those with MND and their family. Often acquaintances pointed it out. No immediate cause for concern; it was assumed that symptoms were due to other things such as the stress of a new job. Did not associate even troublesome symptoms with a potentially serious condition. Sought medical advice when they noticed their condition worsening or experienced additional difficulties. Assumed that muscle weakness was due to poor fitness so many took up exercise.
	Experiences within primary care Some patients were not taken seriously. Failure of GPs to recognise symptoms or the significance of progressive symptoms. Concurrent health problems confused matters, so new symptoms not noticed.
	Diagnosis delays Delays in referral in primary care due to a lack of urgency. Delays when directed to specialities other than neurology. Some took a proactive stance to get a neurologist opinion, some paying for private care for initial consultation or investigative test for a speedier

Study	O'Brien 2011[434]
	diagnosis. Long periods of uncertainty surrounding assessments added to their distress.
	Communication of diagnosis Mixed experiences; for some the process was handled sensitively with appropriate explanation and sympathy. Yet many described interaction as blunt and unsatisfactory, revealing poor communication skills and a lack of consideration of the impact of the diagnosis on the patient and their family. Patients were afforded little privacy or time despite the devastating nature of the diagnosis. The people present and the location where the diagnosis was delivered were commented on. Immediate post-diagnosis support was important for coping. Sympathy for doctors who have to deliver a diagnosis, however there was anger of the poor circumstances under which some individuals received their diagnosis. A number were told they had anterior horn cell disease, but as all were unaware of such a diagnosis, they sought clarity about it without adequate support.
	Responding to the diagnosis Although traumatic, there was relief to have a name for and understand their symptoms. Some were left to cope, with inadequate support, immediately post-diagnosis. Patients should know their follow-up arrangements and have a point of contact for when they went home. Difficult telling the family. Information needs varied, but insufficient explanation was sometimes given. As ALS/MND is variable, generic information about prognosis had implications for those with atypical progression. Comparisons made with care routinely provided for people with cancer (cancer support). Despite the availability of specialist MND support, there was a feeling that provision was better in this group.
Limitations	Themes needed further refinement. Not much detail about the researcher.
Applicability of evidence	Applicable

Study	O'Brien 2011A (part of a larger NIHR-funded research study)
Aim	To explore the views of people with MND and family carers regarding MDT working
Population	Individuals with MND/ALS (n=24); 16 female/9 male), current carers (N=18; 7 female/11 male) and former carers (N=10; 7 female/3 male) of family

Study	O'Brien 2011A (part of a larger NIHR-funded research study)
	members with MND/ALS. Patients mean disease duration = 22.8 months (range =1-156 months). Current carers were caring for family member diagnosed with MND between 1 month and 7.5 years prior to the interview; former carers had been bereaved between 2 months and 7 years at the time of their interview.
Study design	Qualitative interviews
Methods and analysis	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND care and research centre in NW England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only 1 carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the 3 members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	**Having one point of access** Central coordinating role of the MND care centre was commented on by some participants who appreciated that once they were known to the centre, other relevant services would be quickly implemented. Having an easily accessible point of contact where queries were answered and support was provided was crucial to many participants. The continuity this provided was well regarded. Involvement of specialists and the MDT was thought to be beneficial by many. The ease of access to the MDT was also reassuring.
	Specialist knowledge and skills Having an MDT clinic was perceived positively by many people. The specialist knowledge of the professionals involved was thought to be a major advantage. They found that the MND centre staff were able to provide advice based on sound knowledge and experience of the illness, and for some participants, having a specialist MND centre nearby was seen as a way of minimising the effect of limited knowledge of the disease among local health staff.
	Saving time and energy Participants welcomed the prospect of having access to the full range of health professionals during 1 clinic appointment, which avoided numerous separate appointments. Some thought that joint consultations would be an improvement. There were access problems with the MND clinic being central, within the regional neurological centre, particularly for those who were fatigued. Holding MND clinics at local hospices was viewed as a positive solution for those not living near the regional centre. A number said there was also a positive aspect of having had some contact with the hospice, as they became familiar with the setting and staff

Study	O'Brien 2011A (part of a larger NIHR-funded research study)
	would be more open to returning there for support at a later stage.
	Regular follow-ups Positive comments about the follow-up provided by MND nurse specialist. Seeing the same nurse at each appointment was not only beneficial for continuity of care but also for patients' psychological wellbeing. One patient felt that the time between appointments was too long, and due to the rapid deterioration associated with the disease, this could potentially lead to problems.
	Value members of the MDT Involvement of district nurses was often regarded as very useful to patients and carers. It was often perceived as an important link to the rest of the MDT who could often inform other professionals of the patients' needs. It was clear that a good relationship with the GP and close regular contact with them had really made a difference to some patients. One past carer recognised that because the condition is rare it was unlikely that a GP would have experience of the condition, but was pleased when they had made a concerted effort to read up and improve their knowledge of the disease when treating her husband. The role of the OT was crucial in obtaining the appropriate equipment; a proactive approach was frequently described with OTs rushing through alterations. They also used their practical skills and knowledge to create devices for troublesome problems as well as providing useful day-to-day living advice. Speech and language therapist involvement, for maintaining communication and monitoring swallowing, was also generally regarded positively. Physiotherapy was regarded as beneficial. The dietician was also regarded as useful source of advice and support. There was sometimes a lack of clarity of roles and responsibilities of health and social care professionals involved in care, which was confusing if participants did not know the system.
	Working together as a team There were consultations for suggestions for the management of difficulties encountered as a result of illness, which was valued by participants. When the professionals worked together as a team, there was more effective implementation of care. Sometimes as there were so many people involved in care, participants spent a lot of time trying to find the most appropriate person for their concerns. A number thought there was need for a single care coordinator to oversee the collaboration between different agencies. It was important that health professionals were flexible enough to take account of the disease progression. Many participants had experienced issues with social workers, with no allocation or too late in the disease progression. It was felt that early contact with social workers, as with most members of the MDT, would have been beneficial, so that patients become familiar with them. Lack of continuity of care as cases were often closed with social workers when ongoing contact was not required. Then they would be reallocated when needs changed and contact again required.

Study	O'Brien 2011A (part of a larger NIHR-funded research study)
	When social workers involved early, and continued to maintain contact, the system operated in a reassuring manner which put the patient at the centre of the process. They did not have to repeat stories as continuity maintained and patients felt less isolated.
Limitations	Themes needed further refinement. Not much detail about researcher.
Applicability of evidence	Partially applicable

G.3 Prognostic factors

Reference	Capozzo 2015[103]
Study type and analysis	Retrospective cohort study conducted in Italy Outcome was mortality or tracheostomy Cox Proportional Hazards Regression model utilised
Number of participants and characteristics	N=100 (12 died, 17 tracheostomy) Median follow-up: 1.2 years (range 0.02 – 3.89) All patients who were referred to multidisciplinary centre for MND (January 2006 – December 2010) and met inclusion criteria Inclusion criteria: diagnosed with ALS by El Escorial criteria Mean (SD) age: 62 (10) Sex: 45 female, 55 male
Prognostic variable(s)	Age (years) Forced vital capacity (%) ALS functional rating scale revised Site of onset (limb, bulbar) Disease duration (per 5 years) – converted to months for meta-analysis
Confounders OR stratification strategy	BMI (kg/m^2), Sex (male, female), Charlson Comorbidity Index
Outcomes and effect sizes	Age (HR 1.012 [0.971 to 1.054]) Forced vital capacity (HR 0.995 [0.976 to 1.015]) ALS functional rating scale revised (HR 0.956 [0.904 to 1.011]) Site of onset – limb versus bulbar (HR 0.709 [0.293 to 1.716])

Reference	Capozzo 2015[103]
	Disease duration per 5 years (HR 0.246 [0.040 to 1.525]) – converted to months for meta-analysis
Comments	Very high risk of bias due to selection bias Authors declare no financial or other conflicts of interest

Reference	Czaplinski 2006[158] Czaplinski 2006C[160] Czaplinski 2006D[159]
NOTE	The multivariable model from "Amyotrophic lateral sclerosis: early predictors of prolonged survival" was used for this review as it encompassed more of the patient group. Models from the other two papers not included as they use some of the same patients.
Study type and analysis	Retrospective cohort study conducted in the USA Outcome was mortality or tracheostomy Cox Proportional Hazards Regression model utilised
Number of participants and characteristics	N=1034 (477 died, 99 tracheostomy) Follow-up: >20 years Setting: single clinic Inclusion criteria: definite or probable ALS by El Escorial criteria 66.4% male Mean (SD) age at time of disease: 54.1 (13.2)
Prognostic variable(s)	Age at onset (years) Bulbar site of onset versus limb Diagnostic delay (months) Baseline forced vital capacity (% predicted)
Confounders OR stratification strategy	Baseline Appel ALS Score (AALSS), AALSS preslope (change between first symptoms and first exam), Riluzole use (never, ever), NIV therapy (never, ever), PEG therapy (never, ever) – all in final model
Outcomes and effect sizes	Age at onset (HR 1.04 [1.03 to 1.05]) Bulbar site of onset (HR 1.03 [0.82 to 1.29]) Diagnostic delay (HR 0.97 [0.96 to 0.98]) Baseline forced vital capacity (HR 0.98 [0.98 to 0.99])

Reference	**Czaplinski 2006[158]** **Czaplinski 2006C[160]** **Czaplinski 2006D[159]**
Comments	High risk of bias due to selection bias Supported by the MDA and Houston Endowment

Reference	**Desport 1999[179]**
Study type and analysis	Prospective cohort study conducted in France Cox Proportional Hazards Regression model utilised Outcome was mortality
Number of participants and characteristics	N=55 (18 died) Mean (SD) follow up was 7 (4) months. Inclusion criteria: people with probable or definite ALS according to the El Escorial criteria Recruited from one centre between March 1996 and October 1997 – no patients were excluded Mean (SD) age: 63 (11)
Prognostic variable(s)	BMI (<18.5 versus >18.5) Age at onset (years) Site of onset (limb, bulbar) Diagnostic delay
Confounders OR stratification strategy	Vital capacity (<60%), duration of riluzole treatment, presence of gastrostomy
Outcomes and effect sizes	BMI (HR 7.4 [1.7 to 32.1]) Age at onset (no results presented) Site of onset (no results presented)
Comments	Very high risk of bias due to selection bias and detection bias Funding not stated

Reference	Elamin 2015[197]		
Study type and analysis	Cohort study conducted in Ireland and Italy Cox Proportional Hazards Regression model utilised Outcome was mortality Aim: to develop a reliable prognostic model in ALS using information that can be gathered at the first patient encounter		
Number of participants and characteristics	Two population-based cohorts - one in the Republic of Ireland (n=204) and the other in Italy (n=122) – were utilised. Irish cohort: 177 or 204 died by the time of analysis. Inclusion criteria: people with possible, probable or definite ALS according to the El Escorial criteria Exclusion criteria: conditions which could affect neuropsychological function, for example, major hemispheric stroke or alcohol dependence syndrome. Patients were recruited from 2006 to 2011.		
Prognostic tool development	The prognostic tool (ALS Prognostic Index) was developed a randomly selected group of the Irish cohort (n=117), internally validated on the rest of the Irish cohort7 (n=87), and externally validated on the Italian cohort (n=122). Prognostic factors investigated: age at symptom onset, gender, site of disease onset, ALS functional rating scale revised slope [(48-ALSFRS-R score)/disease duration at time of assessment], family history of ALS and/or frontotemporal lobar degeneration in 1st or 2nd degree relative, presence or absence of executive dysfunction. Variables that had a significant effect on survival on univariate analyses were included in multivariate analyses. The ALS Prognostic Index was generated by assigning weighted scores to each factor (higher scores for worse prognoses) guided by the hazard ratio (HR) suggested by the multivariate Cox proportional model. Continuous variables with significant survival effects on both univariate and multivariate analysis were converted to categorical variables. Patients were classified into risk groups based on total index score, with higher scores associated with worse outcome.		
Final tool	Factor		Points
	Site of disease onset	Bulbar or respiratory onset	1
		Spinal onset	0
	ALS functional rating scale revised slope	<0.25 points/month	0
		0.25-0.44 points/month	1
		0.45-0.99 points/month	2
		≥1.0 points/month	3
	Executive dysfunction	Present	1
		Absent	0
Interpretation	Score		

Reference	Elamin 2015[197]		
	0-1: low risk 2-3: medium risk ≥4: high risk		
Validation	Poor prognosis was defined as death within 25 months of disease onset Good prognosis was defined as survival of 50 months or more from onset High risk classification PPV of poor prognosis NPV of good prognosis Low risk classification PPV of good prognosis NPV of poor prognosis	 Internal validation cohort 85.7% 100% 60.1% 100%	 External validation cohort 73.3% 93.3% 59.1% 100%
Comments	High risk of bias due to analysis High applicability Usability is low because it's unclear what the three levels of risk mean for any single patient This work leading to these results was supported by Health Seventh Framework Programme (FP7/2007-2013) (Grant agreement number 259867), the Health Research Board (Grant number H01300), the Italian Ministry of Health (Ministero della Salute, Ricerca Sanitaria Finalizzata, 2010) (Grant RF-2010-2309849) as well as Research Motor Neuron (previously named Motor Neuron Disease Research Foundation), and Research (ALS-Care Project), granted by Italian Ministry of Education, University and Research The authors reported no conflict of interests		

Reference	Gordon 2013[252] Gordon 2010[251]
NOTE	The ALS functional rating scale revised multivariable model from Gordon 2013 was used for this review. The model from Gordon 2010 utilised the same patients.
Study type and analysis	Cohort study conducted in France Cox Proportional Hazards Regression model utilised Outcome was mortality
Number of	N=2037 (1471 died)

Reference	**Gordon 2013[252]** **Gordon 2010[251]**
participants and characteristics	Inclusion criteria: people with probable, laboratory-supported probable, or definite ALS according to the revised El Escorial criteria Single centre study of consecutive patients presenting between 1999 and 2009. Tracheostomy rate <5%
Prognostic variable(s)	Age Site of onset (limb versus bulbar) Diagnostic delay (≤7 months, 7.1-10.6, 10.7-17, >17) ALS functional rating scale revised score (≤35, 36-39, 40-42, >42)
Confounders OR stratification strategy	Region of residence (Paris, not Paris), year of first visit, sex,
Outcomes and effect sizes	Age [no results reported] Site of onset (HR 0.68 [0.61 to 0.77]) Diagnostic delay (≤7 months) 7.1-10.6 (HR 0.95 [0.82 to 1.09]) 10.7-17 (HR 0.80 [0.70 to 0.93]) >17 (HR 0.56 [0.48 to 0.66]) ALS functional rating scale revised score (≤35) 36-39 (HR 0.69 [0.60 to 0.80]) 40-42 (HR 0.46 [0.40 to 0.53]) >42 (HR 0.33 [0.28 to 0.39])
Comments	No serious risk of bias No funding stated

Reference	**Kaufmann 2005[317]**
Study type and analysis	Prospective cohort study conducted in USA Multivariable analysis utilised using a Cox's proportional hazards model Outcome is mortality or tracheostomy

Reference	Kaufmann 2005[317]
Number of participants and characteristics	N=274 but 7 excluded because lost to follow-up Therefore, N=267 (103 died [79] OR had tracheostomy [24], 164 survived) Mean (SD) age at onset was 58 (13), 146 male, 121 female 17 patients removed from final model due to incomplete forced vital capacity information Consecutive patients initially visiting centre between December 1999 and July 2003. Mean follow-up 12 months. Inclusion criteria: people with suspected, possible, probable, or definite ALS according to the El Escorial Criteria Exclusion criteria: none detailed Those who died or had tracheostomy used NIV more than those who survived (57.3% versus 22%) No significant riluzole use difference between groups No stratification by NIV
Prognostic variable(s)	ALS functional rating scale revised at baseline (continuous) Forced Vital Capacity (forced vital capacity), % predicted (continuous) Symptom duration at baseline in years Age at baseline in years Site of symptom onset (upper extremity, lower extremity, bulbar, respiratory)
Confounders OR stratification strategy	Final model (250 patients) Sex (male, female), Riluzole use (ever, never)
Outcomes and effect sizes	(250 participants – 17 had no forced vital capacity recorded) ALS functional rating scale revised at baseline (HR 0.93 [0.9 to 0.96]) Forced Vital Capacity (forced vital capacity), % predicted (HR 0.99 [0.98 to 1.01]) Symptom duration at baseline in years (HR 0.74 [0.63 to 0.87]) Age at baseline in years (HR 1.02 [1.01 to 1.04]) Site of symptom onset (upper extremity was reference) Lower extremity (HR 1.17 [0.66 to 2.07]) Bulbar (1.81 [0.99 to 3.33]) Respiratory (6.52 [2.72 to 15.60])
Comments	Final model: High risk of bias due to selection bias and detection bias Supported by an Irving Scholar Award, K12 Award, Muscular Dystrophy Association “Wings over Wall Street”, NINDS R01 NS 48125 , NINDS R01 NS 48555.

Reference	**Marin 2011[376]** **Gil 2007[240]**
NOTE	Marin 2011 and Gil 2007 recruited ALS patients from the same centre in concurrent time periods. Therefore only data from Marin 2011 has been included in this review to avoid double counting. Marin 2011 was chosen in preference because it better met the review protocol.
Study type and analysis	Cohort study conducted in France Cox Proportional Hazards Regression model utilised Outcome was mortality
Number of participants and characteristics	N=92 (74 died) Inclusion criteria: people with laboratory probable, probable, or definite ALS according to Airlie House criteria. Single centre study of patients diagnosed between 1997 and 2007. Median (IQR) age at diagnosis: 66 (57-73)
Prognostic variable(s)	Weight variation from usual weight. Usual weight defined as weight 6 months before symptoms began (per 5% decrease) Age Bulbar onset ALS functional rating scale at diagnosis Forced vital capacity at diagnosis (≥80% versus <80%) Diagnostic delay
Confounders OR stratification strategy	Sex Manual muscular testing Airlie House criteria at diagnosis (definite or probable versus possible)
Outcomes and effect sizes	Weight variation from usual weight (HR 1.31 [1.08 to 1.60]) Age [no results reported] Bulbar onset [no results reported] ALS functional rating scale at diagnosis [no results reported] Forced vital capacity at diagnosis (≥80% versus <80%) [no results reported] Diagnostic delay [no results reported]
Comments	High risk of bias due to selection bias Authors declare no competing interests

Reference	Paganoni 2011[449]
Study type and analysis	Cohort study conducted in USA Outcome was mortality or tracheostomy or permanently assisted ventilation Cox Proportional Hazards Regression model utilised
Number of participants and characteristics	N=427 (82 died) Mean (SD) follow-up: 335 (251) days Population from three clinical trial databases. Two of the trials were multicentre drug trials, one investigating Celecoxib and the other Topiramate. The final study was a single centre cohort study of sporadic or familial ALS. Mean (SD) age: 54 (13) 64% male, 36% female. Inclusion criteria: people with probable or definite ALS according to the El Escorial criteria
Prognostic variable(s)	Age (years) Time from symptom onset (unclear units) Forced vital capacity
Confounders OR stratification strategy	BMI BMI^2
Outcomes and effect sizes	Age (HR 1.03 [1.01 to 1.05]) Time from symptom onset (HR 0.99 [0.99 to 0.99]) Forced vital capacity (HR [0.97 [0.96 to 0.98])
Comments	High risk of bias due to selection bias and detection bias Supported by the Muscular Dystrophy Association and the Digiovanni Research Fund

Reference	Pailisse 2005[451]
Study type and analysis	Cohort study conducted in France Outcome was mortality Cox Proportional Hazards Regression model utilised
Number of	N=1398 (547 died)

Reference	Pailisse 2005[451]
participants and characteristics	Data taken from a large prospective open label study of riluzole Inclusion criteria: adults with probable or definite ALS Exclusion criteria: serum alanine aminotransferase or aspartate aminotransferase levels over twice the upper limit of normal. All patients were on riluzole Mean (SD) age: 63 (12) 777 male, 621 female
Prognostic variable(s)	Age (≤65, >65) Disease duration (>2 years, <2 years)
Confounders OR stratification strategy	Plasma creatinine, atrophy, pyramidal signs, spasticity, fasciculations, muscle strength, cough (Norris), swallowing (Norris), SVC
Outcomes and effect sizes	Age (RR 0.617 [0.517 to 0.736]) Disease duration (RR 0.456 [0.359 to 0.580])
Comments	High risk of bias due to selection bias and detection bias No funding stated

Reference	Peysson 2008[462]
Study type and analysis	Retrospective cohort study conducted in France Outcome was mortality or tracheostomy Cox Proportional Hazards Regression model utilised
Number of participants and characteristics	N=33 (24 died, 3 had tracheostomy) Inclusion criteria: People (>18 years) with probable or definite ALS by El Escorial criteria who started on NIV Exclusion criteria: concomitant neurological disease, severe pulmonary disease, suspected or possible ALS according to El Escorial criteria. People who refused NIV were excluded from the study. Recruitment: consecutive patients in one centre from 1996 to 2004. Median (range) age at diagnosis: 60 (32-84) 10 bulbar, 23 limb onset. Median (range) time from symptoms to NIV: 28 months (7-96)

Reference	Peysson 2008[462]
	Median (range) time from diagnosis to NIV: 15 months (0-82)
Prognostic variable(s)	Age at diagnosis Site of onset (bulbar, limb)
Confounders OR stratification strategy	Mechanically assisted cough (MAC) Oxygenotherapy
Outcomes and effect sizes	Age at diagnosis (OR 1.06 [1.02 to 1.12]) Site of onset (OR 1.71 [0.60 to 4.90])
Comments	No serious risk of bias No funding stated

Reference	Pinto 2012[465]
Study type and analysis	Cohort study conducted in Portugal Outcome was mortality Cox Proportional Hazards Regression model utilised
Number of participants and characteristics	N=254 (240 died) Inclusion criteria: people with probable or definite ALS as defined by the El Escorial criteria. Exclusion criteria: people who: >80 or <20 years of age, with lung disorders, polyneuropathy, cardiac insufficiency, pace-maker, diabetes mellitus, unable to tolerate the recumbent position, with a confirmed ALS diagnosis longer than 3 months before study entry, when the region of disease onset could not be identified. Recruited from 1 centre between 1997 and 2006 Mean (SD) age: 61 (11)
Prognostic variable(s)	Onset form (bulbar, limb) Age Diagnostic delay (months) Forced vital capacity (<80%, ≥80%)
Confounders OR stratification	Mean phrenic nerve stimulation (<0.4 mV, ≥0.4 mV)

Reference	Pinto 2012[465]
strategy	
Outcomes and effect sizes	Onset form (HR 2.081 [1.546 to 2.186]) Age (HR 1.286 [0.985 to 1.677]) Diagnostic delay (HR 2.247 [1.698 to 2.973]) Forced vital capacity (HR 1.492 [1.118 to 1.991])
Comments	High risk of bias due to selection bias Work was supported by a grant from 'Fundacao para Ciencia e a Tecnologia': SFRH/BD/30714/2006

Reference	Wolf 2014[584]
Study type and analysis	Cohort study conducted in Germany (data taken from a prospective, population-based ALS registry) Multiple logistic regression model utilised Outcome was one-year mortality (or tracheostomy). "Time was measured in months from date of diagnosis to death or to tracheostomy"
Number of participants and characteristics	N=200 (24 lost during early follow-up [17 after diagnosis and 7 after first follow-up]) and were excluded. This left N=176 (96 male, 80 female) One-year mortality was 34% (60 patients), mean (SD) age at diagnosis: 66 (10) Inclusion criteria: people newly diagnosed with possible, probable and definite ALS according to the revised El Escorial criteria, 18 years and over Exclusion criteria: people with pure lower or pure upper motor neurone disease Consecutive patients were enrolled from October 2009 to September 2012. Population patients were taken from was the Rhineland-Palatinate state in south-west Germany. Minimum follow-up was 18 months. No patients reported as began study with gastronomy or NIV BMI 6 months before diagnosis was based on patients statements and susceptible to inaccuracy
Prognostic variable(s)	BMI_Diff (difference between BMI at diagnosis and 6 months before) (<1, 1-<2, ≥2) (87 patients, 31, 55) ALS functional rating scale (quintile 1: 37-40, quintile 2: 34-36, quintile 3: 31-33, quintile 4: 27-30, quintile 5: 00-26) Age (≤65, 66-75, >75); Site of onset (bulbar, limb); Duration of disease (0-6 months, 7-12, 13-24, ≥25)
Confounders OR stratification	

Reference	Wolf 2014[584]
strategy	
Outcomes and effect sizes	BMI_Diff: (<1 is reference) 1-<2 (OR 1.26 [0.39 to 4]) ≥2 (OR 2.8 (1.04 to 7.7) ALS functional rating scale (quintile 1: 37-40 is reference) Quintile 2: 34-36 (OR 1.8 [0.38 to 8.6]) Quintile 3: 31-33 (OR 2.6 [0.55 to 12]) Quintile 4: 27-30 (OR 12.9 [2.8 to 60]) Quintile 5: 00-26 (OR 33.8 [6.7 to 170]) Age (≤65 is reference) 66-75 (OR 1.13 [0.45 to 2.85]) >75 (OR 6.2 [1.5 to 25]) Duration of disease (0-6 months is reference) 7-12 (OR 0.42 [0.15-1.17]) 13-24 (OR 0.45 [0.14-1.4]) 25+ (OR 0.05 [0.01 to 0.48])
Comments	High risk of bias due to selection bias and detection bias Authors declare no competing interests

G.4 Organisation of care

Study	Aridegbe 2013[31]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=417)
Countries and setting	Conducted in United Kingdom; setting: clinics in Sheffield, South Yorkshire
Line of therapy	1st line
Duration of study	Follow up (post intervention): maximum 66 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El-Escorial criteria
Stratum	Overall

Study	Aridegbe 2013[31]
Subgroup analysis within study	Not applicable
Inclusion criteria	Review of records including: diagnoses of 'motor neurone disease', 'motor neuron disease', 'motor neuropathy', 'anterior horn cell disease' and 'amyotrophic lateral sclerosis; between 1997 and 2010
Exclusion criteria	Normal electrophysiology reports; never attended a Sheffield clinic; not diagnosed with MND; date of diagnosis outside study period.
Recruitment/selection of patients	Patients identified from the records held by the Electrophysiological Department of the Royal Hallamshire Hospital as it holds the up-to-date databases documenting patient information and full reports of nerve conduction studies and electromyography.
Age, gender and ethnicity	Age - median (IQR): 63.8 years (58.2-71.8) general neurology clinic group; 62.6 years (55.7-71.3) Multidisciplinary clinic group. Gender (M:F): 102/60 in the general neurology clinic group; 140/115 in the multidisciplinary clinic group. Ethnicity: not reported
Further population details	
Extra comments	There was a statistical significant difference between the two groups for survival at census (15 (9%) in the general neurology clinic group versus 95 (37%) in the multidisciplinary clinic group, p<0.001; site of onset (bulbar: spinal) 60:102 (37%; 63%) versus 69:185 (27%:73%), p=0.03; riluzole use 88 (55%) versus 222 (89%), p<0.001; NIV use 8 (5%) versus 73 (29%), p<0.001
Indirectness of population	No indirectness
Interventions	(n=255) Intervention 1: MDT care - MDT care alone. Team of neurologists, specialist nurses, a respiratory physiologist, physiotherapists and a dietician in a single clinic at the Royal Hallmashire Hospital. The extended team also includes research nurses, occupational therapists, speech and language therapists and social workers. Patients put in contact with local hospice when it was felt they may benefit from this service. Outside of clinic patients are visited regularly from the time of their diagnosis by an outreach team of physiotherapists and occupational therapists. All patients are given access to MND helpline operated daily by a specialist nurse. Also in contact with MND Association regional representative. Duration: patients were seen every 8-10 weeks mean, longer for some patients such as PLS patients (every 3 months), and patients with a very slow disease course. Concurrent medication/care: Riluzole use 89%, NIV use 29%, gastrostomy use 26% (n=162) Intervention 2: Usual care - usual care alone. General neurology clinics at the Royal Hallamshire Hospital (four), neurologists leading the clinics had a primary interest that was not MND. No regular monitoring of the respiratory or nutritional status of the patients. Duration: reviewed less frequently than MDT patients, every 6 months mean. Concurrent medication/care: Riluzole use 55%; NIV use 5%; gastrostomy use 19%

Study	Aridegbe 2013[31]
Funding	Other (UK Motor Neurone Disease Association)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE ALONE versus USUAL CARE ALONE Protocol outcome 1: Survival - Actual outcome: survival from symptom onset; HR 0.58 (95%CI 0.46 to 0.73) reported; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: survival from time of diagnosis; HR 0.51 (95%CI 0.41 to 0.64) reported; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; number of unplanned hospital admissions; reduction in crisis management interventions; hospital length of stay at Define; ALSFRS-R scale

Study	Creemers 2014[150]
Study type	RCT (cluster randomised; parallel)
Number of studies (number of participants)	1 (n=132)
Countries and setting	Conducted in Netherlands; setting: outpatient department of a hospital or rehabilitation centre
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Method of assessment/diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable: not applicable
Inclusion criteria	ALS patients, no more details given (see exclusion criteria)
Exclusion criteria	Cognitive dysfunction (Mini-Mental State Examination score </=20); insufficient mastery of the Dutch language; and institutionalisation. Carers' exclusion criteria was insufficient mastery of the Dutch language.
Recruitment/selection of patients	The rehabilitation medicine consultant of each participating ALS team introduced the study to the eligible patients and their most important informal caregiver.
Age, gender and ethnicity	Age - mean (SD): 63 (11) for case management group + usual care group; 62 (11) for usual care group. Gender (M:F): 121/11. Ethnicity: not reported.
Further population details	

Study	Creemers 2014[150]
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: MDT care plus coordinator - MDT care plus a coordinator. Case management was performed at the individual participant level. The predominant focus of the patient advocacy case management model is more comprehensive coordination of services across the continuum of care, viewed from the patient perspective. Case management was provided by 2 experienced occupational therapists, specialised in ALS care and trained in client-centred practice, who used a client-centred approach to guide the participants. The case manager had an independent position outside, but in close contact with, the ALS team. The Case Manager's role was to be attentive to the needs of the participants. The case manager provided participants all of the information needed to allow individual choices about how their needs would be met. They visited participants at home every 3 months, between visits, contact was made by telephone, email or in writing. At the first visit, the case manager provided participants with additional oral and written information about the procedures and objectives of the case management intervention. The starting point for the case management was any somatic, psychosocial, environmental or care issue raised by the participants and responded to this with one or more steps. This was in addition to: Usual care in the Netherlands is neuropalliative care by multidisciplinary, secondary care teams. Such teams consist of a rehabilitation medicine consultant, an occupational therapist, physical therapist, speech pathologist, dietician, social worker, psychologist, and consultant physicians (in neurology, respiratory, and gastroenterology). Community and social services also have an important role in care for patients with ALS and their caregivers. General practitioners, district nurses, home care services, paramedics, social workers and voluntary workers participate in these services. Duration 12 months. Concurrent medication/care: not applicable. (n=61) Intervention 2: MDT care - MDT care alone. Usual care in the Netherlands is neuropalliative care by multidisciplinary, secondary care teams. Such teams consist of a rehabilitation medicine consultant, an occupational therapist, physical therapist, speech pathologist, dietician, social worker, psychologist, and consultant physicians (in neurology, respiratory, and gastroenterology). Community and social services also have an important role in care for patients with ALS and their caregivers. General practitioners, district nurses, home care services, paramedics, social workers and voluntary workers participate in these services. Duration 12 months. Concurrent medication/care: not applicable.
Funding	Academic or government funding (ZonMw, the Netherlands Organisation for Health Research and Development within the Programme Palliative Care grant agreement, and the Netherlands ALS Foundation).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE PLUS A COORDINATOR versus MDT CARE ALONE Protocol outcome 1: Health related quality of life	

Study	Creemers 2014[150]
- Actual outcome: caregiver strain index (CSI) at 12 months; group 1: mean 7.9 (SD 2.9); n=29, group 2: mean 7.3 (SD 3.2); n=24; caregiver strain index (CSI) 0-13 (top=high is poor outcome); risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: ALSAQ-40 emotional functioning at 12 months; group 1: mean 22.8 (SD 16.4); n=30, group 2: mean 19.1 (SD 14.7); n=27; ALSAQ-40 emotional functioning scale 0-100 (top=high is poor outcome); risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: ALSFRS-R scale at 12 months - Actual outcome: ALSFRS-R at 12 months; group 1: mean 24 (SD 9.3); n=28, group 2: mean 25.1 (SD 11.5); n=25; ALSFRS-R 0-48 (top=high is good outcome); risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Survival; number of unplanned hospital admissions; reduction in crisis management interventions; hospital length of stay

Study	Chio 2006[116]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=221)
Countries and setting	Conducted in Italy; setting: patients from 2 Tertiary ALS centres or 26 neurology departments in Piemonte, Torino and Veruno
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients on the Piemonte and Valle d'Aosta Register for ALS (PARALS)
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients on the PARALS
Age, gender and ethnicity	Age - other: not reported. Gender (M:F): not reported. Ethnicity: not reported
Further population details	

Study	Chio 2006[116]
Indirectness of population	No indirectness
Interventions	(n=97) Intervention 1: MDT care - MDT care alone. 2 Tertiary ALS centres with interdisciplinary teams; management of symptoms based on best available evidence; PEG proposed for weight loss >10% or episodes of severe choking; NIV offered for respiratory symptoms, when FVC was <50% of that predicted or when nocturnal pulse oximetry showed marked desaturations; Riluzole available free of charge from 1996 and offered to all patients. Duration: patients seen every 8 weeks approximately. Concurrent medication/care: not reported. (n=124) Intervention 2: Usual care - usual care alone. 26 neurology departments. The patients did not undergo regular evaluations of nutritional or respiratory status, and therefore received less attention towards the early introduction of PEG, NIV and palliative care. Duration: at least every 6 weeks. Concurrent medication/care: not reported
Funding	Other (Regione Piemonte, Ricerca Sanitaria Finalizzata, and Compagnia San Paolo, Torino, Italy)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE ALONE versus USUAL CARE ALONE Protocol outcome 1: Survival - Actual outcome: Median survival from onset; other: median 1080 versus 775 days, p=0.008; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Hospital length of stay - Actual outcome: Mean duration of hospital stay; group 1: mean 5.8 days (SD 9.5); n=97, group 2: mean 12.4 days (SD 31.6); n=124; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; number of unplanned hospital admissions; reduction in crisis management interventions; ALSFRS-R scale

Study	Cordesse 2015[145]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=2452)
Countries and setting	Conducted in France
Line of therapy	Not applicable

Study	Cordesse 2015[145]
Duration of study	Follow up (post intervention): 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All patients had a diagnosis of probable, possible or definite ALS according to the El Escorial criteria
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Only patients whose diagnosis was definitely established at the time of enrolment in the centre or in the network
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): 62.6 (11.7) patients before network 61.2 (12.9) in network. Gender (M:F): 52.8% male in before network group 54.8% in network group . Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	Intervention 1: MDT care plus co-ordinator - MDT care plus a co-ordinator. Community care network – 4 coordinators of care, one psychologist and one physiotherapist. In addition to: five neurologists, one pneumologist, one gastroenterologist, 2 speech therapists, one physiotherapist, 2 specialised nurses, one dietician and 3 social workers. Duration 3 years. Concurrent medication/care: Not given by group Intervention 2: MDT care - MDT care alone. Community care network without co-ordinator. Duration 5 years. Concurrent medication/care: Not given for each group.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE PLUS A CO-ORDINATOR versus MDT CARE ALONE Protocol outcome 1: Survival - Actual outcome: Survival; HR 0.549 (95%CI 0.439 to 0.687) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Health related quality of life; Number of unplanned hospital admissions; Reduction in crisis management interventions; Hospital length of stay; ALSFRS-R scale

Study	Rooney 2015[495]

Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=719)
Countries and setting	Conducted in Irish Republic; Setting: Hospitals and community based services in the Republic of Ireland and Northern Ireland.
Line of therapy	Not applicable
Duration of study	Other: Diagnosed within 6 years of each other
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	ALS; aged 15 and over; Inclusion on the Register required: extensive confirmatory measures such as clinical examination by a specialist, direct chart review and assessment by a neurophysiologist.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Retrospectively collected from a register.
Age, gender and ethnicity	Age - Mean (SD): Ireland: MDT 62.8 (11.1); general care 68.6 (10.8); Northern Ireland: MDT 65.9 (11.6). Gender (M:F): 389/330. Ethnicity: Not reported
Further population details	
Indirectness of population	Serious indirectness: Patients were aged 15 years and above
Interventions	(n=340) Intervention 1: MDT care plus co-ordinator - MDT care plus a co-ordinator. On each visit the patient and his/her carer saw a neurologist with specialist expertise in AL, a specialist ALS nurse and a neuromuscular multidisciplinary team including a physiotherapist, occupational therapist, speech and swallow therapist, and dietician, and given direct next day access to Respiratory Medicine where indicated. An ALS Care Network Coordinator supported patients throughout the disease as well as provide education to non-specialist allied health professionals to facilitate timely coordinated care. Duration Each visit was between 2 and 3 hours. Concurrent medication/care: NIV introduction aligned to EFNS guidelines. Initiated either in hospital or at home by a specialist nurse with training in management of respiratory impairment in ALS. Radiological gastrostomy tube insertion offered to those experiencing a weight loss of greater than 10% of baseline or increasing dysphagia, and preservation of respiratory function (sniff nasal inspiratory pressure >40cm H20 and forced vital capacity >50% predicted). Gastrostomy is also offered to those with declining respiratory function following successful initiation of NIV. 22.9% received gastrostomies. (n=208) Intervention 2: Usual care plus co-ordinator. ALS/MND Care Network with a ALS Care Network Coordinator, with a nursing background, appointed to coordinate the care of patients with ALS in NI from diagnosis to death. The coordinator makes home visits, attends clinic appointments, and is a source of support and education to patients and

	their local allied health professionals to ensure optimal timeliness and quality of care. A multidisciplinary ALS clinic, comparable to that in the RoI, was not set up in NI until the end of the study period. . Duration Not reported. Concurrent medication/care: Patients are referred to the local respiratory physician, who initiates NIV according to local clinical practice and in accordance with NICE guidelines. Radiological gastrostomy tube insertion is offered to those patients in the RoI and NI experiencing a weight loss of greater than 10% of baseline or increasing dysphagia, and preservation of respiratory function (sniff nasal inspiratory pressure >40cm H20 and forced vital capacity >50% pr4edicted). Gastrostomy is also offered to those with declining respiratory function following successful initiation of NIV in both jurisdictions. 29.2% received gastrostomies. Comments: The NI cohort also attended local neurology services but within the setting of an established and integrated care network supported by a trained care worker. (n=169) Intervention 3: Usual care - Usual care alone. Those not attending the specialised multidisciplinary clinic attended general neurology clinics and did not access integrated specialist multidisciplinary care. . Duration Not reported. Concurrent medication/care: NIV introduction aligned to EFNS guidelines. Initiated either in hospital or at home by a specialist nurse with training in management of respiratory impairment in ALS. Radiological gastrostomy tube insertion offered to those experiencing a weight loss of greater than 10% of baseline or increasing dysphagia, and preservation of respiratory function (sniff nasal inspiratory pressure >40cm H20 and forced vital capacity >50% predicted). Gastrostomy is also offered to those with declining respiratory function following successful initiation of NIV.
Funding	Academic or government funding (The Health Research Board Interdisciplinary Capacity Enhancement Programme; the Health Cooperation programme and the project EUROMOTOR (No259867), from the European Joint Programme in Neurodegeneration (SOPHIA and ALS-CARE) and the Charities Research Motor Neurone and the Irish Motor Neurone Disease Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE PLUS A CO-ORDINATOR versus USUAL CARE PLUS CO-ORDINATOR

Protocol outcome 1: Survival
- Actual outcome: Survival at 6 years; HR 0.59 (95%CI 0.49 to 0.71) Reported; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Health related quality of life; Number of unplanned hospital admissions; Reduction in crisis management interventions; Hospital length of stay; ALSFRS-R scale

Study	**Traynor 2003**[551]

Study	Traynor 2003[551]
Study type	Prospective cohort study
Number of studies (number of participants)	1 (n=344)
Countries and setting	Conducted in Irish Republic; setting: 9 general neurology clinics in Ireland; one multidisciplinary clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: 5 years
Method of assessment of guideline condition	Method of assessment/diagnosis not stated: the people were attendees at the clinic for more than 2 occasions and had been diagnosed with ALS, no details of assessment of ALS method given
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients from the ALS clinic if they were reviewed on more than 2 occasions and the first occurs within 1 year of the time of diagnosis.
Exclusion criteria	Not reported
Recruitment/selection of patients	Patients attending the clinics
Age, gender and ethnicity	Age - mean (range): 65.6 (25.0-92.1) general neurology clinic and 60.1 (19.7-83.0) in the multidisciplinary clinic. Gender (M:F): 147/115 in the general neurology clinic; 47/35 in the multidisciplinary clinic. Ethnicity: not reported.
Further population details	
Indirectness of population	No indirectness
Interventions	(n=82) Intervention 1: MDT care - MDT care alone. Multidisciplinary clinic that combined the existing infrastructure of community services and the services of the Irish Motor Neurone Disease Association with a hospital based specialist team. The core MDT included neurologists, specialist nurses, physical, occupational, and speech therapists, and a pulmonologist, nutritionist, psychologist and social worker. A representative from the IMNDA also attended the clinic. Patients who were in terminal stages of illness, and couldn't attend the clinic were visited by a specialist ALS nurse in their home and palliative care was provided by the ALS clinic staff and local hospice home care services. Duration Patients were reviewed approximately every 6 weeks and contacted by telephone at least once per month. Concurrent medication/care: Riluzole use n=80 (98.8%); NIPPV n=5 (6.1%). (n=262) Intervention 2: Usual care - usual care alone. Neurology clinics staffed by neurologists whose primary interest was not ALS. Clinics were not staffed by ancillary service professionals, or by a liaison from the IMNDA. Pulmonary function tests were not routinely evaluated. Less attention paid to early introduction of gastrostomy feeding or NIPPV and there was no well-defined pathway for rapid hospital admission for urgent intervention or palliative care.

Study	Traynor 2003[551]
	Duration: reviewed less frequently than MDT clinic, that is, biannually. Concurrent medication/care: Riluzole use: n=149 (60.6%); NIPPV use: n=7 (2.7%).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE ALONE versus USUAL CARE ALONE Protocol outcome 1: Survival - Actual outcome: Survival from time of diagnosis; HR 1.47 (95%CI 1.06 to 2.06) reported; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; number of unplanned hospital admissions; reduction in crisis management interventions; hospital length of stay; ALSFRS-R scale

Study	Zoccolella 2007[593]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=130)
Countries and setting	Conducted in Italy; setting: Puglia, Southern Italy
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial World Federation Neurology criteria and Airlie-House revised version
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Newly diagnosed ALS cases from 1 January 1998 to 31 December 1999
Exclusion criteria	Not reported
Recruitment/selection of patients	From a prospective registry of all newly diagnosed ALS cases
Age, gender and ethnicity	Age - median (range): 66 (43.9-80.2) in the general neurological clinics and 64.2 (18.9-77.9) in the multidisciplinary clinics. Gender (M:F): 30/12 in general neurology clinics; 48/36 in multidisciplinary clinics. Ethnicity: not reported.

Study	Zoccolella 2007[593]
Further population details	
Extra comments	Riluzole use in the general neurological clinics was 18 (43%) and 55 (66%) in the multidisciplinary clinics, p=0.02
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: MDT care - MDT care alone. 4 Multidisciplinary ALS clinics, including neurologists with expertise in ALS, a pulmonologist, a nutritionist, a psychologist and physical and speech therapists. Nutritional status and bulbar function closely monitored and patients informed of the benefits of early percutaneous gastrostomy (PEG) placement, according to well established criteria. Patients were followed by ALS MDC if they were visited in at least 2 occasions. Duration: patients were reviewed approximately every 3 months. Concurrent medication/care: 55 (66%) riluzole use; PEG 5 (6%); NIV 2 (2.5%). (n=42) Intervention 2: Usual care - usual care alone. 19 clinics in neurology departments. The neurologist in charge in these centres was a general neurologist whose primary interest was not ALS. In these centres less attention was given to pulmonary function tests and introduction of PEG or non-invasive ventilation (NIV). Duration ALS patients are reviewed less frequently than patients attending MDC (6 months mean). Concurrent medication/care: Riluzole use 18 (43%); PEG 1 (2.5%), NIV 1 (2.5%).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT CARE ALONE versus USUAL CARE ALONE

Protocol outcome 1: Survival
- Actual outcome: Median survival time at 2 years; other: median survival time 17.6 months (MDT) versus 18 months (neurology clinic), log rank= 0.11, p=0.76; risk of bias: very high; indirectness of outcome: no indirectness
- Actual outcome: Adjusted survival at 12 months from diagnosis; HR 0.91 (95%CI 0.44 to 1.89) reported; risk of bias: very high; indirectness of outcome: no indirectness
- Actual outcome: Adjusted survival at 4 years; HR 1.4 (95%CI 0.88 to 2.22) reported; risk of bias: very high; indirectness of outcome: no indirectness
- Actual outcome: Median survival time from diagnosis - bulbar-onset at 2 years; other: median 11.7 months (range 2.9-27.2) MDT versus 23 months (range 7.2-36.8); risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcomes not reported by the study	Health related quality of life; number of unplanned hospital admissions; reduction in crisis management interventions; hospital length of stay; ALSFRS-R scale

G.5 Psychological support

Study	Aoun 2012[27]
Aim	To explore the experiences of MND family carers through to bereavement; including do experiences differ according to prolonged grief status and what are the implications for service delivery.
Population	Bereaved spouses (N=16) of patients with MND (13 women and 3 men). Mean age = 65.19 years, SD = 9.28 (range = 50-82 years). At time of interview, participants had been bereaved for between 1 - 4 years (mean = 27.5 months, SD = 13.6).
Study design	Interview
Methods and analysis	Semi-structured face to face interviews, recorded and transcribed. Interviews began with the question 'tell me about your experience as a carer', and included issues of diagnosis, palliative care, and coping. Thematic analysis was used to analyse the data; emerging ideas were summarised and developed into themes, then cross-checked with other transcripts to develop, refine and collapse themes. Three authors independently reviewed the transcripts and three participants (selection not described) validated the analysis. Any differences in interpretation were further examined until authors were satisfied that themes represented data.
Themes with findings	The work of MND family carers: Practical tasks. Participants discussed the many practical responsibilities they have as carers Exhaustion and trauma. Participants discussed how tasks, particularly those through the night, resulted in exhaustion and interfered with their recreation, sleep and exercise.
	The change in relationship from spouse to carer: Role changes. Participants discussed how their role changed from wife/husband to that of a 'nurse' or 'carer'. Learning new tasks. Participants discussed how they adopted the responsibilities that used to be undertaken by their loved one. Decrease in relationship intimacy. Participants noted a reduction in intimacy in the relationship, due to the change in their role and levels of exhaustion.
	Family caring as a series of losses: Constant loss. Participants described MND as a series of, often fast-paced, losses. Hopelessness. Participants frequently reported feelings of hopelessness.
	Coping mechanisms of family carers: Acceptance versus non-acceptance of diagnosis and death. Some participants discussed how they accepted the notion of their partner dying, while others did not. 'Switching off' affect. Some participants discussed 'switching off' their emotions in order to manage their caring responsibilities. Accommodation of loss. Some participants discussed how their initial grief following the death of their loved one had not gone away but they had grown to live alongside it
	Supportive and palliative care experiences of family carers:

Study	Aoun 2012[27]
	Diagnosis and absence of compassion. Participants reported an absence of compassion from medical professionals in diagnosis and through the illness Timeliness of, and access to, palliative care. Participants reported variation in the availability and timeliness of palliative care. Although most acknowledged they could have used more support their primary aim was to care for their loved one 2 participants expressed dissatisfaction with inadequate level of respite services available to the high needs of MND patients. Bereavement care was not always offered following death and they felt alone. Carers who had a good rapport with the service provider and had more consistent services early on were more satisfied with service provision.
Limitations	None
Applicability of evidence	Applicable

Study	Bolmsjö 2001[69], Bolmsjö 2001a[68], Bolmsjö 2003[70]
Aim	To explore patients' and carers' experiences of MND, and challenge the notion that these groups (i) see it the same way as professionals and (ii) have the same attitudes as each other. To explore the experiences of close relatives of patients with ALS, including ethical issues, to suggest recommendations for support. To explore patients' way of communicating existential issues and what experiences are related to these.
Population	16 participants (8 patients, 6 women; and 8 close relatives, 4 women). Mean age patients = 60 years (range = 53-84 years); mean age relatives = 55 years (range = 38 - 72 years). Patients interviewed in 1997, relatives were interviewed in 2000. Inclusion criteria included patients who could communicate (verbally or through devices), and patients and relatives > 6-months post-diagnosis. Potential participants were chosen with the help of a counsellor and nurse at a neurological clinic.
Study design	Interview
Methods and analysis	Semi-structured interviews, with topics agreed on the basis of previous literature, research team experience, and discussion with colleagues/experts in field: the present situation; the future; information; confidence; meaning, guilt, respect. For each topic, participants were allowed to speak without interruption and until no further info emerged. Relatives' interviews were recorded and transcribed, but participants' interviews were not recorded due to speech difficulties. For patients, the interviewer made notes. Non-essential points were removed if they were not relevant for the study aim.
Themes with findings	Experiences concerning diagnosis and information: The way diagnosis was delivered was important for patients' wellbeing. Some carers reported a lack of sympathy in the diagnosis. There were variations in the way participants received the diagnosis and the method of delivery. Some carers reported having little knowledge of the disease

Study	Bolmsjö 2001[69], Bolmsjö 2001a[68], Bolmsjö 2003[70]
	prognosis, and some carers reported poor knowledge about the availability of supportive equipment.
	Increasing responsibilities: Carers discussed increased number of responsibilities.
	Limited freedom: Carers discussed feelings that the caring role allowed them little freedom.
	Meaning and guilt: Children and grandchildren provided meaning in life, however patients feared passing on the disease to their children.
	The need to confide in someone. Patients did not have a strong urge to confide in someone. Some of the carers expressed a need to confide in others.
	Experiences concerning physical inability: One patient discussed how they viewed their ventilator as a means of control and ability to terminate life, while another patient found the use of the ventilator upsetting.
	The competence of the professionals: Some of the patients expressed trust in the health professionals, while some carers expressed concerns that healthcare staff were not competent.
	Experiences concerning dying with dignity and respect for the person: No narrative; quotes reflect the importance of continuing to live in a way that reflects identity, retaining dignity in death, the importance of pain management and comfortable death.
	The future: Carers discussed how thoughts of the future were distressing and they preferred not to think or talk about it.
Limitations	Quotations interpreted on the basis of pre-specified categories. No details of researcher's role. Little information on analysis so rigour and reliability unclear. Analysis needed greater depth. Unclear if themes reached saturation.
Applicability of evidence	Applicable

Study	Brown 2008[89]
Aim	Explored patients' experiences and how they talk about living and coping with MND.
Population	N=13 with ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis. Aged 39-85 years of age. UK. Invited through the MND Associations' Regional Care Development Advisors.

Study	Brown 2008[89]
Study design	Qualitative study. Interviews.
Methods and analysis	Addressed the research question 'how do people live and cope through MND?' Organised into three parts, the patient narrative guided by the question 'I am interested in learning about how you are living and coping with MND.' Part two the researcher sought further details about particular issues. Part 3 was generic questions including 'what was important to you before your illness and what is important to you now?'
Themes with findings	Sustaining narrative storyline What remains positive in life, looking at what can be achieved rather than no longer possible, underpinned by hope, although knowing that survival may be an ambitious desire. One participant found increasing immobility hard, but keeping up with her family was a keen motivator to use new equipment.
	Enduring narrative storyline Quietly suffering when neither life nor death is the easier option. Enduring was a way to live through an unwelcome and difficult situation. One person through with stoic endurance reflected on others who he considers in worse situations.
	Preserving narrative storyline Fighting death and actively taking opportunities to increase one's chances of survival. Seeking hope and alternates between great optimism and depths of despair. One participant visited a naturalist and took alternative medications as means for a cure, and by eliminating toxins and having special nutrition. He did not stop using conventional medicine.
	Fracturing narrative storyline Loss, breakdown of self, fear of the future, denial of reality and living in a surreal notion of time. The thought of a lost future and having to abandon personal and professional plans is shattering. One participant expressed angst and confusion, reflecting fear and shock at how her life was spiralling out of control and out of time. Her descriptions and language were vivid and filled with descriptions of trauma. There was a glimmer of wanting to take some control, where she is given things to do to help herself. Focusing on what she can do for herself has its downside when the evidence is poor regarding the only medication, survival rates and projected level of physical deterioration which establishes a limit on practical things that she can perform, leaving her with denial. Avoiding the big picture to avoid acceptance as a strategy until things get worse.
Limitations	No details of researcher's role. Findings not validated with participants. Did not explicitly state themes of participants' experiences, more individual's analysis and quotes.
Applicability of evidence	Partially applicable, it featured how people talk about their experience, so was more focused on the storylines rather than themes of their experience.

Study	Cipolletta 2014[135]
Aim	To explore the experience of family members who live with ALS patients until their death
Population	N=13 Family members of people with ALS (Caregivers and non-caregivers)
Study design	Qualitative study. Semi-structured interviews.
Methods and analysis	Interview transcripts analysed using IPA. Bottom-up procedure to analyse transcripts, researcher produced codes form the data. Repeated reading of transcripts to become familiar with the narratives and annotate anything significant. Identified recurrent themes and linked quotes that expressed their essence of their contents. Themes then clustered into super-ordinate themes. Finally re-read all interviews to verify that identified themes were recognisable in the transcripts and all salient themes found. Disagreements between individual interpretations were resolved by discussion.
Themes with findings	Meaning of ALS: Sub-themes: The peculiarity of ALS and its comparison with other illnesses, the explanation of ALS, emotions, coping strategies, personal change, difficult choices: • ALS is described as a thief of identity and memories as they no longer perceived the patient as they used to. It did not leave any hope, is a death sentence and unpredictability of what will happen in the course of the disease throws the family into total uncertainty. It strips off everything apart from lucidity, so the patient is involved with their decay. • The explanation of ALS: Constantly and obsessively wondering what the cause of the disease is. • Most faced illness by trying to find a concrete solution; and or drawing strength from the patient, maintaining a positive attitude, expressing and avoiding emotions. • Illness radically changed the meaning that participants attributed to their lives. Principles and values guiding action, personal identity and weight given to the events changed, participants began to appreciate little things and fully live their lives. They felt lucky and privileged to be healthy, demonstrated increased awareness, became more human, sociable, mature and stronger and, at the same time, more catastrophic. • Difficult choices and crossroads that ALS continually put them in front of, dealing with NIV, euthanasia, or family management.
	Family relationships Sub-themes: centripetal versus centrifugal forces, family role changes, ALS as a family illness, ALS as a family solution, Openness towards the outside world: • Disruption in family dynamics, that made family members move closer together or else move away from each other • Illness triggered role changes such as one patient became a sort of baby and the family member a parent. • Perceived as a family illness as if it was contagious: the patient'[s sorrow also affected those around him/her. • In 1 case ALS represented a solution for ensuring the homeostasis of the family system. Allowed to stay together as it prevented the husband from communicating openly to his wife that he wanted to terminate their relationship

Study	Cipolletta 2014[135]
	• In 2 cases, ALS produced an unexpected openness, availability and permeability towards the outside context.
	Health care context Sub-themes: access to services, information, humanisation: • Overall the relationship with healthcare system perceived as unsatisfactory due to difficulty accessing services and finding information about the illness, this led them to learn on own through direct experience and the internet. • Family members felt there was a lack of humanity and empathy from physicians, they perceived this from the very beginning. • The inadequacy of the social-health context induced strong abandonment and loneliness feelings on the part of the families and the internet helped them face.
Limitations	No details of researcher's role. Reports sub-themes and gives general details of these but does not link the sub-themes to the specific aspects.
Applicability of evidence	Applicable

Study	Fanos 2008[205]
Aim	To explore the meaning of hope in individuals with ALS.
Population	n=16, mean age 54. Forbes Norris MDA/ALS Research Centre at California Pacific Medical Centre, San Francisco, USA. Convenience sample drawn from patients at a multidisciplinary clinic visit.
Study design	Interviews and questionnaire.
Methods and analysis	Themes of hope were identified and categorised. Two standardised instruments used: the forced vital capacity (FVC) scale and the ALS Functional Rating Scale-Revised (ALSFRS-R) for the questionnaire part of the study. For the qualitative part of the study participants were asked to describe the meaning of hope for them and ways to promote it. Interviews were 30 to 60 minutes long and were transcribed. They were also asked to rate themselves on the Hope Scale.
Themes with findings	Hope for a cure The majority expressed hope for a cure and some hoped they had been misdiagnosed. Some hoped to regain lost capacities such as activities they used to take part in. Some expressed desire to live long enough to see child or grandchildren reach adulthood. One participant's choice of life saving interventions – ventilator support was in hope they would find a cure. One participant took comfort in the bible that 'the laying on of hands one can be healed'.

Study	Fanos 2008[205]
	One participant told the physician 'you could cure me'.
	Social support The majority discussed the importance of social support from friends, family, the medical team, and even their pets. Particularly appreciating people who handled their disabilities in good humour, and remained calm when something amiss happened. Engagement with various activities such as bridge, quilting class, doing puzzles, and having a drink with friends kept them hopeful. One participant enjoyed entertainment by hospice workers or positive support from the ALS clinic. One participant enjoyed trips away to maintain a hopeful attitude. Another spending time with loved ones and appreciating the beauty of nature.
	Search for information A lot actively sought the latest research concerning ALS. Using internet, internet groups, and travelling to countries outside the US for treatments. Many found coming into the clinic helpful, being involved in on-going research studies, and were grateful for straight talking of the people in the ALS clinic with information. However some also found seeing others at the Clinic with later stages of MND was distressing. Hope that research would lead to improvement and ultimately a cure. Were happy to participate in various research trials, which may not ultimately help them but may for people in the future with MND.
	Spiritual beliefs Many called on an existing belief in a higher power. Several hoped that God would grant them a miracle and cure them. Some hoped for a better afterlife, and comfort in heaven and seeing lost loved ones. Many tried to find meaning in their suffering. Hoping to move to a position of acceptance.
	Limiting the impact of others Many expressed themes of intrusion of the disease, not being able to continue with their lives as well as limiting the impact of their illness on their loved ones. Some hoped their illness would not progress too rapidly, so they could remain active and independent as long as possible. Many were grateful for technology such as wheelchairs for mobility. Many hoped their loved ones would not suffer.
	Adapting to changing capacities Many reported hope of relinquishing former capacities and to develop new ones. Many said their perspective had changed – instead of enjoying participating in activities with loved ones, they were now able to enjoy watching their play.

Study	Fanos 2008[205]
	Process of mourning lost abilities and taking pleasure in new ones appeared to be very important in maintaining hope.
	Living in the moment Many tried to live each day to the fullest, attempting neither to dwell on their illness nor look far into the future. Many occupying their mind by focusing on daily activities or hobbies. Many discussed the delicate balance of managing hope in not going too far in the direction of sadness or happiness, but rather controlling their emotions today.
	Self-transcendence Many expressed themes relating to acceptance and altruistic concern for others. Helping others was gratifying and kept them hopeful. Many relinquished the self and body, for example many wrote every morning and found it useful to reflect on their lives. Others found meditation helpful in giving meaning to their situation and to move to a stance of acceptance and trust in the process. Many found comfort in recalling childhood memories. One participant reflected that all you can control is how you feel about a situation.
Limitations	Written notes, no other method of transcribing. Themes not validated by participants, but were by an outside rater. Not much detail about researcher. Could have had more detail about what exact questions they asked. Not much detail on ethical issues except approved by the Institutional Review Board.
Applicability of evidence	Applicable.

Study	Foley 2014[220], Foley 2014b[219] Foley 2014d
Aim	To explore and develop a theory about the processes underlying ALS patients' engagement with health services
Population	ALS population (N = 34), Ireland. 17 men, 17 women. Age range = 37 - 81 years. Mean duration of time since symptom onset = 31 months (range = 4 months - 13 years). Nearly a third (N = 10) were deceased by the end of data collection. 8 participants were using either NIV and/or gastrostomy. Recruited from the Irish ALS population-based register between Sept 2011 - Aug 2012.
Study design	Interview
Methods and analysis	Grounded theory methodology. Interviews were conducted with sensitivity to patients' disability; so many patients used AAC devices to aid communication. Interviews opened with asking patients about their experiences of health care services since symptom onset. Interviews contained a mixture of open, probing, prompting, clarifying and verifying questions. Interviews were adapted to incorporate emerging themes. Transcripts were checked by participants, but the final analysis was not checked with participants. Explicit and implicit coding of themes was used, which were

Study	Foley 2014[220], Foley 2014b[219] Foley 2014d
Aim	To explore and develop a theory about the processes underlying ALS patients' engagement with health services
	abstracted into concepts. Similarities and differences between accounts were used to develop larger themes. Memos were used to facilitate theoretical development. A second author checked the analysis. This is the first paper reporting on this data. This paper summarises the main themes.
Themes with findings	Control and reassurance/Exerting control over health services: Participants expressed a strong need to be in control of their care, including engagement in services and choice of treatment. Needed time to process how it will change their lives and to digest the feeling of loss before accepting assistance from healthcare services for example, because it takes time to get used to having a carer in your home helping you with tasks. Wanted independence but then resigned selves to fact that they would become more dependent on healthcare professionals with disease progression. They felt reassurance from healthcare professionals when they felt in control of their care.
	Resignation: Most participants did not want to engage with treatment that could prolong their life, and therefore the duration of distress. Most participants questioned the role of life-sustaining treatment; including non-invasive ventilation and gastrostomy, some questioned the role of supportive care. Only a few wished to live on with high levels of disability.
	Trust: Participants had a strong desire to trust healthcare professionals. Participants were less likely to trust professionals who lacked empathy in the clinical encounter, and more likely to trust those who were knowledgeable, were personable in their approach, and provided reassurance about their care.
	Meaning of loss in ALS: ALS was associated with a perception of continual loss and participants experienced hopelessness about the future. Losses included the physical change, their ability to engage in important aspects of their life, their identity, their feeling of control over their lives, and their future.
	Aging, life stage, and acceptance in ALS: Those 70 years of older were more accepting of ALS and of impending mortality than those in earlier adulthood. All struggled to some degree between fighting and accepting ALS and the losses but accepted it more if they had reached later life, fulfilled their ambitions, raised their children. Overall participants thought it more acceptable for those in later life to die from MND than those who were 'young', as it was thought 'tragic' and some older people with MND would give their own life for a young person to live. Young was considered 50 years old or younger, as they considered themselves young in the context of having MND. Some older participants suggested they accepted it better as they would not have to worry about living an old age with a loss of independence.

Study	Foley 2014[220], Foley 2014b[219] Foley 2014d
Aim	To explore and develop a theory about the processes underlying ALS patients' engagement with health services
	Many spoke of ALS aging them, and this made them more resigned to ALS. Aging and acceptance not only linked to perceptions of physical change but also to perceptions surrounding life stage. Participants who would 'lose out on parenthood' were less accepting than those who had already raised children.
	Family: context to decision making: Participants felt reassured by family but also sought to reassure their family. Participants wanted to know how the ALS would progress for the 'sake of the family', and family (or absence) of was a primary context for opting in or out of services. It was important to have family members backing for the decisions they made about their care, so often took into consideration how accepting their significant other was of change. Looking out for their loved one's well-being could restrict them making decisions they wished for their care. Those with no spouse, partner or children suggested they had more freedom in decision making about their care than those with a family. Assisted suicide was talked about by most, indicating that they should have the right to choose but that it would devastate their family. Balance between drawing support and providing support to loved ones. Some admitted that life-sustaining interventions provokes anxiety for them but they planned to do them for their family. None would seek invasive ventilation; not routinely available in Ireland, but participants deemed invasive ventilation might extend the period of dependency on their families. Resisted being a burden on family but also resigned to fact that they were more dependent on them. Struggle between seeking to alleviate family concerns but needing more assistance from their family.
	Parenthood: impact on decision making: Being a parent was a principal context for how the majority of participants who had children made decisions about their care. Those with young and adolescent children were attuned to the impact it had on their children and all opted in or out of services depending on how their children responded to the presence of health care services in their lives. Overwhelmed by prospect that they would die before raising their children. Yet parenthood often gave them feelings of hope and energy to resist ALS. Middle-aged participants whose children depended on them had as strong a desire as young participants' with children to live. The experience of progressive disability alerted them to the potential impact of life-sustaining treatments and support services on their children. Wishing to minimise disruption to their children's lives and had conflicting emotions to engage with services that could sustain their lives.
Limitations	None

Study	Foley 2014[220], Foley 2014b[219] Foley 2014d
Aim	To explore and develop a theory about the processes underlying ALS patients' engagement with health services
Applicability of evidence	Applicable

Study	Gent 2009[238]
Aim	To explore the experiences of MND carers to identify the coping strategies adopted and the potential implications for service provision
Population	Family carers (N=6) of patients with MND (3 women and 3 men). Mean age = 73.3 years, SD = 7.42 (range = 63-83 years). United Kingdom.
Study design	Interview
Methods and analysis	Participants recruited using convenience sampling via a MND clinical nurse specialist not involved in the study. Semi-structured face to face interviews, recorded and transcribed. Interview schedule contained introductory prompts, factual questions concerning demographic data and medical history, and a series of open-ended prompts to elicit discussion about coping strategies and behaviour. Themes identified were incorporated into the interview schedule for later interviews. Data were organised into emerging themes and sub-themes. The main recurrent themes were identified and labelled using numerical codes, and links drawn between emerging themes and concepts. Process was informed by the analytic hierarchy. Half of the transcripts were analysed independently by another researcher and discussed subsequently by both researchers to ensure that themes were consistent.
Themes with findings	Support for carers Formal statutory and voluntary support mechanisms: Most carers received support from health and social care provides; including both practical support and expert advice and guidance. Informal support mechanisms: All carers received some support from other sources; including family, friends and neighbours
	Technical support: Carers reported how they had received assistive technology from statutory and non-statutory agencies and they were satisfied with the devices. The devices had an impact on both carer and recipient's quality of life. The devices allowed some carers to support their loved one irrespective of their own ill-health, and they improved outdoor mobility and transfers.
	Coping strategies: Managing attitudes and emotions: Carers discussed how they coped with their emotions alongside their caring role. These included strategies such as having a positive approach to caring, show and vent emotions, and focussing on the present. Managing problems. Some carers discussed how they met the needs of their loved one by problem-solving together their needs and how they could be met. Managing time. Carers discussed how it was important to manage time effectively to allow them to continue with their own preferred interests

Study	Gent 2009[238]
	and social activities.
	Nature of the caring role: Providing personal care: Some carers provided considerable personal care while others provided relatively little. The nature and amount of personal care provided was not always consistent. Some family members found it difficult to provide personal care. Providing support at meal times: Some carers provided support at meal times; including selecting foods which could be handled independently or eaten safely when tired, and placing items within reach and in an appropriate receptacle.
Limitations	Unclear if an established method was used for the analysis (for example thematic analysis). Results not validated with participants. Unclear if there was disagreement between researchers on any themes, and if so how this was resolved. Analysis needed greater depth. Role of the researcher unclear.
Applicability of evidence	Partially applicable

Study	Gibbons 2013[239]
Aim	To investigate the lived experience of fatigue in patients with MND.
Population	N=10 patients with MND. Patients with confirmed diagnosis from a regional neuroscience centre in Liverpool, UK.
Study design	Qualitative; semi-structured interviews
Methods and analysis	Patients were those who had expressed fatigue to be a relevant issue prior to inclusion in the study. The interviews were recorded. Transcripts analysis using interpretative phenomenological analysis (IPA).
Themes with findings	Descriptions of fatigue:
	Weakness: clear distinction between fatigue experienced as reversible muscle weakness and fatigue experienced as whole-body tiredness
	Tiredness: those who experienced fatigue as tiredness more than muscular weakness found the feelings of fatigue extreme. Caused by minimal exertion.
	Energy: Commonly experience of fatigue explained as lack of energy, being 'drained' or 'sapped'. Rest was important to overcome the fatigue, for those tired it could be a couple of hours before recovery. For those who explained fatigue as primarily muscle weakness allowed their muscles to recover.
	Concentration: Differing accounts of fatigue-related difficulties in concentration. For some it was sustaining the physical effort component of a task, and for others it was reduced ability to concentrate on, for example, reading.
	Causal factors – dyspnoea and talking: for two participants fatigue had accompanied difficulties in talking and breathing. Where there was this link, it was relieved to some extent by ventilation equipment.

Study	Gibbons 2013[239]
	Progression: All patients said that their fatigue had followed a progressive course.
	Effects of fatigue – Adaptation:
	Reconceptualisation: adapting to not having so much physical energy to do what they used to consider normal.
	Budgeting: make adaptions in life to budget their daily levels of energy; planning rest.
	Planning: of rest prior to and after fatigue-inducing activities.
	Motivation: reduced motivation to carry out activities of daily living that were expected to cause fatigue. Embarrassment at avoiding the 'simple things' because of anticipated fatigue. Having to perform what was previously a simple action, now in a number of steps. Motivation could be higher in some domains but as well as a lot lower in other domains. Social contact was now more effort. Many wished to keep on 'fighting' against the increased fatigue.
	Avoidance: learned response of avoidance of activities that that knew would make them fatigued.
	Frustration: commonly experienced due to increased difficulty or impossibility in doing activities of daily living but still wishing to stay engaged in daily activities.
	Stress: emotional burden of stress was an aggravating factor for fatigue and described by a number of people.
Limitations	No details of open-ended questions used. Did not validate themes with participants.
Applicability of evidence	Partially applicable. Looking specifically at fatigue and chose only those people who had previously spoke about their fatigue.

Study	Herz 2006[271]
Aim	To explore the experience and perceptions of carers of people with MND
Population	11 carers (3 current carers; 8 former carers) who participated in separate focus groups (2 groups of former carers and one groups of current carers. Male = 4, female = 7, wide age range (<35 N=1; 76-85 N = 1). Of current carers, only those with relatives in end stage MND were included. Carers were mainly the partners of patients, but minority of children as carers (N = 3). Adverts were placed in the MND association of NSW newsletter (Australia)
Study design	Focus groups
Methods and analysis	Focus groups included a list of prompts covering topics expected to be important including practical, symptom management, psychological, spiritual, service-oriented and institutional aspects of care, information needs, planning ahead, knowledge of and contact with palliative care. For former carers, topics also included death, advance directives and bereavement. In each section, participants were asked about their needs, how well those needs were met, the advantages and disadvantages of the current system, and how the situation could be improved. Discussions were

Study	Herz 2006[271]
	audiotaped and transcribed. Themes were extracted by the researcher and in discussion with the research team. Interpretation of themes was facilitated by reading of transcripts and reading of wider literature.
Themes with findings	Role of the general practitioner. Participants perceived the GP as an ally, but one with limited time and knowledge about MND.
	Role of the MND Association. Participants appreciated the information and practical support provided by the MND Association.
	Unremitting care. Carers discussed feeling unwilling to relinquish care of their loved one to support services.
	Emotional cost to the carer. The emotional cost as a carer was discussed as being greater than the physical burden, and carers discussed how the emotional impact extends long after the death of their loved one.
	Need for respite. Former, but not current carers, discussed the need for respite, for emotional release and replenishment.
	Accessing help. None of the former carers sought professional support for their emotional needs. Carers discussed a preference to cope without external support.
	Love. Carers expressed love and respect for their loved ones. Caring was seen as test on the love in the relationship, with the act of caring an expression of their love.
	Trapped and drowning. The deterioration in health of the patient and the increasing burden on the carer was described as a 'downhill' spiral and like 'drowning'.
	Financial burden. Some carers with good finances were able to manage, while others expressed a need for greater financial support.
	Access to palliative care. Only a small number of former carers identified contact with palliative care, which had occurred very late in the course of the disease. The specialist support was perceived as greatly beneficial.
	Return to living. Some former carers discussed a return to living following the death of their loved one.
Limitations	Little information on analysis so rigour and reliability unclear. Analysis could have been more in depth. Unclear if themes reached saturation. Findings not validated with participants.
Applicability of evidence	Applicable

Study	Hocking 2006A[275] Hocking 2006[274] Brott 2007[87]
Aim	To explore the experience of living with MND.
Population	N=7 (4 women and 3 men) in New Zealand. Participants were at different stages of MND, with varying mobility. They were diagnosed between 8 months and 4 years previously. One of the participants used an assistive device to communicate.

Study	Hocking 2006A[275] Hocking 2006[274] Brott 2007[87]
Study design	Semi-structured and interviews.
Methods and analysis	Interviews were focused on actual events and situations participants had experienced. Participants were interviewed in their own homes. Interviews were transcribed verbatim and drawn into stories under themes. The analysis was informed by van Manen's 1990 description of the 6 activities or stages in the research process.
Themes with findings	The wobbly body Experience of living with a body that was changing and that they were losing control over. Bodies felt different and moved different so affected activities. Deteriorating performance on familiar activities became the benchmark for progression of the disease. Embarrassment of falls or reliance on others for daily care, activities, such as toileting, showering, cleaning teeth and grooming. Search for explanations to why they had this wobble, seeing different specialists: for example one participant saw a podiatrist as he thought he had a drop foot, 2 locums GPs, doctor referred to orthopaedic specialist, then 2 neurologists, the 3rd neurologist when seen three times finally made diagnosis. In order to cope look for information, many from the internet.
	Doing and being
	Changed world – changed future As participants' lives changed so did their families'. Patients had to tell their families about their diagnosis, which was very difficult. Changed relationships and worries of being a burden due to assistance with showering, dressing and toileting. Relief of 'getting into the health care system' as they then expected help to be at hand, however you had to open up your home to people you didn't know, to assist with highly intimate care. Numbers of people involved in care could be overwhelming, and they wished to be left alone at times. Barely time or energy to see friend. It was important for them to plan ahead so they gained a sense of control. Knowing who to trust regarding seeking, receiving and following advice was important but often given conflicting information.
Limitations	The MNDA of Australia field workers approached prospective participants. The role of the researcher was not clearly explained. The authors did not explain the process of analysis in-depth, so we do not know if there was triangulation of data to arrive at the themes. Stories were sent to participants to check but the themes were not. Particular emphasis was given to the 1st and 3rd theme but not the 2nd theme as the other 2 themes had 'particular relevance to working as a member of a multidisciplinary team to support people with MND who are living in their own home'. Small sample size n=7.

Study	Hocking 2006A[275] Hocking 2006[274] Brott 2007[87]
Applicability of evidence	Applicable.

Study	Hogden 2012A[276]
Aim	To explore clinician perspectives on patient decision-making in multidisciplinary care for ALS, to identify factors influencing decision-making.
Population	N=32 health professionals from 2 specialised multidisciplinary ALS clinics and regional advisors from the Motor Neuron Disease Association in New South Wales, Australia. They included medical, nursing and allied health professionals. Working primarily in acute inpatient, community-based rehabilitation, or palliative care services and attended the monthly ALS clinics in addition to their usual clinical load.
Study design	Qualitative - semi-structured interviews.
Methods and analysis	Convenience sampling used. Structured interview guide developed through a 3-stage process. 12 open-ended interview questions about participant experience with decision-making, barriers and facilitators and improvements to decision-making processes in multidisciplinary care. In-depth Interviews were audio recorded and lasted approximately 60 minutes. 2 group interviews were held with a palliative care nursing team and members of a multidisciplinary ALS clinic team. Transcripts analysed using thematic analysis.
Themes with findings	Influences on decision-making Clinicians reported that their aim was to guide the patient and carer through upcoming decisions, in a timely manner, with the provision of evidence-based information on the available options regularly discussed. They saw it as a cyclical process, responding to recurrent change as the person's condition deteriorated. Their definition of objective of collaborative decision-making was facilitating patient-centred decisions to suit the inevitable changes to patient health and lifestyle.
	Patient factors The clinicians perceived 3 main barriers to decision making: patient acceptance of the diagnosis, the types of information patients sourced, and the patient-carer relationship. They found that poor family dynamics, problems with acceptance and insight as impacting on their relationship with the patient. Health professionals reported little control over these issues, but aimed to respond to the changing needs of patients to the best they could.
	Ability to accept the diagnosis The majority raised concerns with patients who had difficulties coming to terms with the diagnosis of ALS, and adjusting to deterioration as the disease progressed.

Study	Hogden 2012A[276]
	Limited clinical understanding impeded acceptance of the diagnosis by patients and family member, caused by limited public awareness of ALS meant patients delayed seeking a diagnosis and the shock of receiving a terminal prognosis for an unfamiliar condition delayed the patient's and family's ability to take in information. Those who used denial as a coping strategy delayed discussion of planning and decision-making. Cognitive and behavioural changes impacted on patients' health care decision-making. Patients had the capacity to make decisions but the quality and timing of their decisions appeared compromised by lack of motivation and limited insight into their condition and the needs of their families. Many patients described as being 'difficult' and having rigid personalities, particularly in the palliative phase. Because cognitive and behavioural change was not routinely assessed in the clinics, identification of patients at risk of impaired decision-making skills was neither systematic nor standardised. More specific and detailed knowledge of these changes could improve their approach with the patient and carer. Patients who struggled to accept their condition responded passively to physical deterioration, and sought assistance only when their condition was unmanageable. Decisions made at last moment, or after critical timing windows were lost. Crisis management strategies were seen as last resort for those who were unable to come to terms with the changes to their life.
	Types of information patients sourced Credible sources of information were mainstream health services and associations based on empirical evidence, such as ALS patient association information kits and health research-based websites. Non-credible sources lacked an evidence base, but were easily accessed via the internet. Concern over patient's ability to distinguish between non-credible and credible sources. Clinicians reported a sense of responsibility to monitor the quality of information accessed by patients, and to provide guidance on the range of evidence-base information available. Practitioners were wary of crushing patients' sense of hope, but thought that poor quality information compounded their difficulty in accepting the inevitable nature of MND. Some information gave unrealistic expectations of services that could be offered. Patients' wish for a cure led them to collect misleading information and develop false hopes which were counterproductive to accepting and adjusting to MND, and making effective decisions.
	Patient-carer relationship Decisions around employment, artificial nutrition and hydration, home modifications and accommodation had considerable influence on carers' quality of life. Decision-making was disrupted if the patient and carer could not reach agreement, or when the patient's poor decision-making put the well-being of the carer are risk.

Study	Hogden 2012A[276]
	Respondents reported instances where carers had a negative influence on decision-making discussions, such as a gate-keeping role blocking access to the health professional and the patient.
	Health system factors [note that this study is conducted in Australia] Timing of diagnosis and symptom management: Participants from diagnosis, management and end-of-life services expressed concern about the time lag between patients reporting symptoms and receiving a diagnosis of ALS. The heterogeneity and subtlety of ALS symptoms created delays in gaining the diagnosis, and decision-making to optimise symptom management. Limited awareness of ALS by non-specialist health care provider hindered timely referrals to ALS services. Once symptoms were recognised as ALS, access to specialised services became the next challenge for patients and their primary health care providers. Access to health services was difficult for those outside of clinic catchment area, with long waiting lists for services, which impacted on ability to make decisions. Even when accessing specialised services, physical resource constraints compromised care options. Participants reported frustration with long waiting times for equipment, extended delays rendering the equipment obsolete for patients who had deteriorated. Respondents thought well-timed information crucial for patients' decision-making. Patients and family should be informed as early as possible about the diagnosis, prognosis, and expected course of disease progression. Knowing when to do so without overwhelming patient and carer was difficult decision, and specific to each case. Judging optimal timing for provision of information challenged health professionals both as individuals and as a team. It depended on the patient's readiness to hear it. Access to ALS-specific resources: Health professionals stated that the wider health system created barriers to collaborative and patient-centred decision-making. Health service funding was frequently mentioned as blocking the delivery of specialised ALS multidisciplinary clinic services. Health professionals reported frustration with constraints imposed by these factors largely outside of their control. Inter-professional communication: Communications difficulties between health professionals as a barrier to decision-making in multidisciplinary ALS practice. Breakdowns in inter-professional communication disrupted information exchange and implementation of collaborative, patient-centred decisions. Communication with external health providers was also problematic with a lot of time spent trying to contact external practitioners.
	Decision-making facilitators: An MDT model of care enhanced their role in decision-making, when supported by access to ALS research information and clinician education websites.

Study	Hogden 2012A[276]
	Collaborative teamwork, effective communication systems which underpinned that teamwork and evidence-based clinical information promoted meeting the patient at their point of need and improving decision-making. Guidelines were useful for decision making in the MDT ALS team to: assist provision of clear information and to health professionals, patients and families; to provide structure and timeframes to facilitate planning with patients; and to give clarification of roles and responsibilities for decision-making within the MDT. Guidelines also reduced specific gaps in service: the use of routine screening for cognitive and behavioural change, the completion of advance care plans with their patients.
Limitations	Role of the researcher not clearly explained but questions developed by 2 Clinicians with extensive experience in ALS. Themes needed further refinement.
Applicability of evidence	Applicable.

Study	Hogden 2012[277]
Aim	To explore patient experiences of ALS, and to identify factors influencing decision-making in the specialised multidisciplinary care of ALS.
Population	N=14 patients from 2 specialised ALS multidisciplinary clinics in New South Wales, Australia.
Study design	Qualitative - semi-structured interviews.
Methods and analysis	Convenience sampling used. Structured interview guide developed through a 3-stage process. 16 open-ended interview questions about participant experiences with specialised multidisciplinary clinical ALS services, participants' decision-making activity, and improvements in decision-making in multidisciplinary clinical care. In-depth Interviews were audio recorded and lasted approximately 30 minutes then were member-checked. Transcripts analysed using thematic analysis. 11 participants took part in face-to-face interviews while 2 respondents elected to be interviewed by phone. The remaining participant answered questions by email.
Themes with findings	Structural factor: decision-making environment Multidisciplinary clinical ALS services were a supportive decision-making environment by giving disease-specific information, specialised symptom management and care planning, and the opportunity for discussion of treatment options. They reported confidence in the ALS teams because of expertise, specialised knowledge and dedicated ALS service. Representatives from the ALS association attended to support and inform. Offered, where available, research-based information on which to base their decisions. Provided (print and internet) resources on nature and progression of ALS, and available clinical and support services for symptom management. 3-monthly appointments given to regularly discuss patients' current healthcare and psychosocial issues and to plan for anticipated care needs.

Study	Hogden 2012[277]
	The MDT was viewed as main source of assistance outside of the family.
	Interactional factors: patient experiences of ALS Reaction to the diagnosis: Shock on receiving diagnosis. Responses became complex and nuanced as came to understand the meaning of the diagnosis. Three people said the diagnosis confirmed their own conclusions. Two said they had little emotional reaction as they did not understand the implications at the time of diagnosis. One said they had difficulty accepting the diagnosis and was distressed as to lack of cause. Many were frustrated that health professionals could not inform them of their personal survival times and disease trajectories. Yet those who had over a year since diagnosis had greater emotional adjustment to their condition. Two participants who came to terms with the diagnosis expressed a positive outlook, and could reframe the situation as an opportunity to make most out of time left. Others found it difficult to take in medical information and the inevitable nature of their situation. There were diverse reactions to the common experience of an ALS diagnosis. Their reaction influenced their readiness to learn about the condition and participate in specialised MDT ALS care and decision-making.
	Response to deterioration Participants had to make practical adjustments to their lifestyle to retain their independence, including changes to home and workplace environments and travel arrangements. They acknowledged increasing dependence on support from family and health care services. Many re-prioritised so they could maximise their family time and some framed survival goals around children's milestones. Coping mechanisms for their condition were expressed as denial, resilience, or a focus on maintaining current routines and lifestyle. Religion or spirituality did not feature strongly as a source of support or coping. 2 people identified religious beliefs. Regardless of coping strategy their decision-making was guided by a focus on the present, as it was better than thinking about the future. Maintaining current well-being was a higher priority than proactive engagement in decision-making for disease progression.
	Engagement with the multidisciplinary team Reported both positive and negative experiences with health care teams, however most of the negative were related to non-specialised health services, and included extended waiting times for diagnosis, insensitive communication of the diagnosis by generalist neurologists, and communication breakdown between external health care service providers. Participants were satisfied with specialised MDT ALS care and valued their relationships with the clinical ALS team. The specialised care, information and support, ease of communication with the health professionals and importance for specialised services for their on-going care and regular communication and changing needs. They were also their link to ALS research to keep informed of developments

Study	Hogden 2012[277]
	Engagement process enhanced by clinic structure and organisation of regular scheduled appointments. They liked the familiarity of the same setting and staff. They took part in research activities attached to the clinic, as a way to help future patients. One challenge was being face to face with other ALS patients at the clinic who were more advanced stages of the disease. 2 said this negatively impacted coping. They found ways to separate themselves from others to minimise their discomfort.
	Personal factors: patients' personal philosophies Outlook on life Elements of their outlook on life overlapped with their reported coping strategies. Maintaining a positive outlook, being resilient and remaining engaged in normal life were expressed. One framed his outlook as an active avoidance of negative thoughts and experiences, to maintain his sense of well-being. Family relationships emerged as a strong influence on shaping patients' outlook on life, and therefore on decisions for symptom management. Family were reasons to live and motivated people to choose interventions to prolong their lives, for example artificial feeding and hydration or to continue employment. Perceptions of control Respondents wished to preserve their independence and maintain control over their lives as long as possible and this shaped their decisions for lifestyle changes. They specified a wish to have control over the circumstances of their death, wishing to remove the burden from their families. Despite increasing physical degeneration, the majority (78%) reported maintaining control over their daily lives. None considered ALS in control of their lives. Many said preservation of independence and autonomy was a motivating factor behind decisions. Less than a third made decisions independently, preferring to share decision-making with others, for example family support or expertise of health professionals.
	Planning the future Paradoxical attitudes towards the future. Half completed living wills or advance care directives. Under one third identified plans for their future care needs or needs of their families. 28% were reluctant to learn about disease course, preferring family members to seek and interpret information on their behalf. 43% had a 'wait and see' approach, focus on immediate concerns or daily routine rather than future needs. This was reflected in information-seeking: they accessed information from the internet, health professionals and the ALS association. They reported appreciation of the information from the health professionals and the ALS association but a small number chose to not read it. Decision-making was complicated by reluctance to plan for the future, despite inevitable course of disease. Coping with present was preferable

Study	Hogden 2012[277]
	than contemplating the future.
Limitations	Role of the researcher not clearly explained but does explain that the interview guide was developed from the decision-making literature and evaluated by 2 expert clinicians and researches experienced in multidisciplinary ALS care. Themes needed further refinement.
Applicability of evidence	Applicable.

Study	Hogden 2013[278]
Aim	To explore carer participation in decision-making, to identify carer roles, and determine the facilitators and barriers to carer participation in decision-making for ALS multi-disciplinary care.
Population	8 carers of family members with ALS (5 female,3 male), age mean = 56 years (range = 33-76 years). All eight patients they cared for were in the advanced stages of ALS. Duration of care ranged between 6-96 months.
Study design	Interviews
Methods and analysis	Semi-structured interviews containing 10 open-ended informed by the literature and clinical and research experience of ALS. Six participants were interviewed in person, 2 via email. Face to face interviews were audio-taped and transcribed, and all transcripts were validated by participants. Analysis was checked by two co-authors to reach agreement. Transcripts were analysed using thematic analysis. Patterns in the data relevant to the aims of the study were identified to reveal trends and relationships in participants' accounts. Codes were grouped by meaning, creating subthemes. Subthemes were then refined into themes, alongside associated facilitators and barriers.
Themes with findings	Promoting the patient voice: Carers facilitate communication between patient and health professionals, and support patients to make decisions regarding their care.
	Promoting patient health literacy: Carers source and synthesise health information, and filter the amount and content of information for the patient and family, and provide information to the patients. Access to credible and evidence-based information facilitates this.
	Emotional support: Carers provide emotional support for discussion of patient's changing needs.
	Logistical support: Carers provide physical and practical assistance for patients to attend appointments, and help to coordinate services and appointments. This is facilitated by physical and practical support for the carer from family, friends and health services, with a burden of care acting as a barrier to this.
Limitations	Role of the researcher not clearly explained. Questions explicitly shown but a couple of them were closed questions. No details on ethical implications except committee approval. Findings not validated with participants.
Applicability of evidence	Partially applicable

Study	Hughes 2005[284]
Aim	To look at the lives, experiences of services and suggestions for change in people living with MND.
Population	People with MND (N=9) and their carers (N=5), and professionals (N=15) with front line or strategic interests in MND working within three boroughs in London UK: Lambeth, Southwark and Lewisham, among the most socially and economically deprived areas in the UK, covered by King's College Hospital MND Care and Research Centre. People with MND and their families recruited by a database at the MND Care and Research Centre.
Study design	Qualitative, semi-structured interviews, from content of topic guide based on existing literature: living with MND and its impact, experiences of services and suggestions for service changes.
Methods and analysis	The authors excluded anyone with mental health problems, involved in other research or who did not have good command of English. A 'Snowball' technique was used to sample families and professionals. A letter was written to invite participants to an interview. Research questions included: living with MND and its impact; experiences of services; and suggestions for service changes.
Themes with findings	Impacts of MND on people's lives: As MND progresses, it has a debilitating physical effects on the body. MND can limit travel, the pursuit of hobbies and pastimes. Many of the participants were older so disentangling the difficulties of age with that of MND was difficult. One younger participant kept doing what he used to do, socialising etc… but got fatigued a bit earlier. As people 'get used to' living with MND, changes can become routine and 'natural' adjustments were made. Although the increased dependency on spouse and family altered relationship roles and left them feel bad that it had been reversed. One participant tried to conceal the impact of the illness from his spouse. His spouse also worried as he had always dealt with practical matters like finance. Although they felt uncertainty about the future, people at all stages of MND and ages discussed the importance of illness acceptance. Some people ignored their illness as much as they could. This in some cases led to reticent information-seeking. Sometimes carers would restrict the information available to people with MND to protect their loved ones from distress and upset. Professionals recognised that individuals – like everyone - had many different emotions and coping strategies to MND. Professionals were also aware of the effects of MND on people's lives and their struggle to have a quality of life. People with MND felt that there was an overall lack of understanding of MND which impacts on their experience of services.
	Experiences of services: Many people felt unsure about the services they were entitled to, especially when first diagnosed, they were also unsure of where to get information from. Professionals recognised that people with MND would be exposed to a number of forms of information from different sources, which could

Study	Hughes 2005[284]
	potentially be confusing. Some professionals attached priority to MND care. Some people with MND discussed lengthy procedures in referrals and in obtaining an accurate diagnosis. Some people with MND felt that the approach of professionals was distant and divorced. Some people with MND were concerned about professionals' lack of knowledge and understanding of MND and its impact on people's lives. They thought some professionals had incomplete knowledge of MND, and that its rareness was an explanation. Lack of understanding of illness led to problems in accessing service entitlements, such as social security benefits. Some professionals' apparent lack of understanding and knowledge about MND, or their attitudes and approach to users made people with MND reluctant to approach them with questions. Such situations made them feel dissatisfied with the information and services they were receiving. Problems of receiving the right kinds of information at appropriate times led some to seek information for themselves, for example books and leaflets, MND stories in the media, the internet. People with MND did appreciate the complexities of professional information giving and the challenges it brings for professionals. One respondent questioned whether it could be presented any better. Different people have different information-seeking requirements.
	Suggestions for service change: Some people with MND felt the need to improve information and communication between professionals and users. Others wanted information on what to expect in the future, especially if newly diagnosed, wishing practical information about MND and their entitlements to services immediately. One carer found that there was need for more efficient social service responses. Those living with MND longer also wanted information on treatments, therapies and research. Some wished specific information but realised that they needed to work through their own needs. Professionals identified a need for increased knowledge about MND, through improved education and training, for their colleagues. They also thought there should be striving towards better coordination and information exchange between professional teams, especially those in hospitals and the community. Some professionals felt that services should be restructured to reduce demarcation between providers so that professionals could follow-up their caseload between hospitals and the community. These changes were understood to improve coordination and consistency of care. Improvements to services: need for support from people with an understanding of MND, not necessarily professionals.
Limitations	Themes not explicit, more descriptive. Findings not validated by participants. No details of researcher's role.
Applicability of evidence	Applicable.

Study	King 2009[324]
Aim	To present a model that explicates the dimensions of change and adaptation as revealed by people who are diagnosed and live with amyotrophic lateral sclerosis/MND.
Population	N= 25 people with ALS or MND living in metropolitan and rural Victoria, Australia.
Study design	Qualitative study using grounded theory method
Methods and analysis	In-depth interviews, electronic correspondence, field notes, as well as stories, prose, songs and photographs which were important to the participants. QSR NVivo 2 software used to manage data and modelling used to illustrate concepts.
Themes with findings	'On-going change and adaptation' model of decision making Living with uncertainty, not knowing what aspect of life would be 'lost' next.
	Perceiving change External changes outside of their control affect them such as changes in environment which can affect the person's ability to go out or be included; or unpredictable events where their vulnerability is exposed, for example one person dropped a lit cigarette while in wheelchair and could not remove it. Internal: perceiving and grieving of lost physical abilities. Sense of self of control lost when having, for example, emotional lability.
	Reacting to change Undermined self-esteem: distress and frustration impacted on people's sense of well-being, affecting their self-worth and undermining of self-esteem. Frustration from finding everyday tasks hard or impossible, for example emptying the dishwasher. Personal images of being able-bodied, strong and independent were continually challenged. Embarrassment at slurring speech or using a wheelchair in public, difficult to overcome and led to staying at home out of sight. Protecting a public image was important for sustaining self-esteem. Sustained self-esteem: Some threatened by change but others were okay with it, as 'okay', a 'surprise' or a 'challenge'. These participants used the skills developed to deal with challenges to tackle public issues, for example campaigning for rights of people with disabilities, such as in hotels. Some people set new goals in life that could be achieved. Positive reactions advanced participants' self-esteem and self-worth as they regained a sense of self and achievement. Appraising change: making meaning of what happened

Study	King 2009[324]
	The next step after initial response to change was to reflect on what had happened, making sense of it and assess the effect it would have on everyday life. Illness beliefs and beliefs about life generally were modified, promoting a feeling of coping with change and being in control. However as physical abilities deteriorated and life became more restricted, this was more difficult and MND was believed to be in control. MND in control: the perception of not being in control over life events elicited pessimistic assessments about life, such as feelings of hopelessness. Small events triggered this perception and made people feel like MND was in control. 'I have control': when people resolved ways of incorporating a change into daily living they regained a sense of being back in control. Controlling the disease involved proactive strategies, such as designing new care routines. Experiencing and exerting control in decision-making and life promoted feelings of self-worth and personal integrity. When verbal ability deteriorated, constructive, positive, self-talk was an important strategy to find meaning in the changes and plan adaptive strategies to gain a 'sense of control' over MND.
	Adapting to change: selecting strategies People selected strategies to cope with changes (either passive or active). Passive strategies: let events happen without thinking about consequences, sometimes the change was assessed as unremarkable so would not mean much to their lives. Or sometimes it was a form of denial as too hard to cope with, such as pretending it wasn't there. This was sometimes positive as the person was able to focus on what important in life and coping with disease outcomes. Often to protect self-esteem. Active strategies: active adaptive strategies used in daily life to find ways to adapt to the change, such as altering usual support structures by employing a personal care assistant, or using humour to deal with negative inner feelings. Some tried to control their muscle twitching to gain a sense of control.
	Adjusting to change – outcome adjustment Whichever strategy used they assessed its effectiveness based on personal criteria, beliefs, values and understandings.
	Sensing well-being: stress levels The failure or success of adaptation strategies was directly linked to increased or reduced stress levels and a sense of negative or positive well-being respectively. Negative well-being: ineffective strategies generated feelings of 'MND in control' which increased stress levels and impacted on sense of well-being. Different for each individual, for example some embraced using a Lightwriter whereas others found it impacted on self-esteem and image. Positive well-being: when a strategy was deemed effective, they usually felt good about themselves, promoting a sense of achievement for dealing with change in their lives.
	Facing another change Regardless the response to adaptation strategies, decisions and choices about adjusting to change were never complete. There were always new

Study	King 2009[324]
	changes that required decision-making steps to be repeated.
Limitations	Findings not validated by participants. No detail of involvement of other investigator in themes. Themes needed further refinement. Role of the researcher not clearly defined.
Applicability of evidence	Applicable.

Study	Locock 2009[366]
Aim	Examines the relevance of the concepts of biographical disruption and repair to MND.
Population	n=35 people living with MND; n=11 family carers.
Study design	Qualitative interview study.
Methods and analysis	Interviews were conducted at home between one and two hours. The participants were interviewed using a narrative approach, then a semi-structured interview covering additional topics not raised during the narrative section or exploration of topics more in-depth. Interviews were transcribed verbatim. Primarily thematic analysis of the narrative interviews. Coding reports were also read by a second researcher.
Themes with findings	Biographical abruption This conveys a sudden ending, a 'breaking off'. This is commonly reported as a feeling that the diagnosis was a 'death sentence' and that life was in effect already over and they had been denied a future. Imagining life already over, wishing they were dead, wishing 'just to disappear'. For some younger people, knowing that they would not see their children grow up gave them more despair. Missing out on important events, their identity as a parent seeing their children succeed in adulthood, seeing grandchildren, losing out on retirement with partner. Carers, particularly partners, also had abruption. Not a literal 'death sentence' as it is for their relative, but the sudden cutting off of their anticipated future is a form of abruption. Struggle with fear and denial, feeling helplessness and loss.
	Biographical disruption Disruption in activities of daily living, leisure, work and social relationships featured strongly in people's narratives, with growing physical dependence on others and a fractured sense of self and purpose in life. Unable to take part in activities that used to do could be 'a huge loss'. Losing their role in the household, and being dependent on wife for personal care was like being a child. Not being able to speak. Strained personal relationships, in a few cases marital breakdown. Some felt relationships were unchanged or grown stronger, but loss of sexual and physical contact was a common source of sadness.

Study	Locock 2009[366]
	Biographical repair and reconstruction A few narratives emphasised continuing, profound despair. However, despite the terrible prognosis faced, there was a common narrative emphasis on reasserting a sense of normality and control. One participant found that one day they said enough is enough and then trying to stay positive. Another found acceptance as necessary to mobilise self and ensure a good quality of life. Participants had various repairing strategies to restore a sense of normality or learning to live with altered circumstances: Balancing avoidance and acceptance: Ostrich metaphor used to convey choice not to dwell on condition or look too far ahead. Others did a balancing act between avoidance and also needing to face and accept symptom progression – emotionally and for practical arrangements to keep or restore normal functioning. Some narratives moved back and forth between disruption and repair, with repeated reconstruction with each new progression. Keeping hold of the old normality: People sought to restore a sense of normality in different ways, sometimes at different stages in their illness. Finding ways to do the same things they usually do as long as possible was common. If not retired, continuing to work while able was important. Although some wished to stop and concentrate on other more valued aspects of their lives. Being able to continue to drive was important for continuity of identity. Going into a wheelchair was often a negative turning point in peo9ple's narratives, and was to be resisted as long as possible. Acceptance of outside care, although not 'normal' was able to help participant gain normality in her life and marriage. Creating a new normality: When old preferred activities became impossible, people searched for new alternatives, to keep a 'normal life' going and to distract them from thinking about the future. Developments in computer technology played an increasingly important part I providing opportunities for virtual socialising. Living life to the full – a heightened normality: Many people started cramming in all the things they had wanted to do I the rest of their lives, telescoping a previously envisaged normality into a few months or years. Trips and holidays were particularly important – as a distraction, an assertion that life was not yet over and there to be enjoyed, and as milestones to maintain hope. Suggestions that there is a social expectation that people with MND should adopt a positive attitude. Finding new meaning: It brought some couples together, for example from the help with personal care. Changed attitude to live, new value attached to just being and living for the moment and the preciousness of each day. A determination to look for positive meaning might be a helpful way of coping, although could still be characterised by expressions of fear and loss,

Study	Locock 2009[366]
	suggesting a hard stance to maintain in face of such a devastating disease. Biographical flow/continuity: Examples of biographical flow or continuity present in the data, but they were rare enough to be regarded deviant cases. Acceptance of had a good life and of the end.
Limitations	Findings not validated by participants. Role of the researcher not clearly defined.
Applicability of evidence	Applicable.

Study	Locock 2010[364]
Aim	To explore attitudes to peer support among people with MND and their family and carers.
Population	People with MND (N=48), family carers (N=22) interviewed in 2005-2007.
Study design	This was a secondary analysis of data from 2 UK interview studies by the authors. Thematic analysis approach was used.
Methods and analysis	Pooled sample of people with MND from both studies, and pooled sample of family carers from both studies. They did not go back to the initial interview transcripts but relied on initial 'data sorting' to get pooled data on selected theme.
Themes with findings	Valuing camaraderie and comparison Practical comparison: Engaging in support groups was a way of getting advice on dealing with aspects of disability, home adaptations or claiming benefits. Practical access problems rather than not wanting to go were given as reasons for not going to face-to-face support groups. Some people were still working, so attending day meetings was difficult. Other barriers such as fatigue, difficulties travelling and problems interacting face-to-face (those with limited speech). Some worried about getting to the toile, managing drinking or eating, or unfamiliarity of environment. Some enjoyed advising others. One person did not feel that she got much out of the support group as the group was more for spouses of people who had died from MND. They liked the practical side of interaction, but did not benefit from being in a room with others with MND.
	Camaraderie and social comparison: In contrast some enjoyed the camaraderie of just being with others who understood, being with people 'in the same boat'. Some felt part of a 'special group of people' and normalised their identity than being with 'normal' people, a sense of social solidarity. Not dwelling on the condition in the group but meeting 'lively fantastic people' rather than sitting alone at home dwelling.

Study	Locock 2010[364]
	The variability of symptoms and speed of progression meant that some social comparison was hard to avoid. As no chance of recovery, no inspiring examples of recovery. Few people regarded peer interaction as unequivocally positive, it could be frightening to see people with worse symptoms. They had to 'pluck up courage' to go to meeting, but easier over time as adapted to new identity as a person with MND or a carer. The first meeting people felt shocked or frightened but after this gained reassurance and hope from others coping with worse symptoms. One person with PMA form with longer life expectancy worried he would be alarmed or his presence would upset others so did not go initially. Support groups allowed the chance to see people who had survived longer than expected. Comparisons to Stephen Hawking were common and symbolised hope of living longer. Benefits of sharing sadness, fear, anger and sometimes guilt (especially with carers who struggled with role). Source of reassurance not alone and these feelings are normal. Online support groups were similar in providing camaraderie and social comparison, particularly on BUILD.
	Choosing isolation: Some identified that they were 'not a group kind of person', not wishing to share any feelings or personal information regardless the subject. MND in common insufficient reason to socialise. Interaction with those with MND can reinforce feelings of difference and exclusion from normality. Many said that the groups did not target people's needs. Combination of carers, people with the condition where some people liked this but others didn't. One MND patient felt it inappropriate and a carer found it difficult to ask questions in front of those with MND. Avoiding interaction was often linked to the progressive and terminal nature of the condition and not wishing downward comparison. Was difficult to see people deteriorate and to deal with deaths of group members hard. Remote peer support could be useful to those who do not want face-to-face interaction but it can have problems as well such as too much involvement. One person felt that engaging so much that MND was taking over their personality and identity. Choosing isolation from others with MND, even if temporary, restored a sense of normality and self.
Limitations	This was a secondary analysis of Brown (2008) and Locock (2009) - please see limitations for these individual studies.
Applicability of evidence	Applicable.

Study	McKelvey 2012[387]

Study	McKelvey 2012[387]
Aim	To describe communication patterns of individuals with ALS over time as the disease progressed and to understand the lived experiences from the surviving spouses' perspectives.
Population	Bereaved carers (N = 6) (female, 2 male; age range = 42-75 years) of six individuals who had ALS. Time between death and time of interview range = 6-144 months. Time from diagnosis to death range = 10-78 months.
Study design	Interviews
Methods and analysis	Individual semi-structured interviews (60-90mins) audio-taped and transcribed. The interview schedule was comprised of 18 questions with additional prompts for greater detail. Transcripts were checked against the audio recording for accuracy. Three researchers developed the initial codes on two of the transcripts. These codes were categorised and organised into themes. Effort was made to code sections of text left uncoded, and to collapse overlapping themes. Two researchers performed an independent parallel coding process, to re-code the transcripts using the derived themes. The third researcher checked the independent parallel coding process. Any discrepancies between the interpretation of the data by researchers were discussed and agreement reached on all themes.
Themes with findings	Communication styles: Carers discussed their partners' communication styles before and after the onset of ALS.
	Augmentative and alternative communication devices: Carers discussed the importance of AAC devices for patients' quality of life, and discussed their importance in enabling patients to communicate basic needs, share opinions, express feelings, and maintain their social roles in family and society. Carers discussed the importance of finding a system that fit people's (changing) needs. Carers discussed their own novel approaches to maintaining communication, and some of the barriers to using the devices.
	Decision making: Carers discussed how there were lots of decisions to make following the diagnosis, and that their loved ones' role in decision making changed after their diagnosis. Carers supported their loved ones' to get out of the house to live their lives.
	Lifestyle changes: Carers discussed changes in their loved ones' ability to maintain relationships and interact socially.
Limitations	Themes needed further refinement. Role of the researcher not clearly defined.
Applicability of evidence	Partially applicable

Study	Mistry 2013[398]
Aim	To explore how each participant's individual understanding of MND, their feelings, and how their sense of self and identity were affected after their diagnosis. Also to explore the movement from receiving a diagnosis through to coping strategies.
Population	N=7 people with MND who had received a diagnosis of MND in the previous 6 months; recruited from a specialist MND service in North West England.

Study	Mistry 2013[398]
Study design	Qualitative study using interviews, IPA approach.
Methods and analysis	Interviews were conducted in the person's own home. A semi-structured interview schedule was used to guide and prompt interview topics and additional questions for additional information and clarification. The schedule included questions on the diagnostic process, subsequent hospital visits, and the participants' emotions, attitudes, behaviours and thoughts about the diagnosis up to the point of interview. They were given a lot of freedom to discuss and reflect on topics they thought important, in line with IPA approach.
Themes with findings	'Then they dropped the bomb shell': receiving a diagnosis of MND The participants feelings of shock and devastation were apparent as they realised they had been diagnosed with a life threatening condition. The physicality of the shock is emphasised. After diagnosis most tried to make sense of it and to understand how or why they had MND, some felt they were being punished and their life had been 'robbed' from them when they had not harmed anyone. They felt that there was unfairness and questioned what they had done to deserve their diagnosis, typical of a 'search for meaning'(for example Janoff-Bulman, 1989). They said they were unable to take in any other information that was given to them after the MND diagnosis, describing themselves as 'shell-shocked', as they were struggling to make sense of their diagnosis and the possible future implications. Feelings of falling, or being in a dream-like state. The experience of the 'bombshell' of the diagnosis contrasted with their expectations at the start of the medical investigations. When they first had physical/functional changes, they had not thought them significant, thinking them part of the aging process or work hazards. They only sought medical attention when the changes were becoming more significant, although this differed by person. People experienced different symptoms, therefore were referred into different medical specialties related to the initial symptoms they experienced. This was a time of uncertainty where they felt frustrated, worried, confused and angry as they did not know what was causing them to lose control over their bodies and if they would get treatment to stop or slow down the symptoms. People were thought of as a 'puzzle' to their clinicians which evoked feelings of fear, confusion and worry for all participants in the study. Thoughts participants had before received MND diagnosis suggested that although potentially serious that it would be treatable. Yet any hopes of this were destroyed by the 'bomb shell' diagnosis.
	'Got to get to grips with it': learning to live with MND People felt a sense of urgency to get to grips with the diagnosis so to make the most of the time left. Each had their own way to think about their diagnosis and how it would affect them as it progressed, and how to manage the changes. They acknowledged and accepted that they were unable to do anything to change or slow down the progression of their MND and it was not their fault that they had the condition. By maintaining control and reaching a causal understanding they could move onto practical concerns. Although some had difficulties adjusting to diagnosis. One participant had frustration from not knowing what causes it and not being able to plan meant a change in perspective in life, from being meaningful and predictable and to change the way she approached stressful situations.

Study	Mistry 2013[398]
	Other participants were able to make changes by focusing on the implications of the life-limiting disease and unpredictability that were not under their control to help them acknowledge and adjust to their diagnosis. Those who were able to adjust to their diagnosis seemed to start very quickly the process of re-assessing their goals and aims, and as MND symptoms progressed had to make a series of modifications to the tasks and activities in which they used to engage, for example using physical aids or embracing modern technology. Adaptations included using the internet to continue with employment and the use of a mobility scooter to maintain independent movement. There was a positive psychological effect of these as they maintained valued aspects of their lives. Indicating that whilst the level of impairment was important, the functional changes impacted more seriously on their psychological well-being. However functional adaptations are only possible up to a certain point. One participant could not change her view of life and death as she did not have the information necessary to do so – the cause. This may have hindered her ability to produce appropriate coping mechanisms and start the dynamic process of belief modification, coping and adaption.
	'A lot of normal life is lost': experiencing progressive loss Many noticed that their 'normal' previous life was being eroded. Type and frequency of social interactions had changed and sense of control/and autonomy they had over their bodies also altered as they could not complete or engage in specific tasks or activities. One participant found the communication device impeded the normal flow of conversation with his wife, friends and family. Which he felt affected his personality as unable to express himself. Other participants found social interactions reduced as they became self-conscious in public settings. One participant felt that although she had lots of family and friends support she didn't like that she couldn't do things without their support, reminding her that she had MND. Another participant found that explicitly informing people of his condition then they made accommodations for him when they conversed, which made him feel accepted. Freedom and control over bodies dwindled as MND progressed, and felt that this took away their freedom to make choices. One participant felt that as MND progresses he will be alive but not 'living'. As social situations made them uncomfortable they would less likely go out on own. Increasing the reliance on others.
Limitations	Findings not validated by participants. Themes needed further refinement. Role of the researcher not clearly defined. Not enough details on data analysis. Small sample size n=7.
Applicability of evidence	Applicable.

Study	O'Brien 2012 [435], O'Brien 2012b [433]

Study	O'Brien 2012 [435], O'Brien 2012b [433]
Aim	To explore the views of current and former family carers of people with MND and identify their need for and use of support services. To examine current carers' perceptions of barriers to the uptake of social services in the UK.
Population	Individuals with MND/ALS (N = 24/25 (contradictory in report); 16 female; 9 male), current carers (N = 18; 7 female, 11 male) and former carers (N = 10; 7 female, 3 male) of family members with MND/ALS. Patients mean disease duration = 22.8 months (range = 1 – 156 months). Current carers were caring for family member diagnosed with MND between 1 months and 7.5 years prior to the interview; former carers had been bereaved between 2-months and 7 years at the time of their interview.
Study design	Interviews. One paper also reported quantitative data concerning the uptake of social services homecare, but this was not included in this review.
Methods and analysis	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND care and research centre in NW England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only one carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the three members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	Impact on carers: Carers discussed how their caring role was both physically and emotionally draining. Carers attempted to continue caring for their loved one as long as possible, with some carers discussing how they attempted to continue without additional support for as long as possible.
	Information/Entitlement: Carers discussed how they wanted greater information about the disease and its expected progression. Patients and carers also expressed a desire for greater information about what services might be available for their needs, and who they should contact to initiate services. Some carers expressed a lack of clarity regarding the role and responsibilities of health and social care professionals. Carers felt that the burden of caring made it difficult to seek out this information on their own.
	Paid-for in-home carers/Understanding: Patients and carers expressed dissatisfaction with the standard of care provided by paid-for at-home care, which they associated with a lack of specialist knowledge of MND amongst agency staff and their limited time during visits. Carers also expressed dissatisfaction when they experienced a lack of continuity regarding care agency staff.
	Respite care: Respite care was perceived as a positive opportunity to have a break from the caring role. Carers who were uneasy at using respite were reassured when respite services had specialist experience of caring for patients with MND. Carers reported some variability across locations in their ability to access respite, with carers expressing a desire for both advanced and short-term booking for respite services. Some carers reported feelings of guilt where patients were unwilling to agree to respite.
	Counselling: Many carers felt unable to talk to friends and family about the impact of the disease was having on them. Some carers felt that accessing formal counselling would be helpful, particularly post-bereavement, and those who did access formal counselling reported positive

Study	O'Brien 2012 [435], O'Brien 2012b [433]
	experiences. Carers reported some difficulty in accessing counselling, and a lack of knowledge about how to access it.
	Carers' training needs: Carers expressed a need for education and training in manual handling in caring for a patient with disabilities. This was due to safety issues for themselves, as well as to ensure that they could care for their loved one properly. Carers also felt that support and guidance from professionals in how to manage particular situations, including emergency situations, would be useful.
	Normality: Patients and carers expressed a wish to maintain a sense of normality and retain some control of their personal lives.
	Care provision: Participants discussed how they felt that there were limited resources for caring for patients with MND in the community. Participants felt that financial constraints would limit the availability of care available to them to stay at home, despite the additional cost their treatment would cost as an inpatient.
	Putting off care: Some carers found it difficult to admit finding it difficult to cope with caring, and some rejected additional support out of a sense of duty to the patient.
Limitations	Themes needed further refinement and greater depth in places. Role of the researcher not clearly defined.
Applicability of evidence	Partially applicable

Study	O'Brien 2004A[432]
Aim	Exploring the desire for information about MND and the experiences in seeking and obtaining such information in people with different stages of progression.
Population	N=7 people with MND (of varying lengths of time). 3 were men, 4 were women. 3 had bulbar onset and four had limb onset disease. Mean age 66 years (range 57-75), average time from diagnosis to interview 17 months (range 3-50 months).
Study design	Qualitative: semi-structured interviews. Interpretative phenomenological analysis approach was used.
Methods and analysis	Non-probability techniques for sample. In-depth, semi-structured audiotaped interviews. Topics covered included: their understanding of MND, when they first sought information about MND, their experiences when they were given their diagnosis, the source of any information they had received, its clarity and usefulness, whether their current information needs were being met, factors affecting their desire to seek information, the impact of information about MND on their lives in general, the effect of exposure to information available in the media. Interviews were conducted in their own home and lasted between 45 and 90 minutes. The interview was transcribed verbatim. These were read through a number of times with notes taken and then repeated the second and third transcripts to get an impression of content and not areas of commonality as themes. Interviews treated in identical manner. Any emerging themes were incorporated into subsequent interviews to clarify their relevance to other participants. The participants were approached after interview to clarity their own contribution and discuss the emerging

Study	O'Brien 2004A[432]
	themes.
Themes with findings	Information needs increased and decreased for participants over time, and based information-seeking on their attitude to the management of their illness at that particular time. All participants knew where to obtain information if they wished, but some would only encounter information after a 3rd party had screened its content. Three categories of information-seeking emerged, may not have been constant through their illness. Moved between categories depending on individual needs of the time.
	Active seekers: Often started to acquire information about MND early in the illness. Sought information from a variety of sources, verbal, written, visual and electronic. Did not rely on others to screen material for suitability. They can reach a saturation point, where they stop actively seeking, but may re-start later on in their illness when they had new problems although this did not occur in all cases.
	Selective seekers: They did not want to have a full understanding of the potential implications of the illness at the time of their diagnosis. Had access to written and verbal information but did not always use it. Often relied on 'buffers' to acquire information for them, to filter out unsuitable material that could upset them. Purposefully gathered information, seeking details about issues that concerned them at that particular time. Did not seek information about potential problems or general information about MND itself. Coped day-to-day with illness and thought it would be detrimental to have more detailed information about what might not occur.
	Information avoiders: Did not actively seek information, yet not entirely ignorant about illness. They may avoid information due to fear of details of the disease that won't affect them currently. They felt that anticipating future disability would not help their current situation. Always used a 'buffer' to screen information they were exposed to. Anxious about exposure to information about MND. They may change their information-seeking behaviour during the course of illness, but usually only to ask limited, specific questions about particular problems they have at the time.
	Media coverage and unscreened information: Threat of unsolicited information, by media coverage, encountering details of people with more advanced progression of the disease.

Study	O'Brien 2004A[432]
	This can be distressing and one participant felt that this had invaded her personal space in a threatening way. They may find out things meant for their 'buffer', which can upset them. They may avoid newspapers and TV if they have been exposed to unwanted information.
Limitations	Themes needed further refinement and greater depth in places. Not much detail about researcher.
Applicability of evidence	Applicable.

Study	O'Brien 2011[434]
Aim	To explore the personal perspectives of the diagnostic experience for people with ALS/MND and their family carers identifying issues that could impact positively or negatively on these experiences.
Population	Individuals with MND/ALS (n = 24/25) (contradictory in report); 16 female; 9 male), current carers (N = 18; 7 female, 11 male) and former carers (N = 10; 7 female, 3 male) of family members with MND/ALS. Patients mean disease duration = 22.8 months (range = 1 – 156 months). Current carers were caring for family member diagnosed with MND between 1 months and 7.5 years prior to the interview; former carers had been bereaved between 2-months and 7 years at the time of their interview.
Study design	Qualitative interviews
Methods and analysis	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND care and research centre in NW England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only one carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the three members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	Symptom onset: Symptoms went unnoticed by those with MND and their family. Often acquaintances pointed it out. No immediate cause for concern, assumed due to other things such as stress of new job. Did not associate even troublesome symptoms with a potentially serious condition. Sought medical advice when noticed worsening condition or additional difficulties.

Study	O'Brien 2011[434]
	Assumed muscle weakness due to poor fitness so many took up exercise.
	Experiences within primary care: Some patients were not taken seriously. Failure of GPs to recognise symptoms or the significance of progressive symptoms. Concurrent healthy problems confused matters, so new symptoms not noticed.
	Diagnosis delays: Delays in referral in primary care due to a lack of urgency. Delays when directed to specialities other than neurology. Some took proactive stance to get a neurologist opinion, some paying for private care for initial consultation or investigative test for a speedier diagnosis. Long periods of uncertainty surrounding assessments added to their distress.
	Communication of diagnosis: Mixed experiences, some the process was handled sensitively with appropriate explanation and sympathy. Yet many described interaction as blunt and unsatisfactory revealing poor communication skills and lack of consideration for the impact of the diagnosis on the patient and their family. Patients were afforded little privacy or time despite the devastating nature of the diagnosis. People present and location of where diagnosis delivered were commented on. Immediate post-diagnosis support was important for coping. Sympathy for doctors who have to deliver a diagnosis, however there was anger of the poor circumstances under which some individuals received their diagnosis. A number were told they had anterior horn cell disease, but as all were unaware of such a diagnosis, they sought clarity about it without adequate support.
	Responding to the diagnosis: Although traumatic, there was relief to have a name for and understand their symptoms. Some were left to cope, with inadequate support, immediately post-diagnosis. Patients should know their follow-up arrangements and have a point of contact for when they went home. Difficult telling the family. Information needs varied, but insufficient explanation was sometimes given. As ALS/MND is variable, generic information about prognosis had implications for those with atypical progression. Comparisons made with care routinely provided for people with cancer – cancer support.

Study	O'Brien 2011[434]
	Despite the availability of specialist MND support, there was a feeling that provision was better in this group.
Limitations	Themes needed further refinement and greater depth in places. Not much detail about researcher.
Applicability of evidence	Applicable.

Study	Oh 2013[441]
Aim	To explore and capture the lived experiences of wives providing care to husbands with ALS in South Korea.
Population	N=11 wives who care for their husbands with ALS in South Korea.
Study design	Qualitative study.
Methods and analysis	Part of a larger study (Oh, 2011). Used ethnographic methods with semi-structured interviews with photo elicitation, surveys, and participant observation to capture an insight into illness experiences of caring for someone living with ALS from patients and their caregivers. Interviews took place in participants home and transcribed verbatim. Participant observation used to assess physical and social environments and to validate and interpret the data collected with other methods. Asked to talk about their photographs and explain the connections with their experiences of living with ALS. Interviews began with a common question 'please tell me what it is like to live with patients having ALS' and 'please describe your positive or negative experiences in your daily life.', but follow-up questions were guided by each participant's answers and experiences.
Themes with findings	The burden from new roles as the head of family and guardian Being forced quickly into the new role of caregiver required a huge adjustment for the wives. As the husbands took on a more passive role within the family structure, the wives assumed more responsibilities as the family guardian as well as being involved in the caregiving activities. The wives-caregivers acknowledge the increased stress and demands associated with being the head of the household and their lives had been as changed by the disease as their husbands' lives had. One participant said they felt like she was his mum.
	Burden of sexual relationship Change in attitude toward keeping a sexual relationship with their ill husbands. Their husbands' physical decline caused a shift in their marital dynamic from husband and wife to patient and caregiver. Even though the husbands still showed an interest in sex, caring for their personal needs or due to their respiratory difficulty and physical disability led to a loss of sexual desire.
	Burden of relationship with in-laws [This was relevant to the South Korean society].
	Burden of becoming the family decision maker

Study	Oh 2013[441]
	[This was relevant to South Korea only as end-of-life decision making is seen as concern of the family and/or primary caregiver, not the patient].
Limitations	Findings not validated by the participant. Not much detail about researcher. Not much detail on ethical issues except approved by the Institutional Review Board. Online flyer on the website of the Korean Amyotrophic Lateral Sclerosis Association could lead to convenience sampling bias.
Applicability of evidence	Partially applicable. Some aspects related to South Korea only.

Study	Oh 2014A[442]
Aim	Explored the illness experiences from the perspectives of patients with ALS in the sociocultural context of South Korea.
Population	N=15 patients with ALS in South Korea.
Study design	Qualitative study.
Methods and analysis	Part of a larger study (Oh, 2011). Used ethnographic methods with semi-structured interviews with photo elicitation, surveys, and participant observation to capture an insight into illness experiences of living with ALS from patients and their caregivers. Interviews took place in participants home and transcribed verbatim. Participant observation used to assess physical and social environments and to validate and interpret the data collected with other methods. Asked to talk about their photographs and explain the connections with their experiences of living with ALS. Interviews began with a common question 'please tell me what it is like to live with ALS', but follow-up questions were guided by each participant's answers and experiences.
Themes with findings	Realising the facts The diagnosis of ALS was an incomprehensible shock to patients. Most experienced sorrow, fear and loneliness along with the diagnosis. Still hard to accept for one participant 5 years after diagnosis because of the disease's slow progression. The diagnosis itself was stressful and a shock for them, but it became more real when they met other advanced patients. They had fears of death, inability to speak and respirator-dependent situations in the later stage of the disease. Although heard about ALS symptoms it was an intolerable shock when they had a visual encounter with more advanced cases.
	Making sense of ALS Because the causes of ALS have yet to be conclusively identified, patients with ALS reported trouble in making sense of their diagnosis and accepting it. 'Stress' was most common word used when describing what they felt caused the disease.
	Drifting Challenges patients faced and the changes in their physical, emotional and social relationships.

Study	Oh 2014A[442]
	Losing every day: This reflected a steady decline in function and health. Facing new challenges in everyday activities like eating, dressing, walking, toileting, and even breathing. Emotionally disabled: Physical limitation was connected to emotional difficulties and limitation. Because activities decreased because of physical limitations, they were unhappy that they could not participate in their favourite activities. Although they accepted the progression of the disease, they were frustrated. Many expressed despair with current losses and feelings of hopelessness about the possible losses in the future. Changes in relationships: Reorganisation of family relationships and dynamics. Experienced changes in their family relationships and reported feeling a burden to their families. Most talked about grasping the value of family since they had the disease. All married patients experienced changes in their relationships with their spouses. [This related to South Korea's social structure of the family]
	On a New Boat In their pre-ALS lives, patients lived in groups that shared social, financial and educational backgrounds. In their new, post-diagnosis lives (or boats) patients' experiences totally change. Goals of life and health differed from before, and they started to think of experiencing a type of death that they had never imagined. Their social relationships were limited to meeting and interacting with other patients. Their perceptions toward the future had shifted, and they had encountered unforeseen challenges in the end-of-life decision making. Identifying peers: others in the new boat: Most had not heard of ALS or had limited information as it is a rare disease. Because healthcare professionals provided limited information, finding and interacting with other patients with ALS became a highly important illness experience. [relates to the South Korea healthcare system not necessarily anywhere else]. Online ALs communities also allowed patients to communicate to each other. Some learned about impending symptoms and symptom management and shared illness experiences. This was found helpful to cope with the disease. Identifying peers was important for patients to exchange information about the management of ALS, however this could lead to problems, of people sharing own regime and folk remedies, which caused arguments among the participants. Utilising social and government support: appreciated but not enough [content relevant only to South Korea] Losing a common future: Patients experienced the loss of the normal future that they once had. Images of new futures were limited to a bed and eye movement and some

Study	Oh 2014A[442]
	felt that the future would be very hard so did not think about it.
Limitations	Findings not validated by the participant. Not much detail about researcher. Not much detail on ethical issues except approved by the Institutional Review Board. No other method of transcribing except field notes.
Applicability of evidence	Partially applicable. Some aspects related to South Korea only.

Study	Ozanne 2013[445]
Aim	To explore what helps and hinders people with ALS in finding meaning in life
Population	14 people with ALS (7 female, 7 male), age range = 42-80 years (median = 67.5). Duration of the disease ranged between 2-13 years. Participants had all received the ALS diagnosis > six months previously, had no other terminal disease and had the ability to speak comprehensibly (although in interviews, participants could also write individual words or use the letter analogy to clarify ambiguities). Patients in a late terminal stage of MND with severe respiratory insufficiency or loss of intelligible communication were excluded. Maximum variation sampling was used with respect to gender, age, psychological background and physical function.
Study design	Interviews
Methods and analysis	Semi-structured interviews conducted in person. Questions concerned meaningfulness; for example 'what gives you meaning today?', 'what do you experience as being especially important in your life?' Interviews lasted between 20-83 minutes (median = 48). Interviews were audio-recorded and transcribed verbatim. Notes were taken during the interview to support the transcripts. Transcripts were analysis using qualitative content analysis, with focus on the subject, context, and similarities and differences between and within parts of the text. The text was divided into meaning units, with each unit related to the same content and theme, before being coded and abstracted into subthemes. Authors engaged in reflection and discussion to agree on the themes, moving back and forth between the themes and text.
Themes with findings	Experiences and anxiety over life The uncertain journey towards death is more frightening than death itself: Participants experienced anxiety over the uncertainty about how long the disease would take. Each deterioration made participants think about the speed of decline and what would be the next deterioration. Incongruence of wanting to live as long as possible but not to be too incapacitated, thus avoiding thinking about the future. Anxiety over death controls one's life: Hopelessness, anxiety and thoughts about death occupied daily life. Hopelessness arose because of the lack of a cure, and the feeling that nothing had any meaning because they were going to die anyway, or believing that the course of the disease would be distressing.

Study	Ozanne 2013[445]
	Anxiety over death controlled their lives and their condition. The physical loss puts one's whole existence on hold: Loss in physical function resulted in a loss of content in life, with fear of losing more abilities for example to walk and communicate, and not being intelligible yet comprehending everything. Having too much time on hands, including too much time to think about things. Disappointment in being dependent on others. The days felt long for those who lived an active life and starting to think too much, when they had nothing to do during the day. Difficult to find a meaningful content in daily life. Bitterness grows from feelings of unfairness: Participants discussed questions about why they had contracted the disease, and some found it hard to accept the disease, and questioned whether they had done something bad. Loss in religious belief. Feelings of having done well in life made it difficult to accept the disease. Feelings of guilt and shame: Feeling like a burden on families caused feelings of guilt, and sometimes resulted in participants exerting control over their healthcare (for example writing wills) to make things easier for their families. Some isolated selves due to shame of having the disease and disability, and not wanting sympathy. Feelings of existential loneliness: Participants discussed fears of physical and existential loneliness, worrying that those they depended on would die before them. Existential loneliness happened when the family found it hard to talk with each other or when the person with MND felt they had to support their family. Knowing they would leave their family, particularly with young children was hard.
	Finding meaning despite the illness Family and friends give strength: Friends and family gave participants meaning and strength through presence and support. Feelings of being accepted as an individual, along with support from friends, helped them to find meaning. Giving and receiving help: Help from the outside was necessary to make life meaningful, from family, hospital, social services or personal assistants. Meaning came from feeling safe in knowing they could trust to receive the help they might need. Also feeling needed and giving help to others helped participants find meaning. Having one's own life: An active life created a feeling of freedom and meaning. Spending time in nature created meaning and happiness. Work also gave meaning and strength. Accepting the present:

Study	Ozanne 2013[445]
	Living in the moment helped participants to focus on the important things in life here and now. Being near family and friend also contributed. Acceptance of the situation (not the disease) made it easier to find meaning. Hope was important too, for a cure, for the disease stopping or that it wouldn't become much worse, or surviving over a particular time. Life perspectives grow from shallow to deep: Participants discussed having a deeper perspective on life since their diagnosis. It was easier to live in the present and not plan things in advance. They found happiness in small things. The disease showed them what was important in life.
Limitations	Lacking some information on analysis so rigour and reliability unclear. Findings not validated with participants.
Applicability of evidence	Applicable

Study	Olsson 2012[444]
Aim	To explore what factors facilitate and hinder the manageability of living with ALS
Population	N=14 people with ALS (7 female, 7 male), age range = 42-80 years (median = 67.5). Duration of the disease ranged between 2-13 years. Participants had all received the ALS diagnosis > six months previously, had no other terminal disease and had the ability to speak comprehensibly (although in interviews, participants could also write individual words or use the letter analogy to clarify ambiguities). Patients in a late terminal stage of MND with severe respiratory insufficiency or loss of intelligible communication were excluded. Maximum variation sampling was used with respect to gender, age, psychological background and physical function. N=13 next of kin (8 men and 5 women), age range 38-87 years (median 68 years).
Study design	Interviews
Methods and analysis	Semi-structured interviews conducted in person. Questions included 'how has the disease affected your life'?, 'how do you manage the situation?, how are you experiencing your life situation now?', and 'what gives your life meaning?' Interviews lasted between 20-83 minutes (median = 48). Interviews were audio-recorded and transcribed verbatim. Notes were taken during the interview to support the transcripts. Transcripts were analysis using qualitative content analysis, with focus on the subject, context, and similarities and differences between and within parts of the text. The text was divided into meaning units, with each unit related to the same content and theme, before being coded and abstracted into subthemes. Authors engaged in reflection and discussion to agree on the themes, moving back and forth between the themes and text.
Themes with findings	The perspective on oneself Fluctuations in acceptance and burden: Patient: Acceptance and living in the present reduced the pain of thinking about the disease and the future. Focusing on health and an active life enables functioning in everyday life. Changes in integrity and autonomy affect self-esteem and activity.

Study	Olsson 2012[444]
	Forced passivity leads to frustration, negative thoughts, isolation and control issues Next of Kin: Acceptance and living in the present reduce the pain of thinking about the disease and the future. Burden affects fluctuation between possibility and absence of own time. Fear, hate and one's own ill health reduce ability to manage.
	The perspective of the family Fluctuations in support and disparate needs: Patient: Understanding and support strengthen, while guilt and differing communication needs weaken the ability to manage. Children give strength to fight but also lead to worries about their vulnerability. Next of kin: Understanding and support strengthen, while differing communication needs and feelings of being controlled weaken the ability to manage. One's creativity facilitates the common every day, whereas practical liabilities decrease the ability to manage. Children's vulnerability causes qualms of conscience and worries about not withstand to support.
	The perspective of others Fluctuations in real presence and fear: Patient: Own attitude and speech problems control communication with others. Real presence gives strength, while others' fear of the situation reduces the ability to manage. Next of kin: Real presence gives strength, while fear of preconceptions and absence of support reduce the ability to manage
	The perspective of authorities Fighting for support versus not accepting support: Patient: Support creates feelings of security, while pride and shame reduce acceptance of help. Lack of insight among the authorities reduces ability to manage.

Study	Olsson 2012[444]
	Next of kin: Support creates feelings of security, while pride and shame reduce acceptance of help. Help from the outside and communication support facilitate the everyday living.
Limitations	Lacking some information on analysis so rigour and reliability unclear. Findings not validated with participants
Applicability of evidence	Applicable

Study	Oyebode 2013A[448]
Aim	Explore the experience of living with, and caring for, a partner with MND.
Population	N=8. Partners of individuals with MND. Six females and two females (40-70 years), two were working, one was semi-retired and fiver retired; 3 had significant health problems. Their partners had been diagnosed 6-9 months previously, 5 were wheelchair bound, 3 used PeG tubes to feed, 1 used a talking machine to communicate and 2 had significant cognitive deficits.
Study design	Qualitative study: semi-structured interviews.
Methods and analysis	Transcripts analysed from an interpretative phenomenological perspective (IPA). Participants had to be caring for a co-resident spouse of partner with definite or probable MND (El Escorial criteria). An interview guide was used and covered the participant's general thought about living with their partner, their roles in providing support, their relationship with their partner, with significant others and with services, and how these things had impacted upon them and changed over time. Each aspect was asked with open-ended questions and encouraged examples and reflections. Interviews lasted 60-90 minutes. Analysis followed process described by Smith and Osborn (2003). Interviews and transcription undertaken by second author and interpretation was joint between first and second authors.
Themes with findings	Impact on life Having concern for partner's safety: Most were worried about leaving partners at home, worried in case anything happens to them Watch over their partners even those mildly affected, perception of vulnerability linked to their physical symptoms. Having social restrictions: Eating together or dining out could be an issue (those fed through a PEG). Required breaks for themselves but felt guilt when did.

Study	Oyebode 2013A[448]
	Continually tired: Physically tired most of the time, due to sleep disruption by having to turn their partners over and due to night-time PEG feeding. Daytime care needs were also exhausting, such as physically trying to move the person can be extremely hard. This can lead to anxiety and impacts on mood. Struggling with anger and frustration: Time taken over by caring so can't do other things, resent the disease. Dealing with partner's cognitive impairment can be hard, for example they don't remember anything. Anger at the loss of the person and cheated of their future together. Loss of intimacy: Loss of intimacy due to changes in partner's strength, their fragility. Cognitive changes impacted on how easy to feel close. Child-parent dynamic occurred in couples relationships. Difficulty to maintain an intimate roman tic relationship. One participant maintained a sense of intimacy, despite having to provide physical care and relying on a communication machine, she saw him as retaining the same qualities as he had before. Uncertainty around the future: Variation in how long individuals survive with MND was experienced as a source of sadness.
	Adjusting to the situation Trying to be strong: All expressed need to be mentally strong for both of them. Tried not to burden partners by not showing negative feelings in front of them. Retaining a sense of normality in the face of change: Several participants coped by socialising more, giving them a sense of normal life continuing. Appreciation of specialist services:

Study	Oyebode 2013A[448]
	All experienced the specialist MND clinic as supportive and containing. Information given in a sensitive way. Appreciated access to expert knowledge. Hope they experienced knowing about the Service's involvement with research, 'first to know if anything good comes along.' Adopting a problem-solving approach to practical difficulties: Most helpful aspect of contact with professionals was their practical, problem-solving approach 'it's having at their fingertips all the practical advice. So it's the way they handle it… knowing what the problem will be and knowing what you're likely to face.' Carers focused on practical ways of helping their partners, for example making adaptations to their homes – this gave them a sense of control and helped them to cope with the emotional impact of their partners' deterioration. Those with more advanced MND were no longer able to find practical solutions and one participant described how he could also no longer avoid the emotional impact. Living day to day: Most lived day to day. Make the most of each day. Ability to remain positive: Many had ways to find positives, emphasising remaining capabilities or counting their blessings. Some felt that MND gave them time to make decisions and have time together.
Limitations	Findings not validated by participants. More details on questions asked required. Role of the researcher not clearly defined.
Applicability of evidence	Applicable

Study	Taylor 2011a[543]; Taylor 2014[544]
Aim	To understand the impact of life-limiting illness on the expression of sexuality and intimacy for people with MND and their partners, to understand the meaning of sexuality and intimacy for these individuals, and to identify recommendations for healthcare practice.
Population	Individuals with MND (N = 13) and their partners (N = 10); ages ranged between 32 and 82 years. Participants were recruited through one specialist MND clinic. Participants were eligible to participate if they were aware that their illness was life limiting, and they were able to speak English. Exclusion criteria were being unable to consent and if their consultant or specialist nurse felt that they were too ill to participate. One participant

Study	Taylor 2011a[543]; Taylor 2014[544]
	was bisexual and the remainder were heterosexual. Participants were from eight counties in the south of England.
Study design	Interviews.
Methods and analysis	Participants were recruited using purposive sampling to capture a variety of MND phenotypes. Three participants were interviewed once, all other participants were interviewed twice. The second interview took place 2-6 weeks after the first interview. Conversational interview approach was used. The authors report no interview schedule was used, however all individuals were asked question about the following; participants' reasons for taking part in the study, how MND had affected their day to day life, whether MND had affected intimacy or sexuality, and whether health professionals had spoken to them about this. Prompts were also used, and the researcher maintained field notes through the data collection and analysis. Interviews averaged 66 minutes in length, were audio-recorded and transcribed. Heideggerian hermeneutic phenomenology approach was used to analyse data. Analysis involved reading, re-reading and interpreting the transcripts to identify themes, which were confirmed through further reading of the transcripts, This paper reported the descriptive themes identified in the earlier stages of the analysis.
Themes with findings	The importance of touch: Participants discussed how touch was important emotionally and in maintaining their relationship
	The impact of equipment upon relationships: Participants described how assistive equipment (including wheelchairs, hospital beds, reclining armchairs and walking aids) restricted intimacy by affecting the quality and frequency of touch. Where a hospital bed was provided, this signalled a separation of the patient and their partners, which was distressing. This was magnified when the bed was placed in a separate room from where their partner slept. Communication devices may also impact upon the expression of sexuality and intimacy, particularly where they generate an electronic voice of the opposite gender.
	Overcoming the restrictions equipment imposed: Some of the participants were unable to suggest ways they had managed to overcome the restrictions in sexual activity and intimacy. Others had made an effort to overcome the barriers. For example, participants described how efforts to overcome the separation by the introduction of a hospital bed (for example sleeping in the same room, pushing beds together) was greatly beneficial to maintain a physical, sexual and emotional connection.
	The role of the occupational therapist: Most participants said that they had not spoken with any health professional about sexuality or intimacy, and participants were unable to imagine what role an occupational therapist might have to support them with this issue.
	Sexuality and intimacy as embodied experiences: Expressed as embodied, physical experiences to connect with their partner. Non-sexual touch valued to maintain intimacy and to connect.
	Time running out: MND shortening life-span, the participants referred to their remaining time as a couple running out. Heightened awareness that their sexual relationship was coming to an end.
	Barriers to physical expressions of intimacy: many barriers primarily due to the physical effects of MND on the body, although could also be compounded at times by the partner's health or behaviour.
	The failing body as a barrier to intimacy: When movement no longer effortless, intimate touch was clumsy, no escape from disease, even during sex. Impaired balance and risk of falling limited spontaneous hugs. Fatigue further barrier to sexual intimacy. Pain significantly restricted physical contact. Lack of reciprocity. Further restrictions when breathing impaired.

Study	Taylor 2011a[543]; Taylor 2014[544]
	An altered sense of sexual self: impeded sexual intimacy.
	Barriers to intimacy imposed by the partner: Some of the patients had co-existing conditions and partners also had ailments that restricted close physical contact. Often when they became more disabled the partner was unable or unwilling to assume the active sexual role.
	Overcoming the barriers to physical intimacy Realising the positives alongside the negatives: loss within physical relationship was a common themes, but some found advantages too such as separate beds made sleeping pattern better.
	Physically adapting to the changes required: some unable to overcome the barriers and adapted to their changes in their sexual relationship imposed by immobility.
	Increased reliance on alternative forms of intimacy: aware that they hugged more for intimate communication.
	Discussing sexuality and intimacy with health professionals:
	The subject is rarely raised: by health professionals.
	Uncertainty about the health professionals' role: participants were unclear about what HPs could offer as subject never broached, or did not see need for external help.
	Conversations should be optimal: HPs should not require people to discuss this private aspect of their lives, but create opportunities (for example what is available in the way of counselling) and not push too hard.
	Opportunities should be created by the health professional: often did not want to initiate conversation with HPs.
	The importance of privacy: some participants wanted one-to-one conversations with HPs without partner present.
Limitations	Little information on analysis so rigour and reliability unclear. Findings not validated with participants. While the role of the researcher should be accounted for as part of the approach in analysis, no explicit reference in the paper to the role of the researcher. Paper indicates that the results are part of the early analytic process, unclear what happened to these themes in later development.
Applicability of evidence	Partially applicable

Study	Whitehead 2012[576]
Aim	To explore MND patients' and carers' experiences of the final stages of the disease
Population	Patients (N = 24), current carers (N = 18) and bereaved carers (N=10; total N = 52) recruited through a MND care and research centre in NW England, and through adverts in newsletter and by allied health professionals in their contact with patients. Purposive sampling was used to incorporate a wide range of experiences (type of illness, illness duration, severity and PCT provider)

Study	Whitehead 2012[576]
Study design	Interviews
Methods and analysis	Phenomenological approach was taken to gain appreciation of the experiences of living with MND. Narrative interviews, where patients allowed to tell their story. Interview ranged from 45 minutes - 2 hours. A list of subjects (unclear) was used as prompts if needed. Patients with severe speech difficulty were interviews by email. Participants were also given the option to complete a personal diary for up to one year to also be included in the study. Thematic analysis used to analyse; initial codes were identified, reviewed and revised. Overarching themes constructed was codes (no detail) if they captured the 'richness of the phenomenon'. Codes from initial 3 transcripts informed the interpretation of later transcripts - unclear. Some participants (unclear how many) verified the themes
Themes with findings	Anxieties: Patients discussed anxiety about uncertainty in the time the disease would take and in the variability of prognoses. The uncertainty in the progression of the disease and the loss of physical abilities and communication capabilities and whether this would result in loss of personal control and with the ability to have a say in decision making. Fears of the impact on their lives, and in how death would occur. Carers expressed anxiety over whether they will be able to cope the disease advanced, how respond to bereavement, and how their children would cope with the loss.
	End of life decision making and advanced care planning: Some participants felt they needed more information about treatment and care options to be able to make decisions about end of life care. Participants expressed concerns that their wishes were not always heard or adhered to by healthcare professionals.
	Services at the end of life stage: Many participants expressed a wish to die at home. Participants discussed a need for greater support at this time, and there were complaints about limited GP involvement and a lack in continuity of care. Accessing care was perceived as difficult, and services were provided late in the disease trajectory.
	Impact on carers: Caring was associated with a great physical and emotional burden, with carers expressing complex feelings about the death of their loved one. Following bereavement, carers reported complex feelings and distress, however few carers received bereavement support. An opinion expressed by all that as living with the illness became all-consuming for everyone involved, death would bring release for both the patient and their family.
	Euthanasia: Some participants perceived euthanasia to be a favourable option. Other participants were distressed about their potential future health, but felt that euthanasia was against their principles.
Limitations	Little information on analysis so rigour and reliability unclear. No details on role of researcher.

Study	Whitehead 2012[576]
Applicability of evidence	Applicable

G.6 Social care support

Study	Gent 2009[238]
Aim	To explore the experiences of MND carers to identify the coping strategies adopted and the potential implications for service provision
Population	Family carers (n=6) of patients with MND (3 women and 3 men). Mean age =73.3 years, SD =7.42 (range =63-83 years). United Kingdom.
Study design	Interview
Methods and analysis	Participants recruited using convenience sampling via a MND clinical nurse specialist not involved in the study. Semi-structured face-to-face interviews, recorded and transcribed. Interview schedule contained introductory prompts, factual questions concerning demographic data and medical history, and a series of open-ended prompts to elicit discussion about coping strategies and behaviour. Themes identified were incorporated into the interview schedule for later interviews. Data were organised into emerging themes and sub-themes. The main recurrent themes were identified and labelled using numerical codes, and links drawn between emerging themes and concepts. Process was informed by the analytic hierarchy. Half of the transcripts were analysed independently by another researcher and discussed subsequently by both researchers to ensure that themes were consistent.
Themes with findings	**Support for carers** Formal statutory and voluntary support mechanisms: most carers received support from health and social care providers, including both practical support and expert advice and guidance. • Informal support mechanisms: all carers received some support from other sources including family, friends and neighbours.
	Technical support Carers reported how they had received assistive technology from statutory and non-statutory agencies and they were satisfied with the devices. The devices had an impact on both carer and recipient's quality of life. The devices allowed some carers to support their loved one irrespective of their own ill-health, and they improved outdoor mobility and transfers.
	Coping strategies Managing attitudes and emotions: carers discussed how they coped with their emotions alongside their caring role. This included strategies such as having a positive approach to caring, showing and venting emotions, and focussing on the present. • Managing problems: some carers discussed how they met the needs of their loved one by problem-solving together their needs and how they could be met. • Managing time: carers discussed how it was important to manage time effectively to allow them to continue with their own preferred interests and social activities.

Study	Gent 2009[238]
	Nature of the caring role Providing personal care: some carers provided considerable personal care while others provided relatively little. The nature and amount of personal care provided was not always consistent. Some family members found it difficult to provide personal care. Providing support at meal times: some carers provided support at meal times, including selecting foods which could be handled independently or eaten safely when tired, and placing items within reach and in an appropriate receptacle.
Limitations	Unclear whether an established method was used for the analysis (for example thematic analysis). Results not validated with participants. Unclear if there was disagreement between researchers on any themes, and if so how this was resolved. Analysis needed greater depth. Role of the researcher unclear.
Applicability of evidence	Applicable

Study	Herz 2006[271]
Aim	To explore the experience and perceptions of carers of people with MND, with an emphasis on the later stages of the disease
Population	11 carers (3 current carers; 8 former carers) who participated in separate focus groups (2 groups of former carers and 1 group of current carers. Male =4, female =7, wide age range (<35 n=1; 76-85 n=1). Of current carers, only those with relatives in end stage MND were included. Carers were mainly the partners of patients, but minority of carers were children (n=3). Adverts were placed in the MND association of NSW newsletter (Australia).
Study design	Focus groups
Methods and analysis	Focus groups included a list of prompts covering topics expected to be important including practical, symptom management, psychological, spiritual, service-oriented and institutional aspects of care, information needs, planning ahead, knowledge of and contact with palliative care. For former carers, topics also included death, advance directives and bereavement. In each section, participants were asked about their needs, how well those needs were met, the advantages and disadvantages of the current system, and how the situation could be improved. Discussions were audiotaped and transcribed. Themes were extracted by the researcher and in discussion with the research team. Interpretation of themes was facilitated by reading transcripts and wider literature.
Themes with findings	**Role of the general practitioner** Participants perceived the GP as an ally, but one with limited time and knowledge about MND.
	Role of the MND Association Participants appreciated the information and practical support provided by the MND Association.
	Unremitting care Carers discussed feeling unwilling to relinquish care of their loved one to support services.

Study	Herz 2006[271]
	Emotional cost to the carer The emotional cost as a carer was discussed as being greater than the physical burden, and carers discussed how the emotional impact extends long after the death of their loved one.
	Need for respite Former, but not current, carers discussed the need for respite for emotional release and replenishment.
	Accessing help None of the former carers sought professional support for their emotional needs. Carers discussed a preference to cope without external support.
	Love Carers expressed love and respect for their loved ones. Caring was seen as test on the love in the relationship, with the act of caring an expression of their love.
	Trapped and drowning The deterioration in health of the patient and the increasing burden on the carer was described as a 'downhill' spiral and like 'drowning'.
	Financial burden Some carers with good finances were able to manage, while others expressed a need for greater financial support.
	Access to palliative care Only a small number of former carers identified contact with palliative care, which had occurred very late in the course of the disease. The specialist support was perceived as greatly beneficial.
	Return to living Some former carers discussed a return to living following the death of their loved one.
Limitations	Little information on analysis so rigour and reliability unclear. Analysis could have been more in-depth. Unclear if themes reached saturation. Findings not validated with participants.
Applicability of evidence	Applicable

Study	Hogden 2013[278]
Aim	To explore carer participation in decision-making, to identify carer roles, and determine the facilitators and barriers to carer participation in decision-making for ALS multi-disciplinary care.
Population	8 carers of family members with ALS (5 female, 3 male), age mean =56 years (range =33–76 years). All 8 patients they cared for were in the

Study	Hogden 2013[278]
	advanced stages of ALS. Duration of care ranged between 6–96 months.
Study design	Interviews
Methods and analysis	Semi-structured interviews containing 10 open-ended questions informed by the literature and clinical and research experience of ALS. Six participants were interviewed in person, 2 via email. Face-to-face interviews were audio-taped and transcribed, and all transcripts were validated by participants. Analysis was checked by 2 co-authors to reach agreement. Transcripts were analysed using thematic analysis. Patterns in the data relevant to the aims of the study were identified to reveal trends and relationships in participants' accounts. Codes were grouped by meaning, creating subthemes. Subthemes were then refined into themes, alongside associated facilitators and barriers.
Themes with findings	**Promoting the patient voice** Carers facilitate communication between patient and health professionals and support patients to make decisions regarding their care.
	Promoting patient health literacy Carers source and synthesise health information, filter the amount and content of information for the patient and family, and provide information to the patients. Access to credible and evidence-based information facilitates this.
	Emotional support Carers provide emotional support for discussion of patient's changing needs.
	Logistical support Carers provide physical and practical assistance for patients to attend appointments and help to coordinate services and appointments. This is facilitated by physical and practical support for the carer from family, friends and health services, with a burden of care acting as a barrier to this.
Limitations	Role of the researcher not clearly explained. Questions explicitly shown but a couple of them were closed questions. No details on ethical implications except committee approval. Findings not validated with participants.
Applicability of evidence	Applicable

Study	McKelvey 2012[387]
Aim	To describe communication patterns of individuals with ALS over time as the disease progressed and to understand the lived experiences from the surviving spouses' perspectives.
Population	Bereaved carers (n=6) (female=2 male = 4; age range =42–75 years) of six individuals who had ALS. Time between death and time of interview range =6–144 months. Time from diagnosis to death range =10–78 months.
Study design	Interviews
Methods and	Individual semi-structured interviews (60–90mins) audio-taped and transcribed. The interview schedule comprised 18 questions with additional

Study	McKelvey 2012[387]
analysis	prompts for greater detail. Transcripts were checked against the audio recording for accuracy. Three researchers developed the initial codes on 2 of the transcripts. These codes were categorised and organised into themes. Effort was made to code sections of text left un-coded and to collapse overlapping themes. Two researchers performed an independent parallel coding process, to re-code the transcripts using the derived themes. The third researcher checked the independent parallel coding process. Any discrepancies in the interpretation of the data by researchers were discussed and agreement was reached on all themes.
Themes with findings	**Communication styles** Carers discussed their partners' communication styles before and after the onset of ALS.
	Augmentative and alternative communication devices: Carers discussed the importance of AAC devices for patients' quality of life and in enabling patients to communicate basic needs, share opinions, express feelings, and maintain their social roles in family and society. Carers discussed the importance of finding a system that fitted peoples' (changing) needs. Carers discussed their own novel approaches to maintaining communication and some of the barriers to using the devices.
	Decision-making Carers discussed how there were lots of decisions to make following the diagnosis, and that their loved ones' role in decision-making changed after their diagnosis. Carers supported their loved ones' to get out of the house to live their lives.
	Lifestyle changes Carers discussed changes in their loved ones' ability to maintain relationships and interact socially.
Limitations	Themes needed further refinement. Role of the researcher not clearly defined.
Applicability of evidence	Applicable

Study	O'Brien 2012 [435], O'Brien 2012b [433]
Aim	To explore the views of current and former family carers of people with MND and identify their need for and use of support services. To examine current carers' perceptions of barriers to the uptake of social services in the UK.
Population	People with MND/ALS (n=24/25 [contradictory in report]; 16 female; 9 male), current carers (n=18; 7 female, 11 male) and former carers (n=10; 7 female, 3 male) of family members with MND/ALS. Patients' mean disease duration =22.8 months (range =1–156 months). Current carers were caring for family member diagnosed with MND between 1 months and 7.5 years prior to the interview; former carers had been bereaved between 2 months and 7 years at the time of their interview.
Study design	Interviews. One paper also reported quantitative data concerning the uptake of social services homecare but this was not included in this review.
Methods and	Purposive sampling was used to recruit participants with a range of disease severity scores (ALS-HSS). Participants were recruited though an MND

Study	O'Brien 2012 [435], O'Brien 2012b [433]
analysis	care and research centre in north-west England. Additionally, adverts were placed in relevant newsletters and information sheets aimed at the MND community. 'Loosely structured' narrative interviews were conducted, with some prompts where required. Carers were given the opportunity to maintain a personal diary of their experiences, although due to time constraints only 1 carer completed this aspect of the study. Interviews were conducted in participants' homes, were audio-taped and transcribed. Thematic analysis was used to analyse the data. Analysis of transcripts was used to inform later interview schedules. Transcripts were analysed independently by the 3 members of the research team before discussion and agreement on the themes. This resulted in a coding frame for the interpretation of subsequent interviews. Differences and similarities between transcripts were explored through constant comparison. Participants verified the themes chosen.
Themes with findings	**Impact on carers** Carers discussed how their caring role was both physically and emotionally draining. Carers attempted to continue caring for their loved one as long as possible, with some carers discussing how they attempted to continue without additional support for as long as possible.
	Information/entitlement Carers discussed how they wanted more information about the disease and its expected progression. Patients and carers also expressed a desire for more information about what services might be available for their needs and who they should contact to initiate services. Some carers expressed a lack of clarity regarding the role and responsibilities of health and social care professionals. Carers felt that the burden of caring made it difficult to seek out this information on their own.
	Paid-for in-home carers/understanding Patients and carers expressed dissatisfaction with the standard of care provided by paid-for at-home care, which they associated with a lack of specialist knowledge of MND amongst agency staff and their limited time during visits. Carers also expressed dissatisfaction when they experienced a lack of continuity regarding care agency staff.
	Respite care Respite care was perceived as a positive opportunity to have a break from the caring role. Carers who were uneasy at using respite were reassured when respite services had specialist experience of caring for patients with MND. Carers reported some variability across locations in their ability to access respite, with carers expressing a desire for both advanced and short-term booking for respite services. Some carers reported feelings of guilt where patients were unwilling to agree to respite.
	Counselling Many carers felt unable to talk to friends and family about the impact the disease was having on them. Some carers felt that accessing formal counselling would be helpful, particularly post-bereavement, and those who did access formal counselling reported positive experiences. Carers reported some difficulty in accessing counselling as well as a lack of knowledge about how to access it.
	Carers' training needs Carers expressed a need for education and training in manual handling in caring for a patient with disabilities. This was due to safety issues for themselves as well as to ensure that they could care for their loved one properly. Carers also felt that support and guidance from professionals in

Study	O'Brien 2012 [435], O'Brien 2012b [433]
	how to manage particular situations, including emergency situations, would be useful.
	Normality Patients and carers expressed a wish to maintain a sense of normality and retain some control of their personal lives.
	Care provision Participants discussed how they felt that there were limited resources for caring for patients with MND in the community. Participants felt that financial constraints would limit the availability of care to enable them to stay at home, despite the additional cost their treatment would incur as an inpatient.
	Putting off care Some carers found it difficult to admit finding it difficult to cope with caring, and some rejected additional support out of a sense of duty to the patient.
Limitations	Themes needed further refinement and greater depth in places. Role of the researcher not clearly defined.
Applicability of evidence	Applicable.

Study	Taylor 2011a[543]
Aim	To understand the impact of life-limiting illness on the expression of sexuality and intimacy for people with MND and their partners, to understand the meaning of sexuality and intimacy for these people, and to identify recommendations for healthcare practice.
Population	People with MND (n=13) and their partners (n=10); ages ranged between 32 and 82 years. Participants were recruited through 1 specialist MND clinic. Participants were eligible to participate if they were aware that their illness was life-limiting and they were able to speak English. Exclusion criteria were being unable to consent and if their consultant or specialist nurse felt that they were too ill to participate. One participant was bisexual and the remainder were heterosexual. Participants were from 8 counties in the south of England.
Study design	Interviews
Methods and analysis	Participants were recruited using purposive sampling to capture a variety of MND phenotypes. Three participants were interviewed once; all other participants were interviewed twice. The second interview took place 2–6 weeks after the first interview. Conversational interview approach was used. The authors report that no interview schedule was used, however all individuals were asked question about the following: participants' reasons for taking part in the study, how MND had affected their day-to-day life, whether MND had affected intimacy or sexuality, and whether health professionals had spoken to them about this. Prompts were also used, and the researcher maintained field notes through the data collection and analysis. Interviews averaged 66 minutes in length, were audio-recorded and transcribed. Heideggerian hermeneutic phenomenology approach was used to analyse data. Analysis involved reading, re-reading and interpreting the transcripts to identify themes, which were confirmed through further reading of the transcripts. This paper reported the descriptive themes identified in the earlier stages of the

Study	Taylor 2011a[543]
	analysis.
Themes with findings	**The importance of touch** Participants discussed how touch was important emotionally and in maintaining their relationship.
	The impact of equipment upon relationships Participants described how assistive equipment (including wheelchairs, hospital beds, reclining armchairs and walking aids) restricted intimacy by affecting the quality and frequency of touch. Where a hospital bed was provided, this signalled a separation of the patient and their partners, which was distressing. This was magnified when the bed was placed in a separate room from where their partner slept. Communication devices may also impact upon the expression of sexuality and intimacy, particularly where they generate an electronic voice of the opposite gender.
	Overcoming the restrictions equipment imposed Some of the participants were unable to suggest ways they had managed to overcome the restrictions in sexual activity and intimacy. Others had made an effort to overcome the barriers. For example, participants described how efforts to overcome the separation by the introduction of a hospital bed (for example sleeping in the same room, pushing beds together) was greatly beneficial to maintain a physical, sexual and emotional connection.
	The role of the occupational therapist Most participants said they had not spoken with any health professional about sexuality or intimacy, and participants were unable to imagine what role an occupational therapist might have to support them with this issue.
Limitations	Little information on analysis so rigour and reliability unclear. Findings not validated with participants. While the role of the researcher should be accounted for as part of the approach in analysis, no explicit reference was made in the paper to the role of the researcher. The paper indicates that the results are part of the early analytic process; it is unclear what happened to these themes in later development.
Applicability of evidence	Applicable

G.7 Planning for end of life

Study	Aoun 2012[27]
Aim	To explore the experiences of MND family carers through to bereavement, including whether experiences differ according to prolonged grief status and what the implications are for service delivery
Population	Bereaved spouses (n=16) of patients with MND (13 women and 3 men). Mean age =65.19 years, SD =9.28 (range =50–82 years). At time of interview, participants had been bereaved for between 1-4 years (mean =27.5 months, SD =13.6).
Study design	Interview
Methods and	Semi-structured face to face interviews, recorded and transcribed. Interviews began with the question 'tell me about your experience as a carer',

Study	Aoun 2012[27]
analysis	and included issues of diagnosis, palliative care, and coping. Thematic analysis was used to analyse the data; emerging ideas were summarised and developed into themes, then cross-checked with other transcripts to develop, refine and collapse themes. Three authors independently reviewed the transcripts and 3 participants (selection not described) validated the analysis. Any differences in interpretation were further examined until authors were satisfied that themes represented the data.
Themes with findings	The work of MND family carers: • Practical tasks. Participants discussed the many practical responsibilities they have as carers. • Exhaustion and trauma. Participants discussed how tasks, particularly those through the night, resulted in exhaustion and interfered with their recreation, sleep and exercise.
	The change in relationship from spouse to carer: • Role changes. Participants discussed how their role changed from wife/husband to that of a 'nurse' or 'carer'. • Learning new tasks. Participants discussed how they adopted the responsibilities that used to be undertaken by their loved one. • Decrease in relationship intimacy. Participants noted a reduction in intimacy in the relationship, due to the change in their role and levels of exhaustion.
	Family caring as a series of losses: • Constant loss. Participants described MND as a series of, often fast-paced, losses. • Hopelessness. Participants frequently reported feelings of hopelessness.
	Coping mechanisms of family carers: • Acceptance versus non-acceptance of diagnosis and death. Some participants discussed how they accepted the notion of their partner dying, while others did not. • 'Switching off' effect. Some participants discussed 'switching off' their emotions in order to manage their caring responsibilities. • Accommodation of loss. Some participants discussed how their initial grief following the death of their loved one had not gone away but they had grown to live alongside it.
	Supportive and palliative care experiences of family carers: • Diagnosis and absence of compassion. Participants reported an absence of compassion from medical professionals in diagnosis and through the illness. • Timeliness of, and access to, palliative care. Participants reported variation in the availability and timeliness of palliative care.
Limitations	None
Applicability of evidence	Applicable

Study	Bolmsjö 2001[69], Bolmsjö 2001a[68], Bolmsjö 2003[70]
Aim	To explore patients' and carers' experiences of MND, and challenge the notion that these groups (i) see it the same way as professionals and (ii) have the same attitudes as each other. To explore the experiences of close relatives of patients with ALS, including ethical issues, to suggest recommendations for support. To explore patients' ways of communicating existential issues and what experiences are related to these.
Population	16 participants (8 patients, 6 women; and 8 close relatives, 4 women). Mean age patients =60 years (range =53–84 years); mean age relatives =55 years (range =38–72 years). Patients interviewed in 1997, relatives were interviewed in 2000. Inclusion criteria included patients who could communicate (verbally or through devices), and patients and relatives > 6-months post-diagnosis. Potential participants were chosen with the help of a counsellor and nurse at a neurological clinic.
Study design	Interview
Methods and analysis	Semi-structured interviews, with topics agreed on the basis of previous literature, research team experience, and discussion with colleagues/experts in field: the present situation, the future, information, confidence, meaning, guilt, respect. For each topic, participants were allowed to speak without interruption and until no further information emerged. Relatives' interviews were recorded and transcribed, but participants' interviews were not recorded due to speech difficulties. For patients, the interviewer made notes. Non-essential points were removed if they were not relevant to the study aim.
Themes with findings	Experiences concerning diagnosis and information: the way diagnosis was delivered was important for patients' wellbeing. Some carers reported a lack of sympathy in the diagnosis. There were variations in the way participants received the diagnosis and the method of delivery. Some carers reported having little knowledge of the disease prognosis, and some carers reported poor knowledge about the availability of supportive equipment.
	Increasing responsibilities: carers discussed increased number of responsibilities.
	Limited freedom: carers discussed feelings that the caring role allowed them little freedom.
	Meaning and guilt: children and grandchildren provided meaning in life, however patients feared passing on the disease to their children.
	The need to confide in someone: patients did not have a strong urge to confide in someone. Some of the carers expressed a need to confide in others.
	Experiences concerning physical inability: one patient discussed how they viewed their ventilator as a means of control and ability to terminate life, while another patient found the use of the ventilator upsetting.
	The competence of the professionals: some of the patients expressed trust in the health professionals, while some carers expressed concerns that healthcare staff were not competent.
	Experiences concerning dying with dignity and respect for the person: no narrative; quotes reflect the importance of continuing to live in a way that reflects identity, retaining dignity in death, the importance of pain management and comfortable death.
	The future: carers discussed how thoughts about the future were distressing and they preferred not to think or talk about it.

Study	Bolmsjö 2001[69], Bolmsjö 2001a[68], Bolmsjö 2003[70]
Limitations	Quotations interpreted on the basis of pre-specified categories. Little information about the analysis so rigour and reliability are unclear. Analysis needed greater depth. Unclear if themes reached saturation.
Applicability of evidence	Applicable

Study	Foley 2014[220], Foley 2014b[219]
Aim	To explore and develop a theory about the processes underlying ALS patients' engagement with health services
Population	ALS population (n =34), Ireland. 17 men, 17 women. Age range =37–81 years. Mean duration of time since symptom onset =31 months (range =4 months–13 years). Nearly a third (n =10) were deceased by the end of data collection. 8 participants were using either NIV and/or gastrostomy. Recruited from the Irish ALS population-based register between September 2011 - August 2012.
Study design	Interview
Methods and analysis	Grounded theory methodology. Interviews were conducted with sensitivity to patients' disability; many patients used AAC devices to aid communication. Interviewers began by asking patients about their experiences of healthcare services since symptom onset. Interviews contained a mixture of open, probing, prompting, clarifying and verifying questions. Interviews were adapted to incorporate emerging themes. Transcripts were checked by participants, but the final analysis was not checked with participants. Explicit and implicit coding of themes was used, which were abstracted into concepts. Similarities and differences between accounts were used to develop larger themes. Memos were used to facilitate theoretical development. A second author checked the analysis. This is the first paper reporting on this data. This paper summarises the main themes.
Themes with findings	Control and reassurance/exerting control over health services: participants expressed a strong need to be in control of their care, including engagement in services and choice of treatment. Control over end of life care was particularly important.
	Resignation: perceptions of life sustaining and life ending. Participants struggled to live with MND and resigned themselves to death. Most participants questioned the role of life-sustaining treatment, including non-invasive ventilation and gastrostomy.
	Trust: participants had a strong desire to trust healthcare professionals. Participants were less likely to trust professionals who lacked empathy in the clinical encounter, and more likely to trust those who were knowledgeable, personable in their approach, and provided reassurance about their care.
	Meaning of loss in ALS: ALS was associated with a perception of continual loss and participants experienced hopelessness about the future. Losses included the physical change, their ability to engage in important aspects of their life, their identity, their feeling of control over their lives, and their future.
Limitations	None

Study	Foley 2014[220], Foley 2014b[219]
Applicability of evidence	Applicable

Study	Hagena 2014[263]
Aim	To identify what information and support MND patients and their carers want and determine whether there were barriers to taking part in support programmes in a hospice setting.
Population	Focus group containing 8 carers (3 bereaved) and 5 people with MND Postal questionnaire returned by 19 people with MND Focused interviews with 4 carers and 6 people with MND
Study design	Focus group, postal questionnaire, interviews
Methods and analysis	'A Foot in the Door': outreach programme set up to encourage MND patients to accept early introduction to hospice care services, offer support to carers and signpost people to available community services. Focus group participants were shown leaflets, a DVD and other information related to the 'A Foot in the Door' programme. They were asked to reflect and comment on the information, as well as share their thoughts and feelings about accessing hospice care. Palliative physician facilitated. Postal questionnaires were informed by themes from focus groups. Included structured and unstructured questions. Focused interviews up to 1 hour long by members of the research team. Interview topics were chosen on the basis of the focus group and postal questionnaires. Interviewing continued until the point of data saturation.
Themes with findings	Ongoing support and information needs: needs increased as patients and carers accepted diagnosis, however this varies greatly. Participants eventually stopped seeking information – all spoke about realising too much information was no good for them. As the disease progressed, carers often wanted more information than patients.
	Psychosocial support needs: patients expressed feelings of loneliness and isolation. They experienced loss of contact with friends, and diminished ability/confidence to leave house on their own. Two spoke about suicidal thoughts. All felt helplessness and hopelessness. Patients and carers talked about lack of options.
	Barriers to taking part in support programmes: all liked the idea of informal drop-in sessions rather than regular planned sessions they were obligated to attend. Fortnightly sessions were favoured. All showed an identifiable fear of meeting people with more advanced MND. All were amenable to a group for people with different neurological conditions. Varying opinions on whether that is most effective or not.
Limitations	Little information on analysis so rigour and reliability unclear. Findings not validated with participants.
Applicability of evidence	Applicable

Study	Herz 2006[271]
Aim	To explore the experience and perceptions of carers of people with MND
Population	11 carers (3 current carers; 8 former carers) who participated in separate focus groups (2 groups of former carers and 1 group of current carers. Male =4, female =7, wide age range (<35 n=1; 76–85 n=1). Of current carers, only those with relatives in end stage MND were included. Carers were mainly the partners of patients, but minority of children as carers (n=3). Adverts were placed in the MND association of NSW newsletter (Australia).
Study design	Focus groups
Methods and analysis	Focus groups included a list of prompts covering topics expected to be important including practical, symptom management, psychological, spiritual, service-oriented and institutional aspects of care, information needs, planning ahead, knowledge of and contact with palliative care. For former carers, topics also included death, advance directives and bereavement. In each section, participants were asked about their needs, how well those needs were met, the advantages and disadvantages of the current system, and how the situation could be improved. Discussions were audiotaped and transcribed. Themes were extracted by the researcher and in discussion with the research team. Interpretation of themes was facilitated by reading of transcripts and reading of wider literature.
Themes with findings	Role of the GP: participants perceived the GP as an ally, but one with limited time and knowledge about MND.
	Role of the MNDA: participants appreciated the information and practical support provided by the MNDA.
	Unremitting care: carers discussed feeling unwilling to relinquish care of their loved one to support services.
	Emotional cost to the carer: the emotional cost as a carer was discussed as being greater than the physical burden, and carers discussed how the emotional impact extends long after the death of their loved one.
	Need for respite: former, but not current, carers discussed the need for respite for emotional release and replenishment.
	Accessing help: none of the former carers sought professional support for their emotional needs. Carers discussed a preference to cope without external support.
	Love: carers expressed love and respect for their loved ones. Caring was seen as test on the love in the relationship, with the act of caring an expression of their love.
	Trapped and drowning: the deterioration in the health of the patient and the increasing burden on the carer was described as a 'downhill' spiral and like 'drowning'.
	Financial burden: some carers with good finances were able to manage, while others expressed a need for greater financial support.
	Access to palliative care: only a small number of former carers identified contact with palliative care, which had occurred very late in the course of the disease. The specialist support was perceived as greatly beneficial.
	Return to living: some former carers discussed a return to living following the death of their loved one.
Limitations	Little information on analysis so rigour and reliability unclear. Analysis could have been more in-depth. Unclear if themes reached saturation.

Study	Herz 2006[271]
	Findings not validated with participants.
Applicability of evidence	Applicable

Study	Ozanne 2013[445]
Aim	To explore what helps and hinders people with ALS in finding meaning in life
Population	14 people with ALS (7 female, 7 male), age range =42–80 years (median =67.5). Duration of the disease ranged between 2–13 years. Participants had all received the ALS diagnosis >6 months previously, had no other terminal disease and had the ability to speak comprehensibly (although in interviews, participants could also write individual words or use the letter analogy to clarify ambiguities). Patients in a late terminal stage of MND with severe respiratory insufficiency or loss of intelligible communication were excluded. Maximum variation sampling was used with respect to gender, age, psychological background and physical function.
Study design	Interviews
Methods and analysis	Semi-structured interviews conducted in person. Questions concerned meaningfulness; for example 'what gives you meaning today?', 'what do you experience as being especially important in your life?' Interviews lasted between 20–83 minutes (median =48). Interviews were audio-recorded and transcribed verbatim. Notes were taken during the interview to support the transcripts. Transcripts were analysis using qualitative content analysis, with focus on the subject, context, and similarities and differences between and within parts of the text. The text was divided into meaning units, with each unit related to the same content and theme, before being coded and abstracted into subthemes. Authors engaged in reflection and discussion to agree on the themes, moving back and forth between the themes and text.
Themes with findings	Experiences and anxiety over life and death: The uncertain journey towards death is more frightening than death itself. Participants experienced anxiety over the uncertainty about how long they would live, and fears about how death would occur. Anxiety over how death controls one's life. Hopelessness, anxiety and thoughts about death occupied daily life. The physical loss puts one's whole existence on hold. Loss in physical function resulted in a loss of contentment, with fear of losing more abilities. Bitterness grows from feelings of unfairness. Participants discussed questions about why they had developed the disease, and some found it hard to accept the disease. Feelings of guilt and shame. Feeling like a burden on families caused feelings of guilt, and sometimes resulted in participants exerting control over their healthcare (for example writing wills) to make things easier for their families. Feelings of existential loneliness. Participants discussed fears of physical and existential loneliness.
	Finding meaning despite the illness: Family and friends give strength. Friends and family gave participants meaning and strength.

Study	Ozanne 2013[445]
	Giving and receiving help. Help from the outside was necessary to make life meaningful. Also feeling needed and giving help to others helped participants find meaning. Having one's own life. An active life created a feeling of freedom and meaning. Accepting the present. Living in the moment helped participants to focus on the important things in life here and now. Life perspectives grow from shallow to deep. Participants discussed having a deeper perspective on life since their diagnosis.
Limitations	Lacking some information on analysis so rigour and reliability unclear. Findings not validated with participants.
Applicability of evidence	Applicable

Study	Preston 2012[469]
Aim	To explore carers' attitudes and experiences of using the PPC document for advance care planning
Population	Primary carers or bereaved relatives of patients with MND who had died >3 months previously, as identified from a MND Care and Research Centre (n =11). All patients must have completed a PPC document (priorities for care). Participants were 'mostly' >65 years, male, white British and had been living with the patient. Any carers who were non-English, lacking the ability to consent, or experiencing significant health problems were excluded.
Study design	Interviews
Methods and analysis	Semi-structured face-to-face interviews, recorded and transcribed. Thematic analysis was used to analyse the data (no detail). Field diaries were kept (no detail).
Themes with findings	Completion: Persons involved in completion. Most patients completed the PPC document in the presence of a relative or carer and a healthcare professional. Patients discussed the importance of completing the document with a person they had an established relationship with. Timing. Several participants suggested that the PPC document should be completed whilst patients were still able to talk or sign the document themselves. Experience of completion. Most participants reported the completion of the PPC document as positive, particularly for the patient, in affording peace of mind and a sense of relief.
	Document availability to others: Family and friends. The majority of participants showed the PPC document to their family and friends. Healthcare professionals. Participants were less likely to share the PPC document with healthcare staff.
	Importance and influence on the end of life experience:

Study	Preston 2012[469]
	Importance. The PPC document was seen as important in providing peace of mind for the patient and ensuring patients' wishes. Influence on end of life experience. Many participants felt the PPC had little impact on end of life care, with awareness of patients' wishes being more influential.
	Limitations.: A lack of awareness of the PPC document was identified as a major limitation of its use.
Limitations	Little information on analysis so rigour and reliability unclear. Analysis could have been more in-depth. Unclear if themes reached saturation.
Applicability of evidence	Applicable

Study	Ray 2014[478]
Aim	To explore family caregivers' perspectives on dying and the death event of their relative with MND
Population	Partners of patients with a confirmed diagnosis of MND. Originally 29 participants, however only those caregivers who consented to be interviewed after their relative's death were included in this study (n =unclear). Thirteen participants discussed the dying process in the original interviews. Male to female ratio of 1.4:1. Limited demographic data due to death of researcher. Recruited through MND associations (England and Australia) registers between 2003–2006.
Study design	Interviews
Methods and analysis	Secondary analysis of 2 earlier qualitative studies exploring family caregivers' experiences of providing care for a relative with MND. Original interviews were semi-structured interviews at 3–4 month intervals for 18 months. Papers ordered with original methodology. Analysis method unclear – 'description and conceptual ordering' citing grounded theory but not specifically mentioning it. Concept generation achieved through dialogue between researchers.
Themes with findings	Planning for end of life care: few participants discussed having conversations about death or dying with their loved one. Initiating conversations was constrained by the patient's unwillingness and discomfort of family members. Those who did discuss dying and made plans reported positive experiences. However, carers reported distress when plans for death were not communicated effectively or adhered to by healthcare professionals.
	Unexpected dying: negative experiences were described by carers who were unprepared for the deterioration and sudden death of their loved one. Some carers reported feeling unprepared for the symptoms of dying.
	Dignity in the dying body: carers discussed how the illness impacted on patients' dignity, and patients often wanted to be away from the reactions of others in the latter stages of the illness.
	Positive end to MND: carers were able to perceive MND in a positive light also, and discussed how healthcare professionals played a part in

Study	Ray 2014[478]
	creating a positive end of life experience.
Limitations	Little information on analysis so rigour and reliability unclear. Analysis could have been more in-depth.
Applicability of evidence	Applicable

Study	Whitehead 2012[576]
Aim	To explore MND patients' and carers' experiences of the final stages of the disease
Population	Patients (n =24), current carers (n =18) and bereaved carers (n=10; total n =52) recruited through a MND care and research centre in north-west England, and through adverts in newsletters and by allied health professionals in their contact with patients. Purposive sampling was used to incorporate a wide range of experiences (type of illness, illness duration, severity and PCT provider).
Study design	Interviews
Methods and analysis	A phenomenological approach was taken to gain appreciation of the experiences of living with MND. Narrative interviews were conducted, where patients were allowed to tell their story. The interview ranged from 45 minutes – 2 hours. A list of subjects (unclear) was used as a prompt if needed. Patients with severe speech difficulty were interviews by email. Participants were also given the option to complete a personal diary for up to 1 year to also be included in the study. Thematic analysis was used; initial codes were identified, reviewed and revised. Codes from initial 3 transcripts informed the interpretation of later transcripts – unclear. Some participants (unclear how many) verified the themes.
Themes with findings	Anxieties: participants discussed anxiety about uncertainty in the time the disease would take, in the progression of the disease and how this would impact on their lives, and in how death would occur. Carers expressed anxiety over whether they will be able to cope in the future.
	End of life decision-making and advance care planning: some participants felt they needed more information about treatment and care options to be able to make decisions about end of life care. Participants expressed concerns that their wishes were not always heard or adhered to by healthcare professionals.
	Services at the end of life stage: many participants expressed a wish to die at home. Participants discussed a need for greater support at this time, and there were complaints about limited GP involvement and a lack in continuity of care. Accessing care was perceived as difficult, and services were provided late in the disease trajectory.
	Impact on carers: caring was associated with a great physical and emotional burden, with carers expressing complex feelings about the death of their loved one. Following bereavement, carers reported complex feelings and distress, however few carers received bereavement support.
	Euthanasia: some participants perceived euthanasia to be a favourable option. Other participants were distressed about their potential future health, but felt that euthanasia was against their principles.
Limitations	Little information on analysis so rigour and reliability unclear

Study	Whitehead 2012[576]
Applicability of evidence	Applicable

G.8 Pharmacological treatment for muscle problems

Study	De Carvalho 2010[168]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Portugal; setting: Santa Maria Hospital, Portugal
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinically probable, probable-laboratory supported or definite ALS disease defined by the El Escorial criteria
Stratum	People who are not at the end of life
Subgroup analysis within study	Stratified then randomised: population stratification by region of onset (limb versus bulbar) within each treatment arm
Inclusion criteria	Disease duration less than 36 months at study entry, forced vital capacity higher than 60% of the predicted value, ALSFRS between 25 and 38, abductor minimi muscle contraction force >2 on the MRC scale in at least one hand.
Exclusion criteria	Severely affected ALS patients, signs of polyneuropathy or conduction block on the nerve conduction studies, other coincident neurological disease, clinical signs of dementia or a minimal mental state <27, uncompensated medical illness, psychiatric disease, laboratory abnormalities consistent with paraproteinaemia, thyroid or cancer, ECG abnormalities, tracheostomy, gastrostomy, previous participation in other trial, breast feeding, pregnancy or inadequate methods of contraception.
Recruitment/selection of patients	Consecutive recruitment
Age, gender and ethnicity	Age – mean (SD): 58.9 (intervention group) 58.3 (placebo group). Gender (M:F): 21:11 memantine, 21:10 placebo. Ethnicity: unclear.
Further population details	1. Cognitive ability: no frontotemporal dementia. 2. Type of disease: amyotrophic lateral sclerosis.
Extra comments	Results not reported as within trial stratum
Indirectness of population	No indirectness

Study	De Carvalho 2010[168]
Interventions	(n=32) Intervention 1: NMDA receptor agonist – Memantine. Titrated in 5mg weekly increments from starting dose of 5mg id to 10 mg bid. Duration 12 months. Concurrent medication/care: Riluzole. Further details: 1. Self-management: healthcare professional management. (n=31) Intervention 2: Placebo. Placebo tablets visually identical to memantine. Duration 12 months. Concurrent medication/care: Riluzole 50mg bid. Further details: 1. Self-management: self-management (patients given blister packs at each visit).
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MEMANTINE versus PLACEBO Protocol outcome 1: Quality of life (EQ5D, SF36, SF12, SEQUOL) - Actual outcome for people who are not at the end of life: SF36 at 12 months; Group 1: mean 37.3 (SD 10.9); n=32, Group 2: mean 40.7 (SD 16.8); n=31; SF36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score) - Actual outcome for people who are not at the end of life: MRC score for muscular strength at 12 months; Group 1: mean 110 (SD 26.1); n=32, Group 2: mean 105.7 (SD 42.4); n=31; MRC 0-160: top=High is good outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: Mobility (functional independence measure, ALS functional rating score) - Actual outcome for people who are not at the end of life: ALS functional rating score at 12 months; Group 1: mean 20.2 (SD 6.9); n=32, Group 2: mean 20.6 (SD 9.7); n=31; ALSFRS 0-40: top=High is good outcome; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Reduction of muscle cramps (Ashworth scale, MRC score) ; reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) ; patient/carer reported outcomes (pain (VAS), reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) ; adverse effects of treatment (drowsiness, treatment related reduction in mobility, treatment related reduction of functional ability)

Study	Miller 1996[395]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=152)

Study	Miller 1996[395]
Countries and setting	Conducted in USA; setting: 8 centres
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months + 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical and laboratory-supported
Stratum	Overall: no stratum
Subgroup analysis within study	Not applicable: no subgroup analysis
Inclusion criteria	Aged 21 to 85 years of age; definite or probable ALS diagnosis with symptoms for no more than 3 years prior to the study
Exclusion criteria	Forced vital capacity less than 60% of the predicted value or exclusively bulbar symptoms; patients with severe bulbar involvement
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - mean (SD): Gabapentin group 60.3 (11.4), placebo group 56.4 (12.9). Gender (M:F): Gabapentin group 52/27; placebo group 50/20. Ethnicity: not reported.
Further population details	1. Cognitive ability: not applicable/not stated/unclear. 2. Type of disease: not applicable/not stated/unclear.
Extra comments	Phase II trial
Indirectness of population	No indirectness: direct
Interventions	(n=79) Intervention 1: Gaba analogue – Gabapentin. 800mg t.i.d. Duration 6 months. Concurrent medication/care: none. Further details: 1. Self-management: healthcare professional management. (n=70) Intervention 2: Placebo. Placebo t.i.d. Duration 6 months. Concurrent medication/care: none. Further details: 1. Self-management: healthcare professional management.
Funding	Study funded by industry (Parke-Davis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score)
- Actual outcome: Arm megascore decline; other: Gabapentin group: median -0.0025; placebo group: median -0.0040 (p value 0.08); risk of bias: very high; indirectness of outcome: serious indirectness

Study	Miller 1996[395]
- Actual outcome: Rate of decline of maximum voluntary isometric contraction (MVC) strength of 8 arm muscle groups (bilateral shoulder and elbow flexion and extension) at 7 months; other: Gabapentin group: median -0.017; placebo group: median -0.028 (p value); risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Reduction of muscle cramps (Ashworth scale, MRC score) - Actual outcome: Cramps at 7 months; Group 1: 8/79, Group 2: 2/70; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 3: Adverse effects of treatment (drowsiness, treatment related reduction in mobility, treatment related reduction of functional ability) - Actual outcome: Drowsiness at 7 months; Group 1: 20/79, Group 2: 8/70; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: Weakness at 7 months; Group 1: 14/79, Group 2: 6/70; risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Quality of life (EQ5D, SF36, SF12, SEQUOL) ; reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) ; patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) ; mobility (functional independence measure, ALS functional rating score)

Study	Miller 2001[396]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=204)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical and laboratory-supported diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged between 21 and 85 years of age; diagnosis of probable or definite ALS, symptoms for no more than 3 years prior to study
Exclusion criteria	Forced vital capacity of less than 60% of predicted; exclusively bulbar symptoms; concomitant use of riluzole
Age, gender and ethnicity	Age - other: mean 61.3 (S.E 1.3) in gabapentin group and mean 62 (S.E 1.2). Gender (M:F): 127/77. Ethnicity: not reported.

Study	Miller 2001[396]
Further population details	1. Cognitive ability: not applicable/not stated/unclear. 2. Type of disease: not applicable/not stated/unclear.
Indirectness of population	No indirectness: direct
Interventions	(n=102) Intervention 1: Gaba analogue – Gabapentin. 1200mg, 3 times daily. Duration 9 months. Concurrent medication/care: none. Further details: 1. Self-management: healthcare professional management. (n=102) Intervention 2: Placebo. 3 times daily. Duration 9 months. Concurrent medication/care: none. Further details: 1. Self-management: healthcare professional management.
Funding	Study funded by industry (MDA, Warner Lambert Parke Davis and the US FDA Office of Orphan Products Development grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Quality of life (EQ5D, SF36, SF12, SEQUOL))
- Actual outcome: SF12 at unclear; Group 1: mean -0.03 (SD 0.7); n=102, Group 2: mean -0.2 (SD 0.5); n=102; SF-12 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 2: Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score)
- Actual outcome: Rate of decline in maximum voluntary isometric contraction (MVC) strength of 8 arm muscle groups at 9 months; other: Gabapentin group: median -0.017; placebo group: median -0.028; risk of bias: very high; indirectness of outcome: no indirectness
- Actual outcome: Rate of decline in arm megascore at 9 months; other: Gabapentin group: -0.0198; placebo group: -0.0209: difference -0.0011 (95%CI -0.0102 to 0.008) (p value 0.31); risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 3: Mobility (functional independence measure, ALS functional rating score)
- Actual outcome: ALSFRS at 36 weeks; Group 1: mean -6.6 (SD 5.8); n=102, Group 2: mean -5.9 (SD 4.7); n=102; ALSFRS 0-40: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 4: Adverse effects of treatment (drowsiness, treatment related reduction in mobility, treatment related reduction of functional ability)
- Actual outcome: Drowsiness at unclear; Group 1: 10/102, Group 2: 30/102; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcomes not reported by the study	Reduction of muscle cramps (Ashworth scale, MRC score) ; reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) ; patient/carer reported outcomes (pain [VAS], reduction of muscle

Study	Miller 2001[396]
	stiffness, reduction of muscle cramps, reduction of fatigue)

G.9 Non-pharmacological management of muscle problems

Study	Bello-haas 2007[162]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in Canada, USA; setting: not stated
Line of therapy	1st line
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of ALS based on the El Escorial criteria. Early stage ALS was determined by Sinaki and Mulder staging criteria.
Stratum	Overall, people with MND
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinically definite, probable or probable with laboratory-supported ALS. Individuals with mild to moderate weakness in certain, few muscles, and able to perform normal life activities with no or mild limitations. Individuals with forced vital capacity of 90% or higher and ALSFRS score of 30 or greater.
Exclusion criteria	Individuals with a forced vital capacity of less than 90%, or enrolled in an ongoing ALS pharmaceutical trial, or history of neuromuscular dysfunction not related to ALS, or concomitant medical problem interfering with person's ability to participate in intervention, or unwilling or unable to comply with assigned group protocol.
Recruitment/selection of patients	Consecutive individuals
Age, gender and ethnicity	Age - exercise: 56 (mean) ±7.3 (SD); usual care: 51.8 (mean) ±12.6 (SD). Gender (M:F): 16:11. Ethnicity: not stated.
Further population details	1. Cognitive ability: no frontotemporal lobe dementia 2. Type of disease: amyotrophic lateral sclerosis (2/14 in the usual care [control] group with bulbar onset).
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Physical therapy - endurance and strength training. Programme of upper and lower extremity stretching exercises targeting gastrocnemius, hamstring, quadricep, ankle dorsiflexor, shoulder flexor, and extensor muscles. Each stretch for 30 seconds repeated 5 times, followed by a moderate intensity and moderate load resistance upper and lower extremity exercise programme using a training repetition maximum target (moderate intensity and moderate load, 3 sets of 5 repetitions based on initial 6-RM load), at home, without supervision.

Study	Bello-haas 2007[162]
	Physical therapist provided written instructions and diagrams of exercises at initial baseline session. Compliance determined by PT twice weekly by phone, and with questioning during monthly re-evaluation visits. Duration 6 months. Concurrent medication/care: no concomitant treatment. Further details: 1. Self -management (initial session with PT and written instructions at baseline, compliance checked by bi-weekly telephone contact and monthly re-evaluation visits). (n=14) Intervention 2: Usual care. Programme of upper and lower extremity stretching exercises targeting gastrocnemius, hamstring, quadricep, ankle dorsiflexor, shoulder flexor, extensor, adductor and abductor muscles for a count of 30 seconds and repeat each exercise 5 times, to complete programme once daily, at home, with initial assessment with PT at baseline session. Duration 6 months. Concurrent medication/care: two patients were taking riluzole. Further details: 1. Self -management (initial session with PT and written instructions at baseline, compliance assessed twice weekly by PT via phone, and monthly re-evaluation visits). Comments: usual care includes stretching exercise, served as control group.
Funding	Academic or government funding (Funded in part by the amyotrophic lateral sclerosis association [clinical management research grant program])

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENDURANCE AND STRENGTH TRAINING versus USUAL CARE

Protocol outcome 1: Quality of life (EQ5D, SF-36, SF12, SEQUOL))
- Actual outcome for people who are not at the end of life: QoL SF-36 physical function at 6 months; Group 1: mean 21.1 (SD 7.6); n=8, Group 2: mean 14 (SD 3.9); n=10; SF-36 physical function 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for people who are not at the end of life: QoL SF-36 pain at 6 months; Group 1: mean 10.3 (SD 1.3); n=8, Group 2: mean 10.1 (SD 1.5); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for People who are not at the end of life: QoL SF-36 physical role at 6 months; Group 1: mean 6.4 (SD 1.4); n=8, Group 2: mean 5.2 (SD 1.4); n=10; SF-36 0-100 Top=High is good outcome; risk of bias: high; Indirectness of outcome: No indirectness
- Actual outcome for people who are not at the end of life: QoL SF-36 general health at 6 months; Group 1: mean 17.4 (SD 2.8); n=8, Group 2: mean 16.8 (SD 5.8); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for people who are not at the end of life: QoL SF-36 vitality at 6 months; Group 1: mean 16.2 (SD 3.6); n=8, Group 2: mean 15.4 (SD 4.7); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for people who are not at the end of life: QoL SF-36 social function at 6 months; Group 1: mean 8.9 (SD 1.6); n=8, Group 2: mean 7.8 (SD 1.8); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness
- Actual outcome for people who are not at the end of life: QoL SF-36 emotional role at 6 months; Group 1: mean 5.5 (SD 0.9); n=8, Group 2: mean 5.1 (SD 1.6); n=10;

Study	Bello-haas 2007[162]
SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 mental health at 6 months; Group 1: mean 23.9 (SD 2.5); n=8, Group 2: mean 24.5 (SD 3.3); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 physical function at 3 months; Group 1: mean 20.55 (SD 6.53); n=11, Group 2: mean 16.79 (SD 5.55); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 physical role at 3 months; Group 1: mean 5.73 (SD 1.56); n=11, Group 2: mean 5.21 (SD 1.58); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 pain at 3 months; Group 1: mean 9.79 (SD 1.45); n=11, Group 2: mean 9.88 (SD 1.9); n=10; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 general health at 3 months; Group 1: mean 17.64 (SD 2.89); n=11, Group 2: mean 16.62 (SD 6.32); n=13; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 vitality at 3 months; Group 1: mean 13.64 (SD 2.8); n=11, Group 2: mean 15.57 (SD 3.88); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 social function at 3 months; Group 1: mean 8.09 (SD 2.12); n=11, Group 2: mean 8.29 (SD 1.54); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 emotional role at 3 months; Group 1: mean 5.55 (SD 0.93); n=11, Group 2: mean 4.86 (SD 1.23); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: QoL SF-36 mental health at 3 months; Group 1: mean 20.73 (SD 2); n=11, Group 2: mean 20.07 (SD 1.82); n=14; SF-36 0-100: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: Mobility (functional independence measure, ALS functional rating score) - Actual outcome for people who are not at the end of life: mobility (ALS functional rating score) at 3 months; Group 1: mean 33.1 (SD 4.12); n=11, Group 2: mean 30.79 (SD 3.53); n=14; ALS functional rating score 0-4: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: mobility (ALS functional rating score) at 6 months; Group 1: mean 33.8 (SD 4.7); n=8, Group 2: mean 28.1 (SD 4.8); n=10; ALS functional rating score 0-40: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 3: Patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) - Actual outcome for people who are not at the end of life: reduction of fatigue (FSS) at 6 months; Group 1: mean 42.7 (SD 15.2); n=10, Group 2: mean 42.9 (SD 8.7); n=8; FSS 0-63: top=high is poor outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 4: Adverse effects of treatment (drowsiness, treatment related increase in weakness, treatment related reduction of functional ability) - Actual outcome for people who are not at the end of life: maximum voluntary isometric contraction (MVIC) for muscle strength upper extremity megascore at 6 months; Group 1: mean -9.8 (SD 4.6); n=8, Group 2: mean -8.3 (SD 3.6); n=10; risk of bias: high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: maximum voluntary isometric contraction (MVIC) for muscle strength lower extremity megascore at 6 months; Group 1: mean -20 (SD 3.8); n=8, Group 2: mean -23.1 (SD 4.8); n=10; risk of bias: very high; indirectness of outcome: no indirectness	

Study	Bello-haas 2007[162]
Protocol outcomes not reported by the study	Reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power); reduction of muscle cramps (Ashworth scale, MRC score); reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score)

Study	Drory 2001[191]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in Israel; setting: clinic
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial WFN criteria
Stratum	Overall, all people with MND
Subgroup analysis within study	Not applicable
Inclusion criteria	Probable or definite ALS
Exclusion criteria	Lost ability to walk (any assistive device allowed), intermittent or continuous ventilation, patients not able to understand or conform to the instructions.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - mean (range): 60 years (41 to 80). Gender (M:F): 14:11. Ethnicity: not stated.
Further population details	1. Cognitive ability: no frontotemporal dementia (patients excluded if not able to understand instructions). 2. Type of disease: amyotrophic lateral sclerosis (1/14 and 2/11 with bulbar onset for intervention and control respectively).
Indirectness of population	No indirectness
Interventions	(n=14) Intervention 1: Physical therapy - endurance and strength training. Fifteen minutes twice daily, at home, mainly endurance limbs and trunk; review every 2 weeks in clinic; contacted every 2 weeks by phone to check adherence. Duration 12 months. Concurrent medication/care: none stated. Further details: 1. Self-management (also reviewed every 2 weeks in clinic). (n=11) Intervention 2: Usual care. No exercise beyond their usual daily requirement. Duration 12 months. Concurrent medication/care: none

Study	Drory 2001[191]
	Further details: 1. Self-management: not applicable/not stated/unclear
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ENDURANCE AND STRENGTH TRAINING versus USUAL CARE Protocol outcome 1: Quality of life (EQ5D, SF-36, SF12, SEQUOL) - Actual outcome for people who are not at the end of life: health related quality of life (SF-36) at 3 months; Group 1: mean 82.7 (SD 8.1); n=10, Group 2: mean 80 (SD 4.2); n=8; SF-36 (36 item short form health survey) 0-100: top=high is good outcome; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) - Actual outcome for people who are not at the end of life: manual muscle strength (MRC scale) at 3 months; Group 1: mean 76.4 (SD 19.8); n=10, Group 2: mean 87.3 (SD 4.5); n=8; MRC 0-5: unclear - possibly given as a percentage? top=high is good outcome; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: Ashworth scale at 3 months; Group 1: mean 0.2 (SD 0.42); n=10, Group 2: mean 0.75 (SD 0.46); n=8; Ashworth spasticity scale 0-4: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Mobility (functional independence measure (FIM), ALS functional rating score) at any duration of time - Actual outcome for people who are not at the end of life: functional change (ALS functional rating score) at 3 months; Group 1: mean 28.7 (SD 6.1); n=10, Group 2: mean 22 (SD 7.3); n=8; ALS functional rating scale 0-40: top=high is good outcome; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 4: Patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) - Actual outcome for people who are not at the end of life: fatigue severity scale at 3 months; Group 1: mean 32.4 (SD 14.9); n=10, Group 2: mean 44.5 (SD 9.2); n=8; Fatigue severity scale 0-63: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for people who are not at the end of life: pain (VAS) at 3 months; Group 1: mean 1.09 (SD 1.09); n=10, Group 2: mean 2.21 (SD 5.02); n=8; visual analogue scale (VAS) 0-10: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Reduction of muscle cramps (Ashworth scale, MRC score); reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score); adverse effects of treatment (drowsiness, treatment related increase in weakness, treatment related reduction of functional ability)

Study	Di lazzaro 2009[184]
Study	NCT00833820 trial: Di lazzaro 2009[184]

Study	Di lazzaro 2009[184]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Italy; setting: Institute of Neurology, Italy (single centre trial)
Line of therapy	1st line
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: definite or probable ALS according to revised El Escorial criteria
Stratum	Overall, people with MND
Subgroup analysis within study	Stratified then randomised: population stratification by site of onset (bulbar versus non-bulbar), age, sex, disease duration and severity.
Inclusion criteria	Diagnosis of probable or definite ALS, age 18 years or older
Exclusion criteria	Seizure history, concomitant severe medical problems, history of tracheostomy, contraindications for TMS.
Recruitment/selection of patients	Enrolled and allocated to treatment or placebo arm
Age, gender and ethnicity	Age - mean (SD): TMS= 60.2 (SD 6.7); placebo/sham= 55.1 (SD 14.0). Gender (M:F): 15:5. Ethnicity: unclear.
Further population details	1. Cognitive ability: no frontotemporal dementia 2. Type of disease: amyotrophic lateral sclerosis
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Electrotherapy - transcranial electrical stimulation. rTMS performed using butterfly coil held over motor cortex on each hemisphere. Three pulses of stimulation given at 50Hz, repeated every 200 milliseconds for total 600 pulses. Stimulus intensity was 80% of action motor threshold. Duration: 5 consecutive days per month for 12 months. Concurrent medication/care: Riluzole Further details: 1. Self -management: healthcare professional management (n=10) Intervention 2: Placebo/sham. Sham rTMS performed using same stimulator connected to placebo butterfly coil MCF-P-B-65, has no stimulating effect on cortex but produces similar auditory and tactile sensations as the real coil. Site of stimulation and number of stimuli identical to those used for active magnetic rTMS. Duration: 5 consecutive days per month for 12 months. Concurrent medication/care: Riluzole. Further details: 1. Self -management: healthcare professional management
Funding	Academic or government funding (Ministry of health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANSCRANIAL ELECTRICAL STIMULATION versus PLACEBO/SHAM Protocol outcome 1: Reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power)	

Study	Di lazzaro 2009[184]
- Actual outcome for people who are not at the end of life: MRC score at 12 months; Group 1: mean 1.9 (SD 0.8); n=7, Group 2: mean 2.5 (SD 0.9); n=5; MRC scale 0-160: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness Protocol outcome 2: Mobility (functional independence measure, ALS functional rating score) - Actual outcome for people who are not at the end of life: ALSFRS-R score at 12 months; Group 1: mean 23.1 (SD 6.3); n=7, Group 2: mean 21.2 (SD 6); n=5; ALSFRS-R 0-40: top=high is good outcome; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life (EQ5D, SF-36, SF12, SEQUOL)); reduction of muscle cramps (Ashworth scale, MRC score); reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, MRC score); patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue); adverse effects of treatment (drowsiness, treatment related increase in weakness, treatment related reduction of functional ability)

G.10 Saliva management

Study	Alrefai 2009[19]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=24)
Countries and setting	Conducted in Jordan
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children with cerebral palsy
Subgroup analysis within study	Not applicable
Inclusion criteria	A total score of >/= 7 on a rating scale that assesses severity (0-5) and frequency (0-4) of the saliva problem, as evaluated by a clinic physician
Exclusion criteria	Patients who had taken oral treatment for drooling within the past 3 months or had received BoNT injection for any other indication in the past 6 months
Recruitment/selection of patients	Patients were recruited through a local cerebral palsy multidisciplinary rehabilitation centre. Patients who experience a drooling problem were evaluated by the attending physician to assess if they met inclusion criteria for the study. Patients provided consent for all participants.

Study	Alrefai 2009[19]
Age, gender and ethnicity	Age – range: 21 months – 7 years. Gender (M:F): 15 male/9 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not reported but presumably patients had the ability to cough). 2. Severity of swallowing difficulty: not applicable/not stated/unclear (difficult to assess). 3. Type of MND: not applicable/not stated/unclear (cerebral palsy).
Indirectness of population	Serious indirectness: children with cerebral palsy
Interventions	(n=11) Intervention 1: Botulinum toxin injections. A dose of 100 units BoNT, split equally between the two sites. Dose was diluted with normal saline to a concentration of 20 U per 0.1 cc. Ultrasound guidance was not used. Duration: one dose. Concurrent medication/care: no anaesthesia. (n=13) Intervention 2: Placebo. A dose of 100 units of normal saline (0.9%), split equally between the two sites. Ultrasound guidance was not used. Duration: one dose. Concurrent medication/care: no anaesthesia.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: change in median drooling score (carer reported severity and frequency of the saliva problem) at 1 month; median change in drooling score in intervention group = -2 (no IQR reported), median change in drooling score in placebo group = 0 (no IQR reported). Risk of bias; high: indirectness of outcome: serious indirectness.	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control).

Study	Arbouw 2010[30]
Study type	RCT (patient randomised; crossover: 1 week)
Number of studies (number of participants)	(n=23)
Countries and setting	Conducted in Netherlands
Line of therapy	Adjunctive to current care

Study	Arbouw 2010[30]
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: adults with idiopathic Parkinson's disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Idiopathic Parkinson's disease; marked to severe sialorrhoea (>/= 5 on a scale from 1-9); 18 years old; caregiver able to score the extent of sialorrhoea on a daily basis.
Exclusion criteria	Sialorrhea caused by factors other than Parkinson's disease; previous treatment with or hypersensitivity to glycopyrrolate, sorbic acid, or saccharin sodium; myasthenia gravis; symptomatic tachycardia; symptomatic coronary insufficiency; glaucoma; pylorus stenosis; paralytic ileus; prostrate hypertrophy, renal failure; pregnancy or lactation; concomitant use of potassium chloride retard tablets, digoxin, and oral corticosteroids.
Recruitment/selection of patients	Patients recruited from the outpatient service of the participating hospital and via an advert in the journal of the Dutch Parkinson Association.
Age, gender and ethnicity	Age – mean (SD): 70 years (7.8). Gender (M:F): 19 male/4 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear. 2. Severity of swallowing difficulty: not applicable/not stated/unclear. 3. Type of MND: not applicable/not stated/unclear.
Indirectness of population	Serious indirectness: indirect population
Interventions	(n=23) Intervention 1: Glycopyrrolate (sublingual, syringe driver, orally, or via PEG). Oral glycopyrrolate, 1mg (5ml), 3x daily. Dispensed as a 0.2mg/mL admixture (sorbic acid, saccharin sodium). Duration: 1 week. Concurrent medication/care: 1 week washout period between interventions. Background care not described. (n=23) Intervention 2: Placebo. "Identical" to intervention except for glycopyrrolate (3x daily oral admixture, sorbic acid and saccharin sodium). Duration: 1 week. Concurrent medication/care: 1 week washout period between interventions. Background care not described.
Funding	(Funded by the Dutch Parkinson Assoc. and the Stichting Neurologisch Onderzock Twente)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRROLATE (SUBLINGUAL, SYRINGE DRIVER, ORALLY, OR VIA PEG) versus PLACEBO

Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: sialorrhoea final score at last 3 days of the treatment week; Group 1: mean 3.8 (SD 1.6); n=23, risk of bias: low; indirectness of outcome: no indirectness

Study	Arbouw 2010[30]
Protocol outcome 2: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: change in motor symptoms at last 3 days of the treatment week; Group 1: 3/23, Group 2: 4/23; risk of bias: low; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

Study	Basciani 2011[52]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=27)
Countries and setting	Conducted in Italy
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children with cerebral palsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with cerebral palsy and sialorrhoea
Exclusion criteria	Patients with a history of any surgical procedure to the head or neck to reduce salivation; use of any medications for sialorrhoea; use of any pharmacological agents that could affect salivary production.
Recruitment/selection of patients	Children attending an outpatient rehabilitation centre were screened and invited to participate in the study
Age, gender and ethnicity	Age - mean (SD): 6.75 years (1.92). Gender (M:F): 15 male/17 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: not applicable/not stated/unclear (not stated). 3. Type of MND: not applicable/not stated/unclear (cerebral palsy).
Indirectness of population	Serious indirectness: children with cerebral palsy
Interventions	(n=7) Intervention 1: Botulinum toxin injections. 3000/MU does of BoNT-B bilateral injections into the parotid and submandibular glands with ultrasound guidance. Duration: one dose. Concurrent medication/care: local anaesthesia.

Study	Basciani 2011[52]
	(n=7) Intervention 2: Placebo. No treatment. Duration: N/A. Concurrent medication/care: not described.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus NO TREATMENT Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: carer reported severity and frequency of sialorrhoea (Thomas-Stonell scale) at 4 weeks; Group 1: mean 3.1 (SD 0.79); n=7, Group 2: mean 8.3 (SD 0.79); n=7; Thomas Stonell scale 2-9: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: muscle weakness at 4 weeks; Group 1: 0/7, Group 2: 0/7; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

Study	Camp-bruno 1989[101]
Study type	RCT (patient randomised; crossover: 1 week)
Number of studies (number of participants)	(n=27)
Countries and setting	Conducted in USA; setting: day centre
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children, young people and adults with cerebral palsy (95%; n=19)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with severe or very severe drooling (Teacher drooling scale ratings 4 or 5); no medical condition

Study	Camp-bruno 1989[101]
	contraindicating anticholinergic therapy; not receiving neuroleptic medication; seizure-free for at least one year); a history of good school attendance; living in households where carers were reliable administrators of medication during weekends and holiday
Exclusion criteria	None further
Recruitment/selection of patients	Patients attending a day centre were screened with the Teacher Drooling Scale by teachers
Age, gender and ethnicity	Age – range: 4-44 years. Gender (M:F): 11 male/9 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not reported). 2. Severity of swallowing difficulty: not applicable/ not stated/unclear (not reported). 3. Type of MND: not applicable/not stated/unclear (children, young people and adults with cerebral palsy (95%) or other degenerative nervous system disease [5%; n=1]).
Indirectness of population	Serious indirectness: children, young people and adults with cerebral palsy (95%; n=19)
Interventions	(n=20) Intervention 1: Atropine - Atropine sublingual. Benzotropine tablets crushed into soft food, taken 1x daily on arrival at day centre. Initial dose ranged between 0.5mg and 2mg depending on the patient's age and weight. Medication was titrated for the first week on one-to-two day intervals, based on ratings of the symptom severity (Teacher's drooling score and nurse observation). Maximum dose = 6mg; mean dose = 3.8mg per day. Dose was reduced 0.5-1mg based on the presence of side effects. Duration 2 weeks. Concurrent medication/care: not reported. (n=20) Intervention 2: Placebo. 2mg tablets crushed into soft food, taken 1x daily on arrival at day centre. Duration 2 weeks. Concurrent medication/care: not reported.
Funding	Equipment/drugs provided by industry (medication and placebo provided by industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZOTROPINE versus PLACEBO

Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: Teacher's drooling scale at 1-2 weeks; Group 1: mean 2.38 (SD 0.89); n=20, Group 2: mean 3.53 (SD 0.81); n=20; Teacher's Drooling Scale 1-5: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: discontinuation of study medication due to side effects at <2 weeks; Group 1: 3/27, Group 2: 0/27; risk of bias: very high; indirectness of outcome: no indirectness

Study	Camp-bruno 1989[101]
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

Study	Chinnapongse 2012[115]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=54)
Countries and setting	Conducted in USA; setting: outpatient services across 17 sites in the USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: adults with Parkinson's disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (18-85 years); clinical diagnosis of idiopathic Parkinson's disease; marked sialorrhoea with some drooling (sialorrhoea >/= 3 on the Unified Parkinson's Disease Rating Scale)
Exclusion criteria	Movement disorder-related surgery within 6 months of screening; history of aspiration pneumonia; moderate or severe dysphagia (>/= 3 on the swallowing item of the Unified Parkinson's Disease Rating Scale), current or within the previous 6 months; prior salivary gland surgery; received oral pharmacologic treatment for sialorrhoea in the 30 days prior to screening (including anticholinergics or antihistamines); any known exposure or sensitivity to botulinum toxin; used drugs within 5 half-lives of screening that could interfere with neuromuscular function; change in dose or regimen of medications used to treat Parkinson's disease (including changes in deep brain stimulation parameters) 4 weeks before screening or during the trial; evidence of any clinically significant neurologic disease other than idiopathic Parkinson Disease (ALS, myasthenia gravis, Lambert-Eaton syndrome); other medical or psychiatric diseases or conditions, which in the judgement of the investigator could negatively impact the subject's ability to participate in the study; anticipated or scheduled surgery during the trial or major surgery within the 6 months before the study; pregnancy or lactation; history of drug or alcohol abuse currently or within the previous 6 months; participation in another clinical drug or device trial within 30 days of entry or while participating in this study.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – range of means: placebo mean = 71.2 years (11.64); botulinum toxin mean = 71.8 years (8.17). Gender (M:F): 48 male/6 female. Ethnicity: not reported.

Study	Chinnapongse 2012[115]
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: patients with mild swallowing difficulty (patients scoring <3 on swallowing difficulties [as assessed by the Unified Parkinson's Disease Rating Scale]). 3. Type of MND: not applicable/not stated/unclear (Parkinson's disease).
Indirectness of population	Serious indirectness
Interventions	(n=12) Intervention 1: Botulinum toxin injections. 2500 units (0.5ml) Botulinum toxin type B injection to the submandibular glands (250/gland) followed by the parotid glands (1000/gland), no ultrasound. Solution included 0.05% human serum albumin, 0.01 M sodium succinate, 0.1 M sodium chloride at approximately pH 5.6. Duration: 1 dose. Concurrent medication/care: not reported. (n=15) Intervention 2: Placebo. Volume-matched placebo group (0.05% human serum albumin, 0.01 M sodium succinate, 0.1 M sodium chloride at approximately pH 5.6). Duration: 1 dose. Concurrent medication/care: not reported.
Funding	Equipment/drugs provided by industry (drug supplied by Solstice Neurosciences, LLC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO

Protocol outcome 1: Health related quality of life
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: change in drooling impact score at 4 weeks; Group 1: mean -7.2 (SD 4.63); n=12, Group 2: mean -1.9 (SD 2.38); n=15; Drooling impact score 10-40: top=high is poor outcome; risk of bias: high; indirectness of outcome: no indirectness.

Protocol outcome 2: Patient reported outcomes (symptoms, pain, satisfaction)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: change in severity and frequency of saliva problem using Drooling Frequency and Severity Scale (DFSS) at 4 weeks; Group 1: mean -1.73 (SD 1.62); n=12, Group 2: mean -0.81 (SD 1.24); n=15; DFSS 2-9: top=high is poor outcome; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 3: Aspiration pneumonia
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: aspiration pneumonia at 20 weeks; Group 1: 0/12, Group 2: 0/15; risk of bias: high; indirectness of outcome: no indirectness

Protocol outcome 4: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: discontinuation of study medication due to adverse effects at 20 weeks;

Study	Chinnapongse 2012[115]
Group 1: 0/12, Group 2: 1/15; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

Study	Jackson 2009[289]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	USA
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of probable or definite ALS based on World Federation of Neurology criteria
Stratum	Patients experiencing sialorrhoea
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with sialorrhoea refractory to treatment with at least 2 anticholinergic medications or a history of intolerance to anticholinergic medication due to side effects
Exclusion criteria	Patients treated with coumadin, patients with a forced vital capacity < 20% of predicted, patients who had experienced an "uncontrolled" significant episode of medical, psychiatric, or neurological illness (other than ALS) in the past 30 days, patients with a history of substance abuse, patients with a history of non-compliance with treatment on other experimental protocols, and patients who had received botulinum toxin in the past for any indication.
Recruitment/selection of patients	Patients were recruited from ALS centers at University of Kansas Medical Centre, Carolinas Medical Center, and the University of Texas Health Science Center
Age, gender and ethnicity	Age – range of means: intervention age mean = 67 years (6.8); control group age mean = 64 years (11.9). Gender (M:F): 10 male/10 female. Ethnicity: not reported.
Further population details	1. Ability to cough: people with the ability to cough and clear secretions (patients with a forced vital capacity > 20% of predicted). 2. Severity of swallowing difficulty: not applicable/not stated/unclear (not stated). 3. Type of MND: ALS .
Indirectness of population	No indirectness
Interventions	(n=11) Intervention 1: Botulinum toxin injections. 2500 units of botulinum toxin was diluted with normal saline into a total volume of 1ml. Electromyography was used to guide placement of the needle. A total of 8 injections (two per

Study	Jackson 2009[289]
	gland bilaterally) were performed, targeting both parotid and submandibular glands. Each parotid gland was injected at two sites with 0.1cc of the diluted medication (that is, 500 units per gland), directing the needle towards the tail of the parotid, between the sternocleidomastoid muscle and the angle of the mandible. Each supramandibular gland was injected with 0.15cc of diluted medication (that is, 750 units per gland) at two sites, placing the needle percutaneously in the submandibular triangle. Duration: one administration. Concurrent medication/care: if requested, EMLA cream (lidocaine 2.5%/prilocaine 2.5%) was administered to the skin for 30-60 minutes prior to injection. Patients were asked not to increase doses of anticholinergic medications during the study, but they could taper or discontinue them as tolerated. Women who were of child bearing potential were required to use an adequate method of birth control. (n=9) Intervention 2: Suction pump. 1ml of saline. Electromyography was used to guide placement of the needle. A total of 8 injections (two per gland bilaterally) were performed, targeting both parotid and submandibular glands. Each parotid gland was injected at two sites with 0.1cc of the diluted medication (that is, 500 units per gland), directing the needle towards the tail of the parotid, between the sternocleidomastoid muscle and the angle of the mandible. Each supramandibular gland was injected with 0.15cc of diluted medication (that is, 750 units per gland) at two sites, placing the needle percutaneously in the submandibular triangle. Duration: one administration. Concurrent medication/care: if requested, EMLA cream (lidocaine 2.5%/prilocaine 2.5%) was administered to the skin for 30-60 minutes prior to injection. Patients were asked not to increase doses of anticholinergic medications during the study, but they could taper or discontinue them as tolerated. Women who were of child bearing potential were required to use an adequate method of birth control.
Funding	Study funded by industry (study supported by a grant from the National ALS Association and a grant from Solstice Pharmaceuticals. Solstice Pharmaceuticals were not involved in the design or conduct of the study, collection, management, or analysis of data, or preparation, review or approval of the article)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO

Protocol outcome 1: Health related quality of life
- Actual outcome for patients experiencing sialorrhoea: SEIQOL-DW (0-100) at 2 weeks; Group 1: mean 65.3 (SD 24.7); n=11, Group 2: mean 59.3 (SD 25.9); n=9; SEIQOL-DW 0-100: top=high is good outcome; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: Patient reported outcomes (symptoms, pain, satisfaction)
- Actual outcome for patients experiencing sialorrhoea: patient reported symptom severity (0-100) at 2 weeks; Group 1: mean 49 (SD 24); n=11, Group 2: mean 75 (SD 17); n=9; risk of bias: very high; indirectness of outcome: no indirectness
- Actual outcome for patients experiencing sialorrhoea: patient assessment of saliva thickness (0-100) at 2 weeks; Group 1: mean 79 (SD 7); n=11, Group 2: mean 68 (SD

Study	Jackson 2009[289]
23); n=9; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for patients experiencing sialorrhoea: caregiver assessment of saliva thickness (0-100) at 2 weeks; Group 1: mean 66 (SD 25); n=11, Group 2: mean 64 (SD 23); n=9; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for patients experiencing sialorrhoea: caregiver reported symptom severity (1-100) at 2 weeks; Group 1: mean 52 (SD 33); n=11, risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Function measured by disability scores (Ashworth scale) - Actual outcome for patients experiencing sialorrhoea: ALSFRS-R (0-48) at 2 weeks; Group 1: mean 27.9 (SD 8); n=11, Group 2: mean 28.8 (SD 10.6); n=9; Ashworth scale 0-48: top=high is good outcome; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Aspiration pneumonia; unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Lagalla 2006[341]
Study type	RCT (randomised; parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Italy
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: adults with Parksinson's disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with drooling that prevented them from "attaining significant social roles" and who scored >/= 2 on the Unified Parkinson's Disease Rating Scale
Exclusion criteria	Patients with significant dysphagia (as indicated by a score > 2 on the dysphagia scale of the Unified Parkinson's Disease Rating Scale); presence of dental infection; patients who require anticholinergic drugs; a change in drug treatment for Parkinson's disease; previous exposure to BoNTX; contraindications to botulinum toxin; previous surgical intervention for sialorrhoea
Recruitment/selection of patients	Consecutive patients presenting as outpatients meeting inclusion criteria were invited to participate in the study

Study	Lagalla 2006[341]
Age, gender and ethnicity	Age – mean (SD): BoNTX mean = 69.4 years (5.5); placebo mean = 70.5 years (5.5). Gender (M:F): 24 male/8 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: patients with mild swallowing difficulty (a score of 1 or 2 on the dysphagia scale of the UPDRS [normal/rare choking]). 3. Type of MND: not applicable/not stated/unclear (Parkinson's disease).
Indirectness of population	Serious indirectness: Parkinson's disease
Interventions	(n=16) Intervention 1: Botulinum toxin injections. 50 units BoNTX (100 units diluted in 2mL 0.9% sodium chloride saline solution) injected into each parotid gland, no ultrasound. Duration: one dose. Concurrent medication/care: not reported. (n=16) Intervention 2: Placebo. 1.0mL 0.9% saline solution injected into each parotid gland, no ultrasound. Duration: one dose. Concurrent medication/care: not reported.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: siahlorrea subscale of the Unified Parkinson's Disease Rating Scale at 1 month; Group 1: mean 1.8 (SD 0.7); n=16, Group 2: mean 2.8 (SD 0.9); n=16; Unified Parkinson's Disease Rating Scale 0-4: top=high is poor outcome; risk of bias: low; indirectness of outcome: no indirectness - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: patient satisfaction at 1 month; Group 1: 14/16, Group 2: 5/16; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Lagalla 2009[342]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=36)

Study	Lagalla 2009[342]
Countries and setting	Conducted in Italy
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: adults with Parkinson's disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Probable diagnosis of Parkinson's disease; moderate to severe drooling indicated by a score >/=2 on the Unified Parkinson's Disease Rating Scale that cause meaningful social restrictions
Exclusion criteria	Contraindications to BoNTX; having undergone surgery for sialorrhoea; previous exposure to BnTX; change in drug regimen for Parkinson's disease
Recruitment/selection of patients	Consecutive patients referred to the participating centre for advice who met the inclusion criteria were invited to participate in the study
Age, gender and ethnicity	Age – mean (SD): 71.9 years (5.9). Gender (M:F): 26 male/10 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: not applicable/ not stated/unclear (not stated). 3. Type of MND: not applicable/not stated/unclear (Parkinson's disease).
Indirectness of population	Serious indirectness: Parkinson's disease
Interventions	(n=18) Intervention 1: Botulinum toxin injections. 4000 units BTX-B (0.8ml of injectable solution, Neurobloc 5000 U/mL) injected into each parotid gland, no ultrasound. Duration: one dose. Concurrent medication/care: not reported. (n=18) Intervention 2: Placebo. 0.8mL 0.9% saline solution injected into each parotid gland, no ultrasound. Duration: one dose. Concurrent medication/care: not reported.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO

Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction)
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: drooling severity (Unified Parkinson's Disease Rating Scale) at 1 month; Group 1: mean 1.5 (SD 1); n=18, Group 2: mean 3 (SD 0.9); n=18; Unified Parkinson's Disease Rating Scale 0-4: top=high is poor outcome; risk of bias: low; indirectness of outcome: no indirectness

Study	Lagalla 2009[342]
- Actual outcome for patients in an indirect population who are experiencing sialorrhoea: patient satisfaction at 1 month; Group 1: 18/18, Group 2: 7/18; risk of bias: low; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Lin 2008[359]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=13)
Countries and setting	Conducted in Taiwan
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 22 weeks
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children with cerebral palsy
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with cerebral palsy and severe drooling
Exclusion criteria	None reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (SD): 14.2 years (1.8). Gender (M:F): Not reported. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: not applicable/ not stated/unclear (not stated). 3. Type of MND: not applicable/not stated/unclear (not applicable).
Indirectness of population	Serious indirectness
Interventions	(n=6) Intervention 1: Botulinum toxin injections. Botulinum toxin A, one injection of 2 units/kg body weight. Injected into one parotid and the contralateral submandibular gland under ultrasound guidance. Duration: one dose. Concurrent medication/care: not reported. (n=7) Intervention 2: Placebo. Saline (1.50ml). Duration: one dose. Concurrent medication/care: not reported.

Study	Lin 2008[359]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: drooling severity and frequency scale at 2 weeks; Group 1: mean 5.33 (SD 0.82); n=6, Group 2: mean 6.29 (SD 0.76); n=7; drooling severity and frequency scale 0-9: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: drooling severity and frequency scale at 22 weeks; Group 1: mean 5.67 (SD 2.25); n=6, Group 2: mean 6.43 (SD 1.81); n=7; drooling severity and frequency scale 0-9: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); un-planned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Mancini 2003[373]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Italy
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3-months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: patients with Parkinson's disease (70%) and multiple system atrophy (30%)
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of idiographic Parkinson's disease or multiple system atrophy; presence of disabling sialorrhoea (as indicated by a score of 3 or 4 on the Unified Parkinson's Disease Rating Scale); absence of or low severity clinical dysphagia

Study	Mancini 2003[373]
Exclusion criteria	None further
Recruitment/selection of patients	Outpatients at the movement disorders unit were recruited.
Age, gender and ethnicity	Age – mean (SD): BTX mean = 69.6 years (6.1); placebo mean = 69.1 years (6). Gender (M:F): 11 male/9 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: patients with moderate or severe swallowing difficulties (as indicated by a score of 3 or 4 on the Unified Parkinson's Disease Rating Scale). 3. Type of MND: not applicable/not stated/unclear (Parkinson's disease or multiple system atrophy).
Indirectness of population	Serious indirectness: Parkinson's disease (70%) and multiple system atrophy (30%)
Interventions	(n=10) Intervention 1: Botulinum toxin injections. 225 MU of Botulinum toxin was diluted with 0.9% saline to reach a total volume of 1mL. Using ultrasonographic guidance, 0.65ml of the solution was injected into each of the parotid glands, and 0.35ml was injected into each of the submandibular glands. Duration: one dose. Concurrent medication/care: not described. (n=10) Intervention 2: Placebo. 1mL of 0.9% saline was injected using ultrasonographic guidance; 0.65ml of the solution was injected into each of the parotid glands, and 0.35ml was injected into each of the submandibular glands. Duration: one dose. Concurrent medication/care: not described.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: drooling frequency and severity score (2-9) at 2 weeks; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Mier 2000[393]

Study	Mier 2000[393]
Study type	RCT (patient randomised; crossover: 1 week)
Number of studies (number of participants)	(n=39)
Countries and setting	Conducted in USA; setting: outpatient facilities at 2 paediatric hospitals
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 19 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children with cerebral palsy (87%) and developmental difficulties
Subgroup analysis within study	Not applicable
Inclusion criteria	Children aged > 4 years with neuro-developmental disorders and severe sialorrhoea
Exclusion criteria	None reported
Recruitment/selection of patients	Word of mouth recruitment and via adverts placed in hospital examination rooms
Age, gender and ethnicity	Age – mean (range): 10.75 (4.3 - 19 years). Gender (M:F): 18 male/9 female included in the analysis. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: not applicable/ not stated/unclear (severe sialorrhoea [not quantified]). 3. Type of MND: not applicable/not stated/unclear (children with cerebral palsy [87%]).
Indirectness of population	Very serious indirectness: children with cerebral palsy (87%)
Interventions	(n=39) Intervention 1: Glycopyrrolate (sublingual, syringe driver, orally, or via PEG). Capsules of glycopyrrolate 3x daily (or 2x daily in four children, in unknown condition) for 8 weeks. Dose was increased weekly for the first 4 weeks, and the final dose was maintained for the final 4 weeks of treatment. Children who weighed < 30kg began at 0.6mg, increasing weekly to 1.2 mg, 1.8 mg, and 2.4mg. Children weighing > 30 kg began at 1.2 mg, increasingly weekly to 1.8 mg, 2.4 mg, 3.0 mg. Duration: 8 weeks. Concurrent medication/care: not reported. (n=39) Intervention 2: Placebo. Lactose powder or cellulose contained in matching gelatin capsules. Dose was increased weekly for the first 4 weeks, and the final dose was maintained for the final 4 weeks of treatment. Duration: 8 weeks. Concurrent medication/care: none reported.
Funding	Funding not stated

Study	Mier 2000[393]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRROLATE (SUBLINGUAL, SYRINGE DRIVER, ORALLY, OR VIA PEG) versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: mean drooling score at 8 weeks; Group 1: mean 1.85 (SD 9.94); n=27, Group 2: mean 6.33 (SD 9.94); n=27; drooling score 1-9: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: adverse effects resulting in patient discontinuing medication at 8 weeks; Group 1: 7/36, Group 2: 1/30; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

Study	Ondo 2004[447]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=16)
Countries and setting	Conducted in USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: adults with Parkinson's disease
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with Parkinson's disease; clinically meaningful sialorrhoea
Exclusion criteria	Patients with meaningful swallowing difficulty; patients who have taken any other treatment for sialorrhoea during the 30 days prior to the study
Recruitment/selection of patients	Recruited from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic
Age, gender and ethnicity	Age – mean (SD): 70.4 years (11.4). Gender (M:F): 13 male/3 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: patients with

Study	Ondo 2004[447]
	mild swallowing difficulty (no meaningful swallowing difficulty). 3. Type of MND: not applicable/not stated/unclear (Parkinson's disease).
Indirectness of population	Serious indirectness
Interventions	(n=8) Intervention 1: Botulinum toxin injections. 2500 units of botulinum toxin B diluted with normal saline into a total volume of 1mL. 1000 units were injected into each parotid gland and 250 units into each submandibular gland. Duration: one dose. Concurrent medication/care: not described. (n=8) Intervention 2: Placebo. PH-matched placebo. Duration: one dose. Concurrent medication/care: not reported.
Funding	Study funded by industry (funded by a grant from Elan Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: drooling severity and frequency scale at 1 month; Group 1: mean 5.1 (SD 2.1); n=8, Group 2: mean 7.4 (SD 0.5); n=8; drooling severity and frequency scale 2-9: top=high is poor outcome; risk of bias: high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Wu 2011[585]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Taiwan
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3-months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: children with cerebral palsy

Study	Wu 2011[585]
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with cerebral palsy aged 3-16 years; patients with a chronic drooling problem
Exclusion criteria	Recognised chromosomal abnormalities; progressive neurological disorder or severe concurrent illness not typically associated with cerebral palsy; active medical conditions such as epilepsy or infections; any major surgery or nerve block within the 3 months prior to the study; any known allergy to the study drug; inability to chew on gauze
Recruitment/selection of patients	Recruited from an outpatient rehabilitation centre
Age, gender and ethnicity	Age – mean (SD): intervention mean age = 8.6 years (4.1); control mean age = 8 years (3.3). Gender (M:F): 9 male/11 female. Ethnicity: not reported.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: not applicable/ not stated/unclear (unclear). 3. Type of MND: not applicable/not stated/unclear (children with cerebral palsy).
Indirectness of population	Serious indirectness
Interventions	(n=10) Intervention 1: Botulinum toxin injections. Freeze-dried powdered botulinum Type A was mixed with 1mL of saline (0.9% sodium chloride solution) to a concentration of 10 U/0.1. Dose was titrated according to patient weight; 30 U for patient weight < 15kg; 40 U for patient weight from 15 - 25 kg; and 50 U for patient weight > 25 kg. Maximum dose for each submandibular gland was 10 U, and overall maximum dose of 50 U in total. Injection guided by sonography. Duration: one dose. Concurrent medication/care: after the injection, patients received a course of oromotor training by a speech therapist. (n=10) Intervention 2: Placebo. Normal saline injection, guided by sonography. Duration: one dose. Concurrent medication/care: after the injection, patients received a course of oromotor training by a speech therapist.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BOTULINUM TOXIN INJECTIONS versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: carer reported drooling severity at 1 month; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions; Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control)

Study	Zeller 2012[591]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	(n=38)
Countries and setting	Conducted in USA; setting: 10 US clinical trial sites
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Patients in an indirect population who are experiencing sialorrhoea: patients with cerebral palsy, mental retardation or neurological disorder
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients weighing at least 27lb (12.2kg) and previously diagnosed with cerebral palsy, mental retardation or other neurologic condition associated with problem drooling; patients with oral feeding problems or who used a tube for feeding
Exclusion criteria	Patients with mild drooling (drooling resulted in wetness of lips and chin but clothes did not become damp on most days; patients who had use glycopyrrolate liquid within 24 hours of baseline; patients who had used anticholinergic or cholinergic medications prohibited by the protocol within three plasma half-lives of that medication prior to baseline; patients with medical conditions contraindicating anticholinergic therapy or treatment with the study medication; positive pregnancy test for any female patients of childbearing age
Recruitment/selection of patients	The study was conducted between November 2002 and April 2007. A temporary hold was placed on enrolment from November 2005 to September 2006 pending receipt of orphan drug designation for glycopyrrolate liquid
Age, gender and ethnicity	Age – mean (SD): intervention mean age = 10.2 years (3.8); control mean age = 8.7 years (4). Gender (M:F): 22 male/14 female. Ethnicity: 72% white; 25% black or African-American; 3% other.
Further population details	1. Ability to cough: not applicable/not stated/unclear (not stated). 2. Severity of swallowing difficulty: patients with moderate or severe swallowing difficulties (clothing wet approximately 5-7 days a week). 3. Type of MND: not applicable/not stated/unclear (cerebral palsy [mixed population]).
Indirectness of population	Very serious indirectness: 83.3% of patients had cerebral palsy, other patients had unspecified other disorders
Interventions	(n=20) Intervention 1: Glycopyrrolate (sublingual, syringe driver, orally, or via PEG). Oral solution glycopyrrolate administered 3x daily. Dosage was titrated weekly over the first four-week period, with the optimum dose reached by the end of week 4. Dosage never exceeded 1.5-3mg per dose based on weight. Five dosages were evaluated: 0.02 mg/kg, 0.04/mg/kg, 0.06 mg/kg, 0.08 mg/kg, and 0.1 mg/kg. After the optimum dose was reached, patients continued

Study	Zeller 2012[591]
	on the medication for a further 4 weeks. Mean dose = 0.15 mg/kg. Duration: 8 weeks. Concurrent medication/care: none described. (n=18) Intervention 2: Placebo. Placebo oral solution, matching study drug in colour and taste. Dosage was titrated weekly over the first four-week period, with the optimum dose reached by the end of week 4. Duration: 8 weeks. Concurrent medication/care: as the investigators anticipated continued drooling problems in the placebo condition, caregivers were specifically encouraged to keep patients in the study until at least week 4.
Funding	Study funded by industry (study funded by Shinogi Inc. All authors are employed by, or have acted as an advisor to, Shinogi Inc)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GLYCOPYRROLATE (SUBLINGUAL, SYRINGE DRIVER, ORALLY, OR VIA PEG) versus PLACEBO Protocol outcome 1: Patient reported outcomes (symptoms, pain, satisfaction) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: change in drooling problem at 8 weeks; Group 1: mean 3.94 (SD 1.95); n=19, Group 2: mean 0.71 (SD 2.14); n=17; Modified Teacher's Drooling Scale (mTDS) 1-9: top=high is poor outcome; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: satisfaction at 8 weeks; Group 1: 19/19, Group 2: 10/18; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Adverse effects (increased muscle weakness negating improved saliva control, side effects which cause cessation of use even if improved saliva control) - Actual outcome for patients in an indirect population who are experiencing sialorrhoea: Adverse effects resulting in patient discontinuing treatment at 8 weeks; Group 1: 1/20, Group 2: 1/18; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Health related quality of life; aspiration pneumonia; function measured by disability scores (Ashworth scale); unplanned admissions; hospital admissions

G.11 Equipment and adaptations to aid activities of daily living and mobility

Study	Gruis 2011
Aim	To understand patients' self-reported satisfaction with various types of assistive technology.
Population	Patients with ALS.

Study	Gruis 2011		
	96 patients identified, 63 patients completed survey. Median age 62 years (IQR: 52, 72); males 37 (59%); limb-onset symptoms 52 (83%); median duration between the diagnosis and survey 26 months (17, 50), and median ALS-FRS-R score was 25 (18, 33).		
Setting	Patients from the University of Michigan, multidisciplinary clinic, USA.		
Methods	A telephone survey administered and responses recorded anonymously. Included topics: demographics, caregivers and dwelling, functional impairments and assistive devices. Demographic information was taken from the US Census Bureau 2006-2008 American Community Survey 3-6 year estimates. Functional status measured by the ALS Functional Rating Scale-Revised. Asked about their frequency of use, perceived usefulness, and satisfaction with several different types of assistive devices (Mobility: cane, walker, non-motorised wheelchair, motorised scooter at home or store, motorised wheelchair, ankle brace, sliding or transfer board, in-home hydraulic lift; communication: writing on paper, portable erase board, letter, word, or picture board, laptop computer, PDA or Palm Pilot, Electronic speaking device; eating: modified eating utensils, wrist braces, mobile arm supports)		
Themes with findings		Devices used most	16/33 devices surveyed were designated high frequency use with devices used “often or always” by 20-55% of respondents: walker, motorised wheelchair, ankle brace for ambulation, sliding transfer board, writing on paper to communicate, laptop computer, personal digital assistance (PDA), modified eating utensils, wrist braces, slip-on shoes, arm rails by the toilet, elevated toilet seat, shower seat, shower bars, speaker phone and electric seating controls for a recliner or wheelchair).
		Devices with high frequency use with high or very high median rating for how well the device worked and satisfaction with the device	The ankle brace, transfer board, all bathroom devices, slip-on shoes, speaker phone and electronic seating controls
		High median ratings for how well devices worked, but	Walkers, motorised wheelchairs, PDAs, laptop computers

Study	Gruis 2011		
		lower satisfaction scores	
		Low frequency use but rated as very high for how well device worked and satisfaction	Motorised scooters; letter, word or picture boards; electronic bed controls; sound or voice-activated environmental controls
		Low or very low median ratings of usefulness and satisfaction	Button hook, dressing stick with hook, long-handled reaching tool
Limitations	Indirect – was not asking patients what they thought they required, but more about what received. Unclear data collection methods		

Study	Peters 2009
Aim	To establish the needs for support services for people with Primary Lateral Sclerosis.
Population	Patients with Primary Lateral Sclerosis. 40 patients and caregivers mailed the questionnaire, 25 returned it. 22 patients were contacted by telephone for additional follow-up. 13 male patients, 12 women patients. Mean age 59 years old, mean age of symptom onset 45 years old
Setting	USA. Over the telephone.
Methods	17-item closed ended questionnaire (2-4). Developed from a pilot study which had several open-ended questions sent to 45 patients. Medical charts reviewed for information about age at onset of symptoms, age at time of diagnosis, history of onset of the use of canes, walkers

Study	Peters 2009		
	and wheelchairs.		
Themes with findings	Physical/occupational therapy needs	Assistance with activities of daily living	Mobility (76%) Household help with chores such as cleaning (40%) Help with cooking (36%) Help with dressing/personal hygiene (32%) Independent (16%) Serviceable speech (88%) Good respiratory function, requiring no ventilator assistance (96%)
			All used some form of gait assistive device Cane, walker or wheelchair
	Burden of illness		Retired because of illness (48%)
			Changed jobs – patients or caregivers (32%)
			Modified their households: Modified showers of tubs for safety, adding ramps and lifts
Limitations	Unclear how participants were selected. Methods of analysis of qualitative data not reported so rigour and reliability unclear. Small sample size, caution is needed before generalising results from numerically small qualitative studies to a wider population Indirect – was not asking patients what they thought they required, but more about what they did, or had to change.		

G.12 Nutrition

Study	Dorst 2013[189]
Study type	RCT (patient randomized; parallel)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in Germany; setting: not reported
Line of therapy	Adjunctive to current care
Duration of study	Intervention and follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial criteria

Study	Dorst 2013[189]
Stratum	Overall: does not say the status of the person's swallowing or ability to feed or if cognitive impairment was present
Subgroup analysis within study	Not applicable: no subgroup analyses
Inclusion criteria	Definite, probable or laboratory supported ALS according to El Escorial criteria
Exclusion criteria	Arteriosclerosis, coronary heart disease, severe liver or kidney diseases, patients on cholesterol-lowering drugs, patients with percutaneous endoscopic gastrostomy (PEG)
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (SD): 62.0 (10.2). Gender (M:F): 15/11. Ethnicity: not reported.
Further population details	1. Type of MND: ALS
Extra comments	All patients had suffered from weight loss prior to inclusion in the study
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Dietary supplement – food fortification. High fat content food supplement. Duration 12 weeks. Concurrent medication/care: normal food intake, no details given. (n=14) Intervention 2: Dietary supplement – food fortification. High carbohydrate content supplement. Duration 12 weeks. Concurrent medication/care: normal food intake, no details given.
Funding	Study funded by industry (Fresenius (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) and by the German ALS Network Group and the Helmholtz Virtual Institute Ulm)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH FAT versus HIGH CARBOHYDRATE

Protocol outcome 1: Patient/carer reported outcomes (for example satisfaction)
- Actual outcome: diarrhoea at 12 weeks; Group 1: 1/12, Group 2: 0/14; risk of bias: very high; indirectness of outcome: no indirectness

Protocol outcome 2: Change in weight/BMI
- Actual outcome: weight gain (kg/month) at 12 weeks; Group 1: mean 0.52 kg/month (SD 0.159); n=8, Group 2: mean 0.28 kg/month (SD 0.159); n=8; risk of bias: very high; indirectness of outcome: no indirectness

- Actual outcome: Change in BMI at 12 weeks; Group 1: mean 0.6 BMI (SD 0.7); n=8, Group 2: mean 0.18 BMI (SD 1.43); n=8; risk of bias: very high; indirectness of outcome: no indirectness

Study	Dorst 2013[189]
Protocol outcomes not reported by the study	Quality of life; hospital admissions; survival

Study	Silva 2010[520]
Study type	RCT (patient randomized; parallel)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in Brazil; setting: neuromuscular outpatient clinic of Campinas University (UNICAMP)
Line of therapy	Adjunctive to current care
Duration of study	Intervention and follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial criteria (1998)
Stratum	Overall: not reported
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with clinically definite ALS, either with bulbar or appendicular onset, regularly assisted in the clinic
Exclusion criteria	Patients with nasogastric tube or gastrostomy, on assisted mechanical ventilation, without intervening neurological illnesses
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – mean (range): 53 (32 to 69). Gender (M:F): 14/2. Ethnicity: not reported.
Further population details	1. Type of MND: ALS
Indirectness of population	No indirectness
Interventions	(n=8) Intervention 1: Dietary supplement – food fortification. 70% Milk whey protein isolate and 30% modified starch; patients did not receive the supplement concurrently with Riluzole; patients administered it themselves and were instructed to keep the product in a refrigerator and to solubilize it before administration; on an individual basis, assays to the adequate viscosity were performed with orange juice (pH=4.0 and 1.5% of solid components). Frequency: twice per day. Concurrent medication/care: usual diet of the patient. (n=8) Intervention 2: Dietary supplement – food fortification. Maltodextrin. Frequency: twice per day. Concurrent medication/care: usual diet of patient
Funding	Academic or government funding (Conselho Nacioanl de Desenvolvimento Cientifico e Tecnologico (National Council

Study	Silva 2010[520]
	for Scientific and Technological Development))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MILK WHEY PROTEIN ISOLATE versus MALTODEXTRIN Protocol outcome 1: Change in nutritional status - Actual outcome: % change in nutritional adequacy at 16 weeks; other: 13.27% increase in nutritional adequacy in milk whey protein isolate group 11.2% in maltodextrin group; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: change in mid-arm muscle circumference at 16 weeks; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: change in tricipital skinfold at 16 weeks; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Patient/carer reported outcomes (for example satisfaction) at define - Actual outcome: ALSFRS-R at 16 weeks; risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Change in weight/BMI - Actual outcome: change in BMI at 16 weeks; risk of bias: very high; indirectness of outcome: no indirectness - Actual outcome: change in weight at 16 weeks; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Quality of life; survival; hospital admissions

G.13 Cough effectiveness

Study	Mustfa 2003-1[417]
Study type	RCT (randomised; crossover: unclear)
Number of studies (number of participants)	1 (n=26)
Countries and setting	Conducted in United Kingdom; setting: King's College Hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial criteria used by neurologist
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: bulbar and non-bulbar patients
Inclusion criteria	Not reported. Healthy patients also included in study but data were separate.

Study	Mustfa 2003-1[417]
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age – other: not reported but reports 'women' (and men) included. Gender (M:F): 32/15. Ethnicity: not reported.
Further population details	1. People who are obese: not applicable/not stated/unclear. 2. People who are using NIV for respiratory failure: not applicable/not stated/unclear. 3. People who have a tracheostomy: not applicable/not stated/unclear. 4. Type of MND: not applicable/not stated/unclear.
Indirectness of population	Direct
Interventions	(n=26) Intervention 1: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – mechanical cough assist device (mechanical insufflation-exsufflation). MI-E coordinated with the patients' cough effort, using a mechanical in-exsufflator (ME-I interface was a face mask). In-exsufflation pressures and times were not reported. Duration: unclear. Concurrent medication/care: none. (n=26) Intervention 2: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – insufflation. Insufflation with the in-exsufflator incrementally increased to the maximum tolerated pressure prior to coughing. Duration: unclear. Concurrent medication/care: none. (n=26) Intervention 3: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – exsufflation. Manually initiated exsufflation using the mechanical in-exsufflator device (the negative pressure was gradually titrated to the maximum tolerated exsufflation), initiated just prior to coughing. Duration: unclear. Concurrent medication/care: none. (n=26) Intervention 4: Active cycle of breathing techniques (TEE, breathing control, huffing) – manual cough assisted coughing technique (quad coughing, assisted coughing). Manually assisted cough using abdominal pressure. Duration: unclear. Concurrent medication/care: none. (n=26) Intervention 5: Unassisted cough. Maximal unaided coughs. Duration: unclear. Concurrent medication/care: none.
Funding	Other (Muscular Dystrophy Association of America; Motor Neurone Disease Association; The King's MND Care and Research Centre; National Health Services Research and Development)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus INSUFFLATION	

Study	Mustfa 2003-1[417]
Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 264 L/min (SD 73); n=26, Group 2: mean 226 L/min (SD 86); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus EXSUFFLATION Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 264 L/min (SD 73); n=26, Group 2: mean 279 L/min (SD 87); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 264 L/min (SD 73); n=26, Group 2: mean 244 L/min (SD 83); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 264 L/min (SD 73); n=26, Group 2: mean 217 L/min (SD 84); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSUFFLATION versus EXSUFFLATION Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 226 L/min (SD 86); n=26, Group 2: mean 279 L/min (SD 87); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSUFFLATION versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING)	

Study	Mustfa 2003-1[417]
Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 226 L/min (SD 86); n=26, Group 2: mean 244 L/min (SD 83); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSUFFLATION versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 226 L/min (SD 86); n=26, Group 2: mean 217 L/min (SD 84); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXSUFFLATION versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 279 L/min (SD 87); n=26, Group 2: mean 217 L/min (SD 84); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXSUFFLATION versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 279 L/min (SD 87); n=26, Group 2: mean 244 L/min (SD 83); n=26; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF L/min at Unclear; Group 1: mean 244 L/min (SD 83); n=26, Group 2: mean 217 L/min (SD 84); n=26; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Survival; health related quality of life; patient/carer reported outcomes; hospital admissions (and unplanned admissions) and length of hospital stay; reduction of chest infections.

Study	Mustfa 2003-2[417]
Study type	RCT (randomised; crossover: unclear)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: El Escorial criteria used by neurologist
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported. Healthy patients also included in study but data were separate.
Exclusion criteria	Not reported
Age, gender and ethnicity	Age – other: not reported but reports 'women' (and men) included. Gender (M:F): 32/15. Ethnicity: not reported.
Further population details	1. People who are obese. 2. People who are using NIV for respiratory failure. 3. People who have a tracheostomy. 4. Type of MND.
Indirectness of population	Direct
Interventions	(n=21) Intervention 1: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – mechanical cough assist device (mechanical insufflation-exsufflation). MI-E coordinated with the patients' cough efforts, using a mechanical in-exsufflator. ME-I interface was a face mask. In-exsufflation pressures and times not reported. Duration: not reported. Concurrent medication/care: none. (n=21) Intervention 2: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – exsufflation. Manually initiated exsufflation using the mechanical in-exsufflator device (the negative pressure was gradually titrated to the maximum tolerated exsufflation), initiated just prior to coughing. Duration: not reported. Concurrent medication/care: none. (n=21) Intervention 3: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – insufflation. Insufflation with the in-exsufflator incrementally increased to the maximum tolerated pressure prior to a maximal cough. Duration: not reported. Concurrent medication/care: none. (n=21) Intervention 4: Active cycle of breathing techniques (TEE, breathing control, huffing) – manual cough assisted coughing technique (quad coughing, assisted coughing). Manually assisted cough using abdominal pressure. Duration: not reported. Concurrent medication/care: none.

Study	Mustfa 2003-2[417]
	(n=21) Intervention 5: Unassisted cough. Maximal unaided coughs. Duration: not reported. Concurrent medication/care: none.
Funding	Other (Muscular Dystrophy Association of America; Motor Neurone Disease Association; The King's MND Care and Research Centre; National Health Services Research and Development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus EXSUFFLATION

Protocol outcome 1: Peak cough flow
- Actual outcome: PCF, L/min at Not reported; Group 1: mean 212 L/min (SD 75); n=21, Group 2: mean 225 L/min (SD 76); n=21; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus INSUFFLATION

Protocol outcome 1: Peak cough flow
- Actual outcome: PCF, L/min at Not reported; Group 1: mean 212 L/min (SD 75); n=21, Group 2: mean 188 L/min (SD 64); n=21; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING)

Protocol outcome 1: Peak cough flow
- Actual outcome: PCF, L/min at Not reported; Group 1: mean 212 L/min (SD 75); n=21, Group 2: mean 197 L/min (SD 63); n=21; risk of bias: very high; indirectness of outcome: no indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus UNASSISTED COUGH

Protocol outcome 1: Peak cough flow
- Actual outcome: PCF, L/min at Not reported; risk of bias: very high; indirectness of outcome: no indirectness

Study	Mustfa 2003-2[417]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXSUFFLATION versus INSUFFLATION Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 225 (SD 76); n=21, Group 2: mean 188 (SD 64); n=21; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXSUFFLATION versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 225 L/min (SD 76); n=21, Group 2: mean 197 L/min (SD 63); n=21; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXSUFFLATION versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 225 L/min (SD 76); n=21, Group 2: mean 178 L/min (SD 61); n=21; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSUFFLATION versus MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 188 L/min (SD 64); n=21, Group 2: mean 197 L/min (SD 63); n=21; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSUFFLATION versus UNASSISTED COUGH Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 188 L/min (SD 64); n=21, Group 2: mean 178 L/min (SD 61); n=21; risk of bias: very high; indirectness of outcome: no indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MANUAL COUGH ASSISTED COUGHING TECHNIQUE (QUAD COUGHING, ASSISTED COUGHING) versus UNASSISTED COUGH	

Study	Mustfa 2003-2[417]
Protocol outcome 1: Peak cough flow - Actual outcome: PCF, L/min at Not reported; Group 1: mean 197 (SD 63); n=21, Group 2: mean 178 (SD 61); n=21; risk of bias: very high; indirectness of outcome: no indirectness	
Protocol outcomes not reported by the study	Survival; health related quality of life; patient/carer reported outcomes; hospital admissions (and unplanned admissions) and length of hospital stay; reduction of chest infections

Study	Rafiq 2014[476]
Study type	RCT (randomised; parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in United Kingdom; setting: not reported
Line of therapy	1st line
Duration of study	Intervention and follow up: 12 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: not reported
Stratum	Overall: not reported
Subgroup analysis within study	Not applicable: not reported
Inclusion criteria	Clinically definite or probable ALS according to the El Escorial criteria; evidence of respiratory failure meeting the criteria for intervention with non-invasive ventilation (NMIV), including one or more of the following parameters: symptoms of respiratory muscle weakness (such as orthopnoea, unrefreshing sleep); decline in respiratory function parameters; or nocturnal or day time hypercapnia.
Exclusion criteria	Failing a trial of NIV (for reasons such as claustrophobia, laryngospasm); susceptibility to pneumothorax (such as a history of bullous emphysema or barotrauma); significant comorbidity which might reduce life expectancy; frontotemporal cerebral dysfunction that was clinically evident and noticeable to the family.
Recruitment/selection of patients	Attending the Sheffield Care and Research Centre for Motor Neurone Disorders.
Age, gender and ethnicity	Age (years): MI-E group: 60.2 (15.2); breath-stacking group: 64.1 (10.5) Gender (M:F): 33:7 Ethnicity: not reported.
Further population details	1. People who are obese: not applicable/not stated/unclear. 2. People who are using NIV for respiratory failure: not applicable/not stated/unclear. 3. People who have a tracheostomy: not applicable/not stated/unclear. 4. Type of MND: not applicable/not stated/unclear.
Extra comments	None.

Study	Rafiq 2014[476]
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – mechanical cough assist device (mechanical insufflation-exsufflation). Duration: not reported. Concurrent medication/care: all prescribed riluzole. (n=21) Intervention 2: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – lung volume recruitment technique (LVR bag). Duration: not reported. Concurrent medication/care: all prescribed riluzole.
Funding	Other author(s) funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) versus LUNG VOLUME RECRUITMENT TECHNIQUE (LVR BAG) Protocol outcome 1: Survival - Actual outcome: Median survival at 12 months; other: median 266 days in MI-E group; 535 days in the breath-stacking group; HR 1.94 (0.87 to 4.33) risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 2: Hospital admissions (and unplanned admissions) and length of hospital stay - Actual outcome: Total number of hospitalisation at 12 months; RR 1.45 (0.3 to 7.01) risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 3: Reduction of chest infections - Actual outcome: Total number of chest infection at 12 months; RR 1.06 (0.31 to 3.62); risk of bias: very high; indirectness of outcome: indirect Protocol outcome 4: Hospital admissions (and unplanned admissions) and length of hospital stay - Actual outcome: Number of patients with any hospitalisation; OR 0.87 (0.16 to 4.73); risk of bias: very high; indirectness of outcome: no indirectness Protocol outcome 5: Reduction of chest infections - Actual outcome: Number of patients with at least one chest infection; OR0.78 (0.16 to 3.8); risk of bias: very high; indirectness of outcome: indirect	
Protocol outcomes not reported by the study	Patient/carer reported outcomes;

Study	Senent 2011[513]
Study type	RCT (randomised; crossover: 10-15 minutes)
Number of studies (number of participants)	1 (n=16)
Countries and setting	Conducted in France; setting: day-hospital
Line of therapy	1st line
Duration of study	Not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	People with significant respiratory dysfunction
Subgroup analysis within study	Not applicable
Inclusion criteria	Stable patients with ALS who had been on home mechanical ventilation for >2 months and were enrolled during scheduled routine day-hospital visits
Exclusion criteria	Occurrence of any 'respiratory event' in the preceding month; presence of a tracheostomy; unassisted peak cough flow >270 litre/minute
Recruitment/selection of patients	All patients scheduled for a routine visit at the centre for 3 months
Age, gender and ethnicity	Age - mean (SD): 63 (57-68). Gender (M:F): 12/4. Ethnicity: not reported.
Further population details	1. People who are obese: not applicable/not stated/unclear. 2. People who are using NIV for respiratory failure: People who are using NIV for respiratory failure (people using home mechanical ventilation for more than 2 months). 3. People who have a tracheostomy: people who do not have a tracheostomy. 4. Type of MND: ALS.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – lung volume recruitment technique (LVR bag). Expiratory abdominal thrust after air stacking on spontaneous deep breath, using a silicone resuscitator. Duration: unclear. Concurrent medication/care: three manual cough techniques were applied 1 hour previously. Comments: The techniques were applied at 10 to 15 minute intervals. (n=16) Intervention 2: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – lung volume recruitment technique (BiPAP). Expiratory abdominal thrust from end-inspiratory volume using bi-level pressure ventilator with normal settings. Duration: unclear. Concurrent medication/care: three manual cough techniques were applied 1 hour previously. Comments: The techniques were applied at 10 to 15 minute intervals.

Study	Senent 2011[513]
	(n=16) Intervention 3: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – lung volume recruitment technique (iPAP). Expiratory abdominal thrust from end-inspiratory volume obtained by increasing inspiratory positive airway pressure, iPAP, to +30cmH2O. Duration: unclear. Concurrent medication/care: three manual cough techniques were applied 1 hour previously. Comments: The techniques were applied at 10 to 15 minute intervals. (n=16) Intervention 4: Devices (maximal insufflation capacity techniques/lung inflation capacity techniques) – mechanical cough assist device (mechanical insufflation-exsufflation). MI-E assisted cough using a face mask interface. Maximum insufflation and exsufflation pressure were gradually increased to -40cmH2O and +40cmH2O. Four to six in-exsufflation cycles were given with a 1 to 3 second inter-cycle pause. Insufflation and exsufflation times were not reported. Duration: unclear. Concurrent medication/care: three manual cough techniques were applied 1 hour previously. Comments: The techniques were applied at 10 to 15 minute intervals. (n=16) Intervention 5: Unassisted cough. Duration: unclear. Concurrent medication/care: none. (n=16) Intervention 6: Active cycle of breathing techniques (TEE, breathing control, huffing). Coached unassisted cough (encouraging the patient to inspire as deeply and spontaneously as possible before the coughing effort. Duration: unclear. Concurrent medication/care: none. (n=16) Intervention 7: Active cycle of breathing techniques (TEE, breathing control, huffing) – manual cough assisted coughing technique (quad coughing, assisted coughing). Coached unassisted cough (encouraging the patient to inspire as deeply and spontaneously as possible before the coughing effort), with an added abdominal thrust, at the beginning of the cough expiration phase, from the physiotherapist. Duration: unclear. Concurrent medication/care: none.
Funding	Academic or government funding (Association pour le Developpement et l'Organisation de la Recherche (ADOREP), Paris, France; Association d'Entraide des Polio et handicapes (ADEP))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (LVR BAG) versus LUNG VOLUME RECRUITMENT TECHNIQUE (BIPAP) Protocol outcome 1: Patient/carer reported outcomes	

Study	Senent 2011[513]
- Actual outcome: Subjective evaluation of efficacy; other: median (IQR): LVR bag 7 (5-8); BiPAP 7 (6-8) VAS 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): LVR bag 6 (5-8); BiPAP 8 (7-8); risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow at Unclear; other: median (IQR): LVR bag 284 (146 to 353); BiPAP: 212 (99-595); risk of bias: very high; indirectness of outcome: serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (LVR BAG) versus LUNG VOLUME RECRUITMENT TECHNIQUE (IPAP) Protocol outcome 1: Patient/carer reported outcomes - Actual outcome: Subjective evaluation of efficacy; other: median (IQR): LVR bag 7 (5-8); iPAP 6 (5-7) VAS scale: 0-10 top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): LVR bag 6 (5-8); iPAP 6 (5-7) VAS scale: 0-10 top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow; other: median (IQR): LVR bag 284 (146 to 353); iPAP: 233 (100-389); risk of bias: very high; indirectness of outcome: serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (LVR BAG) versus MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) Protocol outcome 1: Patient/carer reported outcomes - Actual outcome: Subjective evaluation of efficacy; other: median (IQR): LVR bag 7 (5-8); MIE 8 (6-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): LVR bag 6 (5-8); MIE 7 (3-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow; other: median (IQR): LVR bag 284 (146-353); MIE 488 (243-605); risk of bias: very high; indirectness of outcome: serious indirectness	

Study	Senent 2011[513]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (BIPAP) versus LUNG VOLUME RECRUITMENT TECHNIQUE (IPAP) Protocol outcome 1: Patient/carer reported outcomes - Actual outcome: Subjective evaluation of efficacy; other: median (IQR): BiPAP 7 (6-8); iPAP 6 (5-7) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): BiPAP 8 (7-8); iPAP 6 (5-7) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow; other: median (IQR): BiPAP: 212 (99-595); MIE 488 (243-605); risk of bias: very high; indirectness of outcome: serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (BIPAP) versus MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) Protocol outcome 1: Patient/carer reported outcomes - Actual outcome: Subjective evaluation of efficacy; other: median (IQR): BiPAP 7 (6-8); MIE 8 (6-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): BiPAP 8 (7-8); MIE 7 (3-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow; other: median (IQR): BiPAP: 212 (99-595); MIE 488 (243-605); risk of bias: very high; indirectness of outcome: serious indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LUNG VOLUME RECRUITMENT TECHNIQUE (IPAP) versus MECHANICAL COUGH ASSIST DEVICE (MECHANICAL INSUFFLATION-EXSUFFLATION) Protocol outcome 1: Patient/carer reported outcomes - Actual outcome: Subjective evaluation of efficacy; other: median (IQR): iPAP 6 (5-7); BiPAP 7 (6-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness - Actual outcome: Subjective evaluation of comfort; other: median (IQR): iPAP 6 (5-7); MIE 7 (3-8) VAS scale 0-10: top=high is good outcome; risk of bias: very high; indirectness of outcome: serious indirectness	

Study	Senent 2011[513]
Protocol outcome 2: Peak cough flow - Actual outcome: Peak cough expiratory flow; other: median (IQR): iPAP 233 (100-389); MIE 488 (243-605); risk of bias: very high; indirectness of outcome: serious indirectness	
Protocol outcomes not reported by the study	Survival; health related quality of life; hospital admissions (and unplanned admissions) and length of hospital stay; reduction of chest infections

G.14 Experience of discontinuation of NIV

Study	Baxter 2013[56]
Aim	To describe carer and healthcare professional experiences of end-of-life care of MND patients using NIV
Population	Family carers and healthcare professionals. N=9 family carers and n=15 healthcare professionals. Relating to n=10 patients. UK study. The healthcare professional participants included: n=2 neurological support team physiotherapists; n=4 community matrons; n=3 neurological support team occupational therapists; n=1 rehabilitation nurse specialist; n=2 Macmillan nurse specialists; n=2 Primary care physicians; n=1 district nurse.
Study design	Qualitative longitudinal study; semi-structured interviews
Methods and analysis	In-depth interviews with family carers, carried out 1 month after the death of the patient; interviews with healthcare professionals nominated by these carers as being closely involved in the care in the final months of the disease. Patients recruited consecutively when they decided to try NIV. Sampling continued until saturation of data. Data collected May 2010 to April 2012, from time of initiation of NIV to death, when the interviews were carried out. Interviews lasted 45-60 minutes using a pre-defined interview schedule. Two interviewers carried out, audio-recorded and transcribed the interview verbatim. Thematic analysis used with systematic coding and NVivo 8 software. Consistency checked and noted differing views in the data. Data anonymised and discussed with team to establish consensus.
Themes with findings	**Unexpected speed of deterioration** • End of life was more rapid than expected and this adversely impacted the plan for end of life care (healthcare professionals and carers). The rapidity was a positive element for some as easier for families (healthcare professionals and carers)
	Hospitalisation versus dying at home • All patients had wanted to die at home, but a few had not been able to. Patients didn't want to go to hospital in case they were admitted (healthcare professionals and carer) • Healthcare professionals said that timing could account for not being able to die at home. Advanced care plans required careful timing and staff with knowledge of care plan needed to be available at critical points of rapid deterioration (healthcare professionals)

Study	Baxter 2013[56]
	• Patients who had been admitted arrived via emergency calls to ambulance service (carer and healthcare professionals). • Professionals highlighted difficult decision for carers and healthcare professionals about whether to telephone an ambulance or not (healthcare professional).
	Attempts to resuscitate • Participants reported that 2, almost 3, of the patients had been subjected to attempts to resuscitate, which had been highly distressing for the families (healthcare professional and carer). • Some had advance directives, but others did not and the healthcare professional found it challenging to bring up the subject of end of life to these patients who were not raising the topic (healthcare professional). • Difficult optimal timing to discuss in a rapidly progressing disease; NIV initiation was an opportunity to one participant (healthcare professional).
	Decision-making regarding the withdrawal of NIV • Five patients had NIV in 24-hour operation at the point of death. • One regular night-time user discontinued during the final month by stopping using the system – due to the fitting and removal of the mask being too onerous as physical functioning declined. • One regular night-time user passed away during the daytime, and 3 low users (less than 4 hours/night or day) also did not have the system operating at time of death. • Any potentially difficult decisions regarding whether and how the system should be discontinued at end of life did not arise for these NIV users. • Participants recalled discussion with the patients who had the system in 24-hour use regarding whether they wished to continue, and they had decided to (healthcare professional).
	Peaceful final moments • Little difference in description of final days and hours of those who died with mask in situ from those who did not. Descriptions tended to be of a peaceful end, with no reports of choking or struggling for breath in final moments (carers).
	Turning off the machine • Potential issue was the machine continuing to operate after the patient had died, making it unclear to carers if they were actually dead as it still looked like they were breathing (carers). • Two staff highlighted the importance of families having a clear understanding of the way the machine functioned at the end-of-life phase to overcome this concern (healthcare professionals).
	Professional uncertainty regarding the use of NIV • Carers identified the professionals most closely involved in the care of the patient in the final phase. Many found medical professionals to have limited involvement, and decisions regarding end-of-life NIV were made by professionals in community teams (healthcare professionals). • These participants described some uncertainty regarding how best to manage NIV in the final stage and whether usage should be withdrawn

Study	Baxter 2013[56]
	(healthcare professionals). • The strategy of weaning down usage was considered for 2 patients, but recalled as being used for patients outside this study (healthcare professionals). • Uncertainty regarding when to withdraw NIV seemed partly influenced by the perception that NIV was being used as a ventilator, rather than as providing support (healthcare professionals).
	Positive impacts of NIV use • Carers of regular users outlined positive impacts in terms of extending life and supporting breathing (carers). • Carers of low users described how patients perceived only limited benefits from the system or had found the physical limitations as the disease progressed to be an obstacle to use (carers). • Positive healthcare professional perceptions were described in terms of the system providing comfort and reassurance (healthcare professionals).
	Concerns regarding NIV use • The majority of participants described positive experiences of NIV usage at end of life, 3 professionals mentioned concerns. Two healthcare professionals recalled that the mask could muffle patient attempts to communicate (healthcare professionals). • One of the healthcare professionals said that patient dependence on the mask being in place obstructed the provision of mouth care in the final phase (healthcare professionals).
Limitations	Analytic process is described but more detailed required. No details of role or researcher.
Applicability of evidence	Applicable

Study	Faull 2014[206]
Aim	To identify issues and challenges that palliative medicine doctors encounter in relation to the withdrawal of NIV in MND patients
Population	N=134 palliative care doctors in the UK; n=8 (6.2%) of the doctors had not cared for a MND patient who used NIV and n=46 (35.4%) had not been involved in the actual withdrawal of NIV at the request of a patient; n=76 (58.5%) had been directly involved in the withdrawal of NIV.
Study design	Survey; electronic questionnaire. Piloted with registrars in palliative medicine at one hospice, seeking comment and undergoing revision in order to inform reliability and validity.
Methods and analysis	Electronic questionnaire sent to members of the Association of Palliative Medicine of Great Britain and Ireland. Participants rated how practically, emotionally and ethically challenging they found the process of NIV withdrawal. 11 point Likert scale used (0=not at all challenging; 10=very challenging).

Study	Faull 2014[206]
Themes with findings	**Practical challenges** • 42% of doctors who had undertaken withdrawal scored 7 or more on the 0-10 scale (0=not at all challenging; 10=very challenging). • They had concerns such as whether or not to wean ventilation, how to manage distressing symptoms, the use of sedative drugs (what and how) together with who should remove the mask were posed in the free text. • Huge time and planning burden inherent in the process and difficulties of communication with patients in terms of timing, sensitivity and limitations of such discussions in the face of disease progression and in the absence of any prior advance decisions or planning. • The need for NIV withdrawal to be a multidisciplinary team (MDT) decision was a recurrent theme, commenting on inherent challenges faced in terms of the need to support all involved, including the patient, family and staff. Managing conflicts that arise from differences in opinions within the MDT were also emphasised as practical challenges.
	Ethical challenges • Seen as less than the practical and emotional challenges, yet were still considerable. • Key themes were timing and appropriateness of withdrawal, the need for intentions to be clear to all and the time taken to discuss ethical issues with staff, and the issues related to capacity and ADRTs. • Some construed the process as causing the death and potentially open to external criticism. • The complexity of the ethical stance, that withdrawal of a treatment that is no longer requested by the patient is allowing death to occur, rather than causing death, may not be fully appreciated by all involved, even by the healthcare professionals within the team. • The process of NIV withdrawal, for some at least, feels different to the withdrawal of other treatments.
	Emotional challenges • Most of the respondents scored 7 or more and 20% scored 9 or 10 on the 0-10 scale for whether they were challenged emotionally by the process (0=not at all challenging; 10=very challenging). • Emotional burden, involving managing the emotions of others (patient, family and staff) throughout the process, was the most common theme. • Supporting others and conflict resolution formed part of this burden. • Concerns about causing harm or distress to the patient were also common. • Perhaps the most complex emotional issue was death being related to an action, albeit not the intention of the action.
Limitations	Survey, therefore the participants are prompted in their responses. Some of the participants had not been involved in the withdrawal of NIV and the results were not separated. Analytic process is described but more detailed required. No details of role of researcher.
Applicability of evidence	Partially applicable: applicable where information provided by those who were involved in the withdrawal of NIV.

Appendix H: Economic evidence tables

None

Appendix I: GRADE tables

I.1 Prognostic factors

Table 24: Predicting one year mortality

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	One year mortality	Control	Relative (95% CI)	Absolute		
Weight loss - BMI change 1 to <2 versus <1												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 1.26 (0.39 to 4.07)	-	VERY LOW	CRITICAL
Weight loss - BMI change ≥2 versus <1												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	OR 2.8 (1.04 to 7.54)	-	VERY LOW	CRITICAL
ALS functional rating scale score - 34-36 versus 37-40												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 1.8 (0.38 to 8.53)	-	VERY LOW	CRITICAL
ALS functional rating scale score - 31-33 versus 37-40												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 2.6 (0.55 to 12.29)	-	VERY LOW	CRITICAL

ALS functional rating scale score - 27-30 versus 37-40												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	--	OR 12.9 (2.8 to 59.43)	-	VERY LOW	CRITICAL
ALS functional rating scale score - 00-26 versus 37-40												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	OR 33.8 (6.7 to 170.52)	-	VERY LOW	CRITICAL
Age - 66-75 years versus ≤65 years												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 1.13 (0.45 to 2.85)	-	VERY LOW	CRITICAL
Age - >75 years versus ≤65 years												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	OR 6.12 (1.5 to 25)	-	VERY LOW	CRITICAL
Diagnostic delay - 7-12 months versus 0-6 months												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 0.42 (0.15 to 1.17)	-	VERY LOW	CRITICAL
Diagnostic delay - 13-24 months versus 0-6 months												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	-	-	OR 0.44 (0.14 to 1.4)	-	VERY LOW	CRITICAL
Diagnostic delay - >25 months versus 0-6 months												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	OR 0.07 (0.01 to 0.48)	-	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed the null line

Table 25: Predicting mortality or tracheostomy (time to event)

Quality assessment							Number of patients		Effect	Quality	Importance

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mortality (time to event)**	**Control**	**Relative (95% CI)**	**Absolute**		
Site of onset - Bulbar versus limb												
4	Observational studies	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	None	-	-	HR 1.44 (1.08 to 1.92)	-	VERY LOW	CRITICAL
Site of onset - Lower extremity versus upper extremity												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	-	-	HR 1.17 (0.66 to 2.07)	-	VERY LOW	CRITICAL
Site of onset - Bulbar versus upper extremity												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	-	-	HR 1.82 (0.99 to 3.33)	-	VERY LOW	CRITICAL
Site of onset - Respiratory versus upper extremity												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	HR 6.51 (2.72 to 15.6)	-	VERY LOW	CRITICAL
Age - higher versus lower (years)												
5	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	HR 1.03 (1.03 to 1.04)	-	VERY LOW	CRITICAL
Diagnostic delay - higher versus lower (months)												
5	Observational studies	Serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	None	-	-	HR 0.98 (0.97 to 1)	-	VERY LOW	CRITICAL
Diagnostic delay - 7.1-10.6 months versus 0-7 months												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	-	-	HR 0.95 (0.82 to 1.09)	-	VERY LOW	CRITICAL
Diagnostic delay - 10.7-17 months versus 0-7 months												
1	Observational	No serious	No serious	No serious	No serious	None	-	-	HR 0.81 (0.7	-	LOW	CRITICAL

	studies	risk of bias	inconsistency	indirectness	imprecision				to 0.93)			
Diagnostic delay - >17 months versus 0-7 months												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	HR 0.56 (0.48 to 0.66)	-	LOW	
Forced vital capacity - higher versus lower (%)												
4	Observational studies	Serious[1]	Serious[4]	No serious indirectness	No serious imprecision	None	-	-	HR 0.98 (0.97 to 1)	-	VERY LOW	CRITICAL
Forced vital capacity - <80% versus >/=80%												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 1.49 (1.12 to 1.99)	-	VERY LOW	CRITICAL
ALS functional rating scale/ALS functional rating scale revised score - higher versus lower												
2	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 0.94 (0.91 to 0.96)	-	VERY LOW	CRITICAL
ALS functional rating scale/ALS functional rating scale revised score - 36-39 versus ≤35												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 0.69 (0.6 to 0.8)	-	LOW	CRITICAL
ALS functional rating scale/ALS functional rating scale revised score - 40-42 versus ≤35												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 0.46 (0.4 to 0.53)	-	LOW	CRITICAL
ALS functional rating scale/ALS functional rating scale revised score - >42 versus ≤35												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 0.33 (0.28 to 0.39)	-	LOW	CRITICAL
Weight loss - <18.5 BMI versus ≥18.5												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 7.39 (1.7 to 32.1)	-	VERY LOW	CRITICAL
Weight loss - Weight change (per 5% decrease)												

1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	none	-	-	HR 1.31 (1.08 to 1.6)	-	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Heterogeneity, I2>75%, p</=0.01
3 Downgraded by 1 increment if the confidence interval crossed the null line
4 Heterogeneity, I2>50%, p</=0.01

Table 26: Predicting mortality

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mortality (relative risk)**	**Control**	**Relative (95% CI)**	**Absolute**		
Age - 65 years												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	RR 0.62 (0.52 to 0.74)	-	VERY LOW	CRITICAL
Diagnostic delay - >2 years versus <2 years												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	RR 0.46 (0.36 to 0.58)	-	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 27: Predicting mortality or tracheostomy (all participants had non-invasive ventilation from the beginning of the study)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mortality (people on NIV)**	**Control**	**Relative (95% CI)**	**Absolute**		

Site of onset (NIV only) - Bulbar versus limb												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	-	-	OR 1.71 (0.6 to 4.9)	-	VERY LOW	CRITICAL
Age (NIV only) - higher versus lower (years)												
1	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	OR 1.07 (1.02 to 1.12)	-	LOW	CRITICAL

1 Downgraded by 1 increment if the confidence interval crossed the null line

I.2 Organisation of care

Table 28: Clinical evidence profile: MDT plus case management versus MDT alone for MND - RCT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT plus case management versus MDT alone**	**Control**	**Relative (95% CI)**	**Absolute**		
ALSAQ-40 (follow-up 12 months; range of scores: 0-100; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	n=30	n=27	-	MD 3.7 higher (4.37 lower to 11.77 higher)	VERY LOW	CRITICAL
ALSFRS-R (follow-up 12 months; range of scores: 0-48; better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	n=28	n=25	-	MD 1.1 lower (6.77 lower to 4.57 higher)	VERY LOW	CRITICAL
CSI (follow-up 12 months; range of scores: 0-13; better indicated by lower values)												
1	Randomised	Very	No serious	No serious	Serious[2]	None	n=29	n=24	-	MD 0.6 higher (1.06	VERY	CRITICAL

	trials	serious[1]	inconsistency	indirectness						lower to 2.26 higher)	LOW	

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Clinical evidence profile: MDT plus co-ordinator versus MDT alone– before and after study

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT plus co-ordinator**	**MDT**	**Relative (95% CI)**	**Absolute**		
Survival time from diagnosis - Survival time from diagnosis (maximum 8 years follow-up) (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	HR 0.55 (0.44 to 0.69)	not pooled	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 30: MDT versus general neurology

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT**	**General neurology**	**Relative (95% CI)**	**Absolute**		
Survival time from onset of symptoms (adjusted) – Aridegbe, 2013												
1	Observational studies	Very serious	No serious inconsistency	No serious indirectness	No serious imprecision	None	n=255	n=162	HR 0.58 (0.46 to 0.73)	-	VERY LOW	CRITICAL
Survival time from diagnosis (adjusted) 5 years - Aridegbe, 2013												

1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n=255	n=162	HR 0.51 (0.41 to 0.63)	-	VERY LOW	CRITICAL
Survival time from diagnosis (adjusted) 6 years – Rooney, 2015												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n=340	n=377	HR 0.59 (0.49 to 0.71)	-	VERY LOW	CRITICAL
Survival time from diagnosis (adjusted) 5 years - Traynor, 2013												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	n=82	n=262	HR 0.68 (0.48 to 0.96)	-	VERY LOW	CRITICAL
Survival time from diagnosis (adjusted) 1 year - Zoccolella, 2007												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	n=84	n=42	HR 0.91 (0.44 to 1.88)	-	VERY LOW	CRITICAL
Survival time from diagnosis (adjusted) 4 years – Zoccolella, 2007												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	n=84	n=42	HR 1.4 (0.88 to 2.23)	-	VERY LOW	CRITICAL
Median survival from onset												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	n=19	n=221	-	Median survival time for intervention group 1080 days; median survival for control group 775 days	VERY LOW	CRITICAL
Mean duration of hospital stay (better indicated by lower values) (adjusted), Chio, 2006												
1	Observational studies	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	n=97	n=124	-	MD 6.6 lower (12.47 to 0.73 lower)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Downgraded by 2 increments as unable to analyse imprecision as median survival times reported

I.3 Pharmacological treatment for muscle problems

Table 31: Memantine versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Memantine	Placebo	Relative (95% CI)	Absolute		
Health related quality of life SF36 (follow-up 12 months; measured with: SF-36 score (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	32	31	-	MD 3.4 lower (10.42 lower to 3.62 higher)	VERY LOW	CRITICAL
MRC (muscle strength) (follow-up 12 months; measured with: Questionnaire; range of scores: 0-160; better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	32	31	-	MD 4.3 higher (13.15 lower to 21.75 higher)	VERY LOW	CRITICAL
ALSFRS (follow-up 12 months; measured with: Final scores (range 0-40); range of scores: 0-40; better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	32	31	-	MD 0.4 lower (4.57 lower to 3.77 higher)	LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 32: Gabapentin versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gabapentin	Placebo	Relative (95% CI)	Absolute		
Median arm megascore rate of decline (better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	n=79 -0.0025 per day N=100 -0.0198 per week	n=70 -0.0040 per day N=96 -0.0209 per week	-	Not pooled	VERY LOW	CRITICAL
Median MVC rate of decline												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	n=79 -0.017 per week N=100 -0.020 per week	n=70 -0.028 per week N=96 -0.021 per week	-	Not pooled	VERY LOW	CRITICAL
Drowsiness												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	50/181 (27.6%)	10.6%	RR 2.64 (1.61 to 4.33)	174 more per 1000 (from 65 more to 353 more)	MODERATE	IMPORTANT

Weakness												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	14/79 (17.7%)	8.6%	RR 2.07 (0.84 to 5.09)	92 more per 1000 (from 14 fewer to 352 more)	VERY LOW	CRITICAL
Cramps												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[4]	Serious[3]	None	8/79 (10.1%)	2.9%	RR 3.54 (0.78 to 16.14)	74 more per 1000 (from 6 fewer to 439 more)	VERY LOW	CRITICAL
ALSFRS at 36 weeks (better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	n= 65	n= 63	-	MD 0.7 higher (1.13 lower to 2.53 higher)	MODERATE	CRITICAL
SF-12 (better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	n= 65	n= 63	-	MD 0.17 higher (0.04 lower to 0.38 higher)	LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Unable to analyse data as medians given and incompletely reported

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

4 Not decrease in muscle cramps

I.4 Non-pharmacological management of muscle problems

Table 33: Clinical evidence profile: Resistance exercise versus usual care

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Resistance exercise**	**Usual care**	**Relative (95% CI)**	**Absolute**		
Physical function at 6 months (follow-up 6 months; control group=14; measured with: SF-36 (0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 7.1 higher (1.31 to 12.89 higher)	LOW	CRITICAL
SF-36 physical role at 6 months (follow-up 6 months; control group=5.2; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 1.2 higher (0.1 lower to 2.5 higher)	LOW	CRITICAL
SF-36 pain at 6 months (follow-up 6 months; control group=10.1; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	10	-	MD 0.2 higher (1.09 lower to 1.49 higher)	VERY LOW	CRITICAL
SF-36 general health at 6 months (follow-up 6 months; control group=16.8; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	10	-	MD 0.4 higher (3.49 lower to 4.69 higher)	VERY LOW	CRITICAL
SF-36 vitality at 6 months (follow-up 6 months; control group=15.4; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	10	-	MD 0.8 higher (3.04 lower to 4.64 higher)	VERY LOW	CRITICAL
SF-36 social function at 6 months (follow-up 6 months; control group=7.8; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 1.1 higher (0.47 lower to 2.67 higher)	LOW	CRITICAL
SF-36 emotional state at 6 months (follow-up 6 months; control group=5.1; measured with: SF-36 (range 0-100; better indicated by higher values)												

1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	10	-	MD 0.4 higher (0.77 lower to 1.57 higher)	VERY LOW	CRITICAL
SF-36 mental health at 6 months (follow-up 6 months; control group=24.5; measured with: SF-36 (0-100); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	10	-	MD 0.6 lower (3.28 lower to 2.08 higher)	VERY LOW	CRITICAL
ALSFRS at 6 months (follow-up 6 months; control group=28.1; measured with: ALSFRS (range 0-40); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 5.7 higher (1.29 to 10.11 higher)	LOW	IMPORTANT
FSS (follow-up 6 months; control group=42.9; measured with: FSS (range 0-63); better indicated by lower values)												
1	Randomised trials	Very serious[4]	No serious inconsistency	No serious indirectness	Very serious[2]	None	22	8	-	MD 0.2 lower (11.38 lower to 10.98 higher)	VERY LOW	IMPORTANT
Maximum voluntary isometric contraction - Maximum voluntary isometric contraction-upper extremity (follow-up mean 6 months; measured with: MVIC megascore (lower better)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 0.1 higher (3.78 lower to 3.98 higher)	LOW	IMPORTANT
Maximum voluntary isometric contraction - Maximum voluntary isometric contraction-lower extremity (lower better)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	10	-	MD 6.2 higher (0.21 lower to 12.61 higher)	LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 34: Clinical evidence profile: Range of motion versus usual care

Quality assessment							Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ROM exercise	Usual care	Relative (95% CI)	Absolute		
SF-36 at 3 months (follow-up 3 months; control group=80; measured with: SF-36 (range 0-100); better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	10	8	-	MD 2.7 higher (3.1 lower to 8.5 higher)	VERY LOW	CRITICAL
MRC at 3 months (muscle strength) (follow-up 3 months; control group=87.3; measured with: MRC (0-160); better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	8	-	MD 10.9 lower (23.56 lower to 1.76 higher)	VERY LOW	CRITICAL
Ashworth scale at 3 months (follow-up 3 months; control group=0.75; measured with: Ashworth (range 0-4); better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	8	-	MD 0.55 lower (0.96 to 0.14 lower)	VERY LOW	CRITICAL
ALSFRS at 3 months (follow-up 3 months; control group=22; measured with: ALSFRS (range 0-40); better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	8	-	MD 6.7 higher (0.38 to 13.02 higher)	VERY LOW	IMPORTANT
FSS at 3 months (follow-up 3 months; control group=44.5; measured with: FSS (range 0-63); better indicated by lower values)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[2]	None	10	8	-	MD 12.1 lower (23.32 to 0.88 lower)	VERY LOW	IMPORTANT
Pain (VAS) (follow-up 3 months; control group=2.21; measured with: VAS (range 0-10); better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	very serious[2]	None	10	8	-	MD 1.12 lower (4.66 lower to 2.42 higher)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs*

Table 35: Clinical evidence profile: Transcranial magnetic stimulation versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TMS	Placebo	Relative (95% CI)	Absolute		
MRC (follow-up 12 months; control group=2.5; measured with: MRC (range 0-160); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	5	-	MD 0.6 lower (1.59 lower to 0.39 higher)	VERY LOW	CRITICAL
ALSFRS-R (follow-up 12 months; control group=21.2; measured with: ALSFRS-R (range 0-40); better indicated by higher values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	7	5	-	MD 1.9 higher (5.13 lower to 8.93 higher)	VERY LOW	IMPORTANT

[1] *Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias*
[2] *Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs*

I.5 Saliva management

Table 36: Clinical evidence profile: Botulinum toxin versus placebo in patients with MND

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MND botulinum toxin	Placebo	Relative (95% CI)	Absolute		
Health related quality of life (SEIQOL-DW; 0-100) (follow-up 2 weeks; measured with: SEIQOL-DW; range of scores: 0-100; better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	11	9	-	MD 6 higher (16.35 lower to 28.35 higher)	VERY LOW	CRITICAL

Caregiver assessment of severity of sialorrhoea (0-100) (follow-up mean 2 weeks; range of scores: 0-100; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11	9	-	MD 18 lower (42.23 lower to 6.23 higher)	VERY LOW	CRITICAL
Caregiver assessment of saliva thickness (0-100) (follow-up 2 weeks; range of scores: 0-100)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	11	9	-	MD 2 higher (19.07 lower to 23.07 higher)	VERY LOW	CRITICAL
Patient assessment of severity of sialorrhoea (follow-up 2 weeks; range of scores: 0-100; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	11	9	-	MD 26 lower (44.01 to 7.99 lower)	VERY LOW	CRITICAL
Patient assessment of saliva thickness (0-100) (follow-up 2 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	11	9	-	MD 11 higher (4.59 lower to 26.59 higher)	LOW	CRITICAL
Function (Ashworth scale 0-48) (follow-up 2 weeks; measured with: Ashworth (ALSFRS-R); range of scores: 0-48; better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11	9	-	MD 0.9 lower (9.29 lower to 7.49 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Botulinum Toxin versus placebo in patients in indirect populations

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Botulinum toxin injections**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Change in impact of drooling on daily activities (follow-up 4 weeks; range of scores: 10-40; better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	12	15	-	MD 5.3 lower (8.18 to 2.42 lower)	LOW	CRITICAL

Patient reported sialorrhoea severity (follow-up 1 months; better indicated by lower values)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	42	42	-	SMD 1.39 lower (1.87 to 0.90 lower)	MODERATE	CRITICAL
Patient reported change in sialorrhoea severity (follow-up 4 weeks; measured with: Drooling Frequency and Severity Scale (DFSS); range of scores: 2-9; better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	12	15	-	MD 0.92 lower (2.03 lower to 0.19 higher)	VERY LOW	CRITICAL
Change in drooling score (carer reported severity and frequency of saliva problem; 2-9)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Not estimated[6]	None	11	13	-	Median change in drooling score in the intervention group was -2 Median change in drooling score in the control group was 0	LOW	CRITICAL
Frequency and severity of drooling (follow-up 2-weeks; assessor unclear; range of scores: 1-9; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	6	7	-	MD 0.96 lower (1.82 to 0.10 lower)	VERY LOW	CRITICAL
Patient satisfaction (follow-up 1 months)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	32/34 (94.1%)	35.1%	RR 2.6 (1.65 to 4.09)	562 more per 1000 (from 228 more to 1000 more)	MODERATE	CRITICAL
Dysphagia (range of scores: 0-4; better indicated by lower values)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[2]	No serious imprecision	None	39	36	-	MD 0.15 lower (0.7 lower to 0.39 higher)	MODERATE	CRITICAL
Dysphagia (follow-up mean 1 months)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	0/7 (0%)	0%	See comment	-	VERY LOW	CRITICAL

Aspiration pneumonia (follow-up 20 weeks)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	0/12 (0%)	0%	See comment[f]	-	LOW	CRITICAL
Adverse effects resulting in patients discontinuing medication (follow-up 20 weeks)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	0/12 (0%)	6.7%	Peto OR 0.17 (0 to 8.54)	67 fewer per 1000 (from 244 fewer to 110 more)[4]	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment as the evidence included an indirect population
3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Calculated as analysis used Peto Odds Ratio
5 Could not be calculated as zero events in both arms
6 Could not be estimated as only median values reported

Table 38: Botulinum Toxin versus no treatment in patients in indirect populations

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Botulinum toxin**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Carer reported severity and frequency of sialorrhoea (follow-up 4 weeks; range of scores: 2-9; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	7	7	-	MD 5.2 lower (6.03 to 4.37 lower)	VERY LOW	CRITICAL
Muscle weakness (follow-up 4 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	0/7 (0%)	0%	See comment[3]	-	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment as the evidence included an indirect population
3 Could not be calculated as zero events in both arms

Table 39: Glycopyrrolate versus placebo in patients in indirect populations

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycopyrrolate	Placebo	Relative (95% CI)	Absolute		
Carer reported severity of sialorrhoea (follow-up 4 days - 8 weeks; range of scores: 1-9; better indicated by lower values)												
3	Randomised trials	No serious risk of bias	Serious[2]	Serious[3]	No serious imprecision	None	69	67	-	MD 2.28 lower (4.45 to 0.11 lower)[5]	LOW	CRITICAL
Carer satisfaction with medication (follow-up 8 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Very serious[3]	Serious[4]	None	19/19 (100%)	55.6%	RR 1.76 (1.17 to 2.66)	423 more per 1000 (from 95 more to 923 more)	VERY LOW	CRITICAL
Change in motor symptoms (follow-up 4-7 days)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Serious[3]	Very serious[4]	None	3/23 (13%)	17.4%	RR 0.75 (0.19 to 2.98)	43 fewer per 1000 (from 141 fewer to 345 more)	VERY LOW	IMPORTANT
Adverse effects resulting in patient discontinuing treatment (follow-up 8 weeks)												
2	Randomised trials	Very serious[1]	Very serious[2]	Very serious[3]	Serious[4]	None	8/56 (14.3%)	4.4%	RR 3.41 (0.75 to 15.56)	106 more per 1000 (from 11 fewer to 641 more)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment because the point estimates varied widely across studies
3 Downgraded by 2 increments if the evidence included an indirect population, and downgraded by 2 increments if the majority of the evidence was a very indirect population
4 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
5 Analysis conducted using random effects

Table 40: Benztropine versus placebo in patients in indirect populations

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benztropine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Drooling severity (follow-up 1-2 weeks; measured with: Teacher drooling scale; better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	No serious imprecision	None	20	20	-	MD 1.15 lower (1.68 to 0.62 lower)	VERY LOW	CRITICAL
Adverse effects resulting in patients discontinuing medication (follow-up <2 weeks)												
1	Randomised trials	Very serious[1]	No serious inconsistency	Serious[2]	Serious[3]	None	3/27 (11.1%)	0%	OR 7.99 (0.8 to 80.28)	111 more per 1000 (from 21 fewer to 243 more)[4]	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment as the evidence included an indirect population
3Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
4 Absolute effect calculated as data analysed using Peto OR

I.6 Nutrition

Table 41: Clinical evidence profile: high fat content versus high carbohydrate content

Quality assessment							**Number of patients**		**Effect**		**Quality**	**Importance**
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High fat content versus high carbohydrate content**	**Control**	**Relative (95% CI)**	**Absolute**		
Weight gain (better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8	8	-	MD 0.24 higher (0.08 to 0.4 higher)	VERY LOW	CRITICAL
Change in BMI (better indicated by lower values)												

1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	MD 0.42 higher (0.62 lower to 1.46 higher)	VERY LOW	CRITICAL
Diarrhoea												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	1/8 (12.5%)	0%	Peto OR 7.39 (0.15 to 372.38)	-	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 42: Clinical evidence profile: milk whey protein supplement versus maltodextrin (control group)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Milk whey protein supplementation versus maltodextrin**	**Control**	**Relative (95% CI)**	**Absolute**		
Change in weight (better indicated by higher values) at 4 months												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	Not pooled	VERY LOW	CRITICAL
Change in BMI (better indicated by higher values) at 4 months												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	Not pooled	VERY LOW	CRITICAL
TSF (mm) (better indicated by lower values) at 4 months												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	Not pooled	VERY LOW	CRITICAL
MAMC (cm) (better indicated by lower values) at 4 months												

1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	Not pooled	VERY LOW	CRITICAL
Change in ALSFRS-R (better indicated by lower values) at 4 months												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	8	8	-	Not pooled	VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Could not calculate imprecision as results given as medians

I.7 Cough effectiveness

Table 43: MI-E versus exsufflation

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E**	**Exsufflation**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 14.05 lower (45.6 lower to 17.51 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 44: MI-E versus insufflation

Quality assessment							Number of patients		Effect		Quality	Importance
Number of	**Design**	**Risk of**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**MI-E**	**Insufflation**	**Relative (95%**	**Absolute**		

studies		bias				considerations			CI)			
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 30.81 higher (0.57 to 61.04 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 45: MI-E versus manual

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E**	**Manual**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 17.46 higher (12.37 lower to 47.3 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 46: MI-E versus unassisted

Quality assessment	Number of patients	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MI-E	Unassisted	Relative (95% CI)	Absolute		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 40.28 higher (10.55 to 70.01 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 47: Exsufflation versus insufflation

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exsufflation	Insufflation	Relative (95% CI)	Absolute		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 44.19 higher (12.67 to 75.72 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 48: Exsufflation versus manual

Quality assessment							Number of patients		Effect		Quality	Importance
Number of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Exsufflation	Manual	Relative (95%	Absolute		

studies		bias				considerations			CI)			
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 31.18 higher (0.01 to 62.36 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 49: Exsufflation versus unassisted

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Exsufflation**	**Unassisted**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 53.69 higher (22.65 to 84.72 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 50: Insufflation versus manual

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Insufflation**	**Manual**	**Relative (95% CI)**	**Absolute**		

PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 12.7 lower (42.17 lower to 16.76 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 51: Insufflation versus unassisted

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Insufflation**	**Unassisted**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	47	-	MD 9.6 higher (19.67 lower to 38.86 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 52: Manual versus unassisted

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Manual**	**Unassisted**	**Relative (95% CI)**	**Absolute**		

PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	47	52	-	MD 22.06 higher (6.01 lower to 50.13 higher)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 53: MI-E versus BiPAP

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E**	**BiPAP**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 488 (243-605) and in BiPAP was 212 (99-595)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 8 (6-8) and in BiPAP 7 (6-8)	VERY LOW	IMPORTANT
Patient reported outcomes – comfort (better indicated by higher values)												

1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 7 (3-8) and in BiPAP was 8 (7-8)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 54: MI-E versus IPAP

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E**	**IPAP**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in Mi-E was 488 (243-605) and in IPAP was 233 (100-389)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 8 (6-8) and in IPAP was 6 (5-7)	VERY LOW	IMPORTANT

Patient reported outcomes – comfort (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in Mi-E was 7 (3-8) and in IPAP was 6 (5-7)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 55: MI-E versus LVR

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E**	**LVR**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 488 (243-605) and in LVR was 284 (146-353)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 8 (6-8) and in LVR was 7 (5-8)	VERY LOW	IMPORTANT

Patient reported outcomes – comfort (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in MI-E was 7 (3-8) and in LVR was 6 (5-8)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 56: BiPAP versus IPAP

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BIPAP**	**IPAP**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by lower values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 212 (99-595) and in IPAP was 233 (100-389)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 7 (6-8) and in IPAP was 6 (5-7)	VERY LOW	IMPORTANT

Patient reported outcomes – comfort (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 8 (7-8) and in IPAP was 6 (5-7)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 57: BIPAP versus LVR

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BIPAP**	**LVR**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 212 (99-595) and in LVR 284 (146-353)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 7 (6-8) and the median in LVR 7 (5-8)	VERY LOW	IMPORTANT

Patient reported outcomes – comfort (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in BiPAP was 8 (7-8) and in LVR 6 (5-8)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 58: IPAP versus LVR

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IPAP**	**LVR**	**Relative (95% CI)**	**Absolute**		
PCF (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in IPAP was 233 (100-389) and in LVR was 284 (146-353)	VERY LOW	IMPORTANT
Patient reported outcomes – efficacy (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in IPAP was 6 (5-7) and in LVR was 7 (5-8)	VERY LOW	IMPORTANT

Patient reported outcomes – comfort (better indicated by higher values)												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	16	16	-	Median in IPAP was 6 (5-7) and in LVR 6 (5-8)	VERY LOW	IMPORTANT

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 59: MI-E versus breath-stacking

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MI-E versus breath-stacking technique**	**Control**	**Relative (95% CI)**	**Absolute**		
Survival												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.94 (0.87 to 4.33)	Median survival in MI-E was 266 days and in breath-stacking 535 days	⊕OOO VERY LOW	CRITICAL
Chest infection - number of patients with at least one chest infection												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	-	-	OR 0.78 (0.16 to 3.8)	See comment[5]	⊕OOO VERY LOW	IMPORTANT
Chest infection - total number of chest infections												

1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	very serious[2]	none	-	-	1.06 (0.31 to 3.62)	See comment[5]	⊕OOO VERY LOW	IMPORTANT
Hospitalisation - number of patients with any hospitalisation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	OR 0.87 (0.16 to 4.73)	See comment[5]	⊕OOO VERY LOW	IMPORTANT
Hospitalisation - total number of hospitalisations												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	RR 1.45 (0.3 to 7.01)	See comment[5]	⊕OOO VERY LOW	IMPORTANT
PCF												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	-	-	PCF increased by 0.9 l/min/month in the MI-E group and declined by 5.77 l/min/month in the breath-stacking group, p=0.43. Baseline values differed significantly (p<0.001): 120 l/min for MI-E and 215 l/min for breath stacking.	-	⊕OOO VERY LOW	IMPORTANT
Quality of life (MCS)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	-	-	MCS maintained above 75% of baseline for a median of 205 days in the MI-E group and 329 days in the breath-stacking group (p=0.41)	-	⊕OOO VERY LOW	CRITICAL
Quality of life (SAQLI sym)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	-	-	SAQLI sym was maintained above 75% of baseline for 205 days in the MI-E group and 280 days in the breath-stacking group (p=0.59)	-	⊕OOO VERY LOW	CRITICAL

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Number of patients with chest infection, not reduction in chest infection.
4 Total number of chest infections, not reduction in chest infections.
5 Adjusted figures reported so absolute number could not be analysed.
6 Imprecision could not be calculated as data could not be analysed, but the confidence interval crossed 1.

Appendix J: Forest plots

J.1 Prognostic factors

ALS functional rating scale/ALS functional rating scale revised

Figure 22: Mortality/mortality or tracheostomy (time to event)

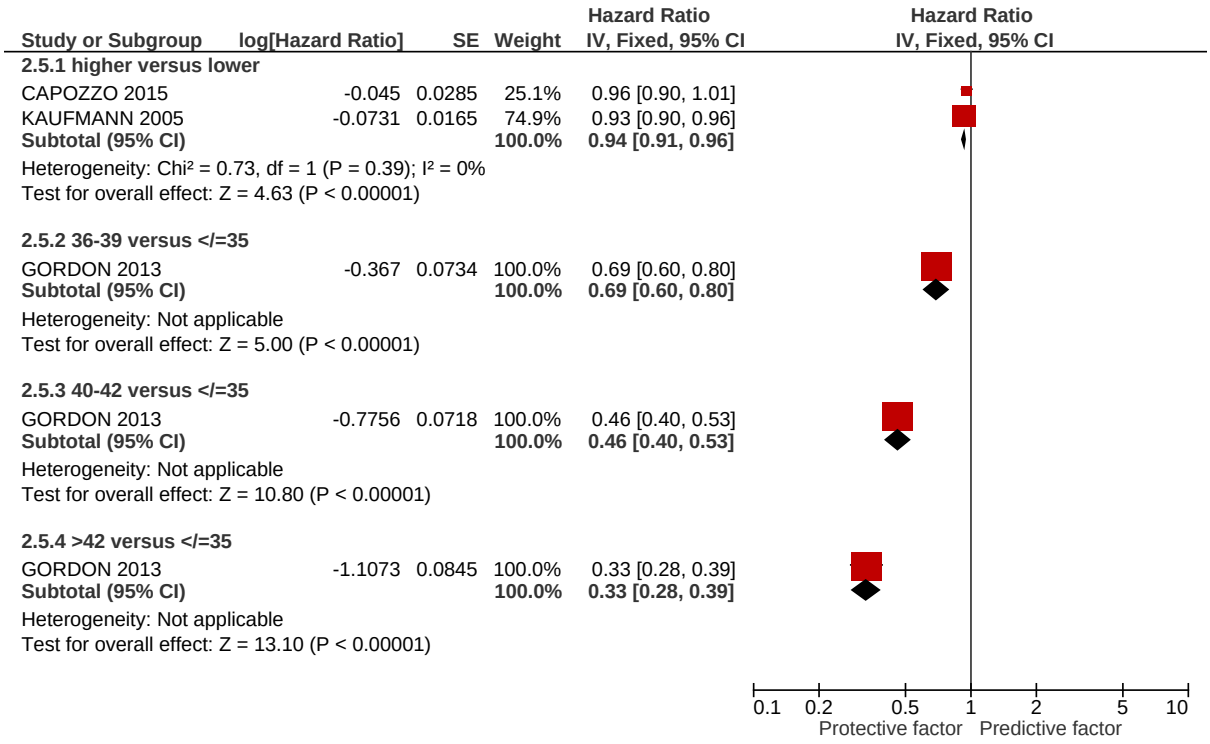
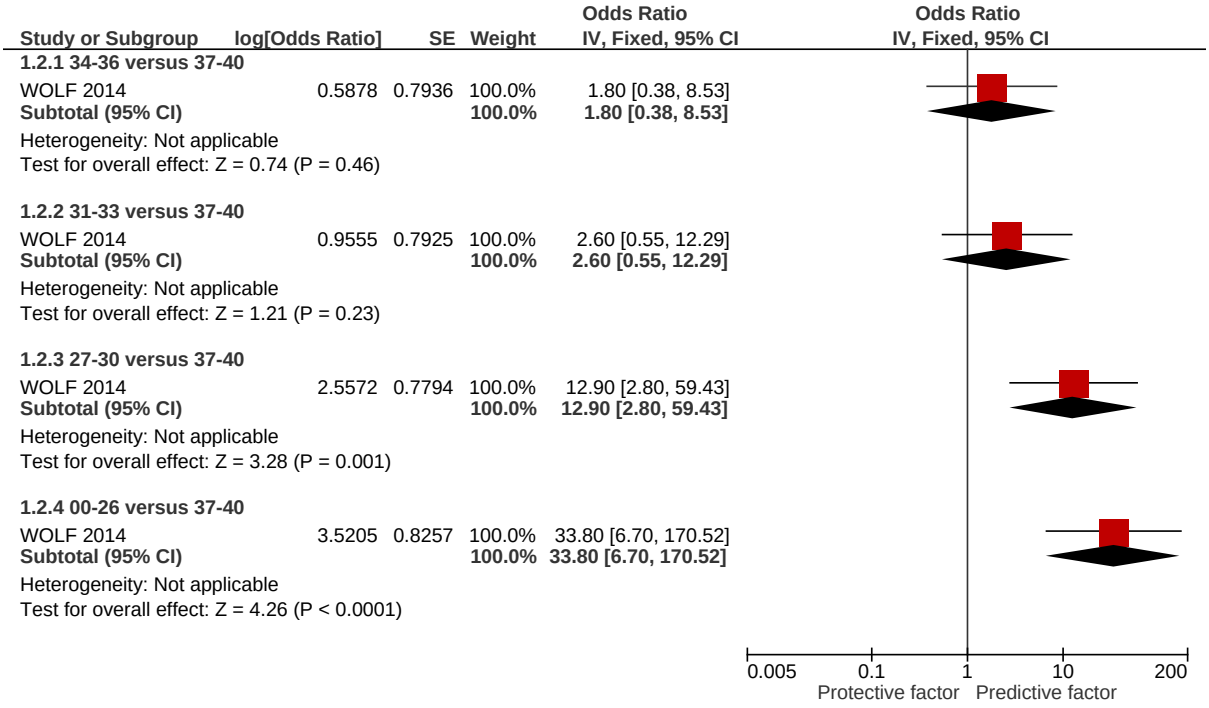


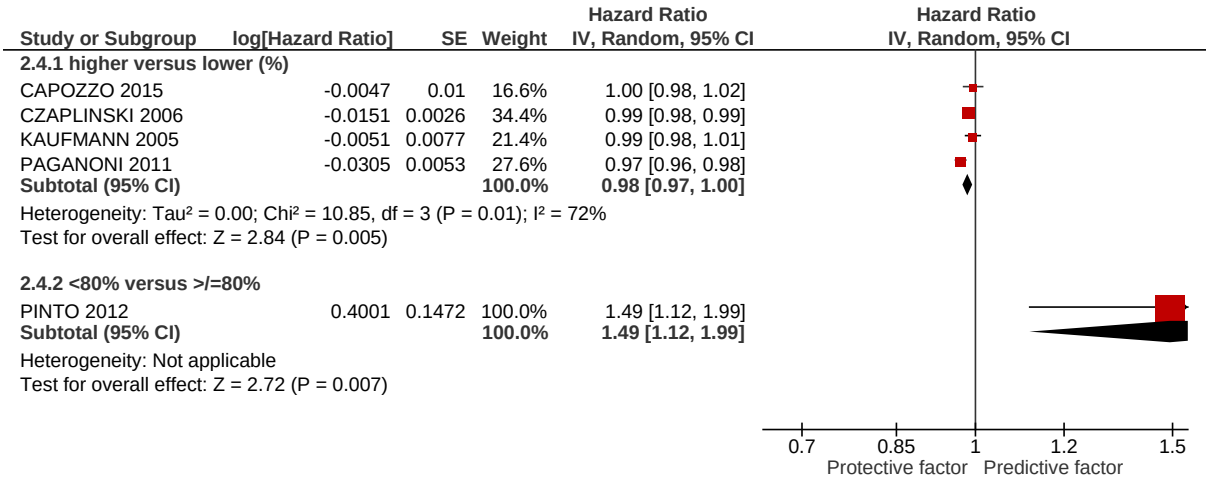
Figure 23: One year mortality



1

2 **Forced vital capacity**

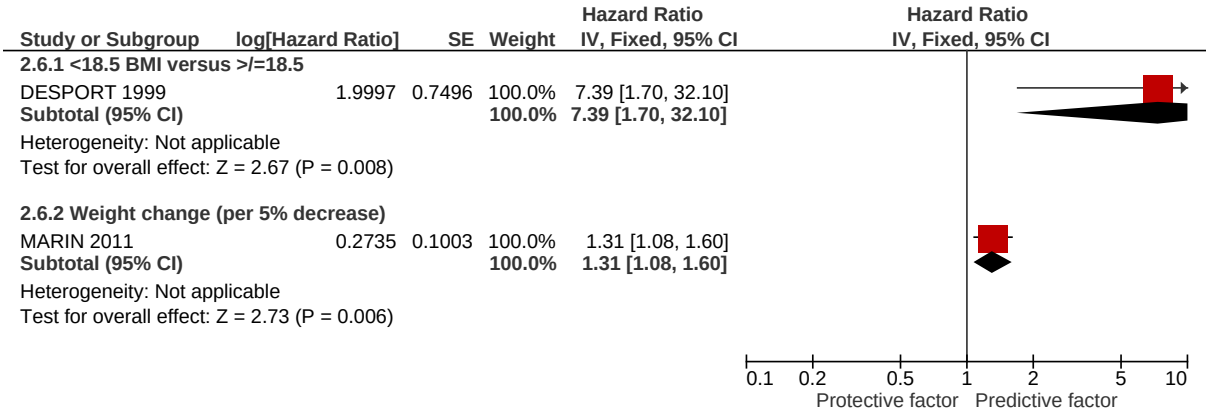
Figure 24: Mortality/mortality or tracheostomy (time to event)



3

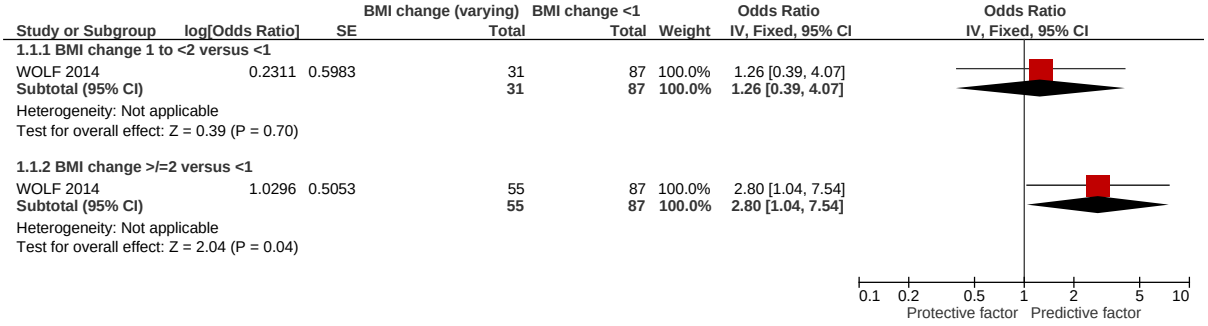
1 **Weight loss**

Figure 25: Mortality/mortality or tracheostomy (time to event)



2

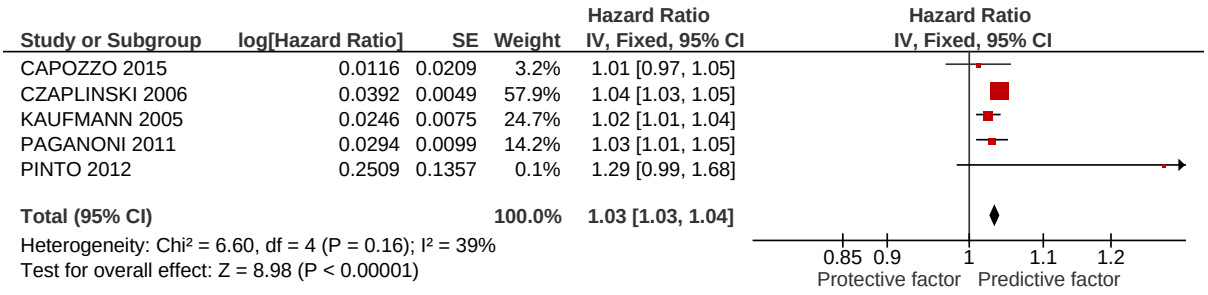
Figure 26: One year mortality



3

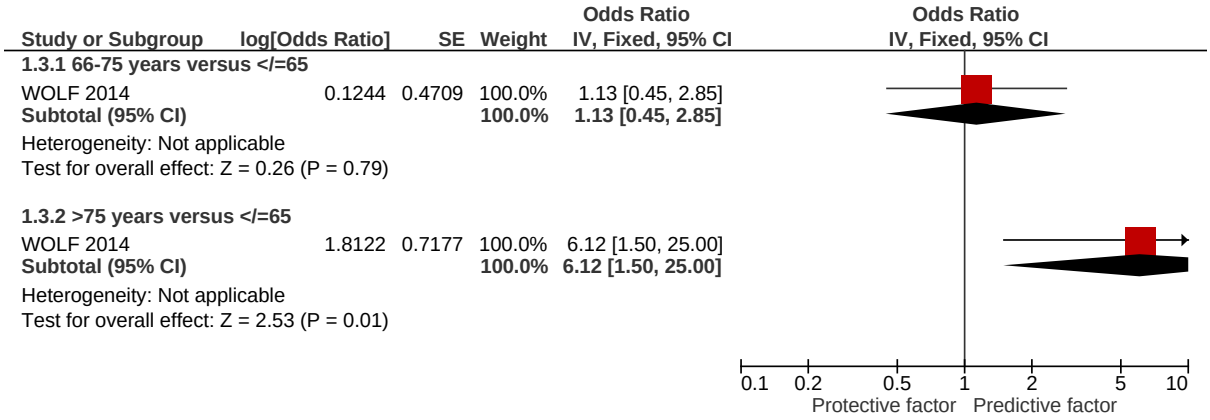
4 **Age**

Figure 27: Mortality/mortality or tracheostomy (time to event)



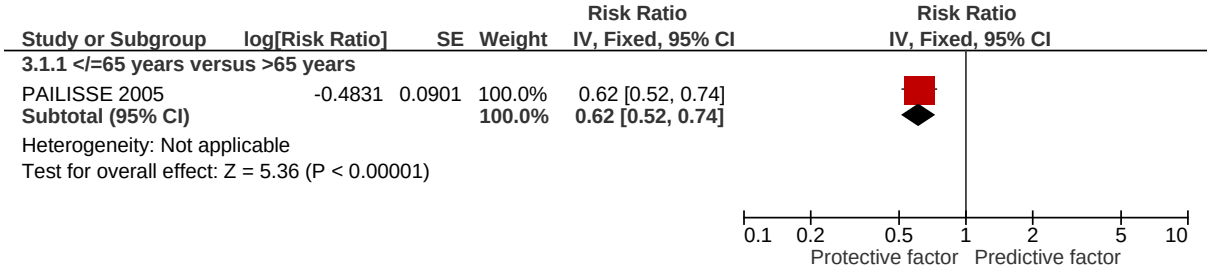
5

Figure 28: One year mortality



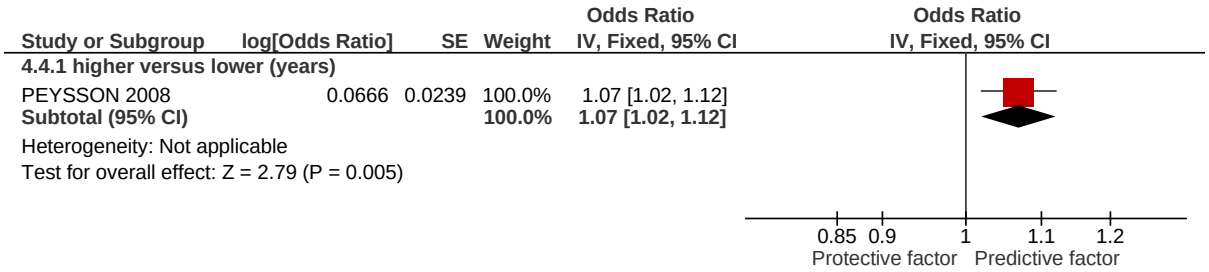
1

Figure 29: Mortality



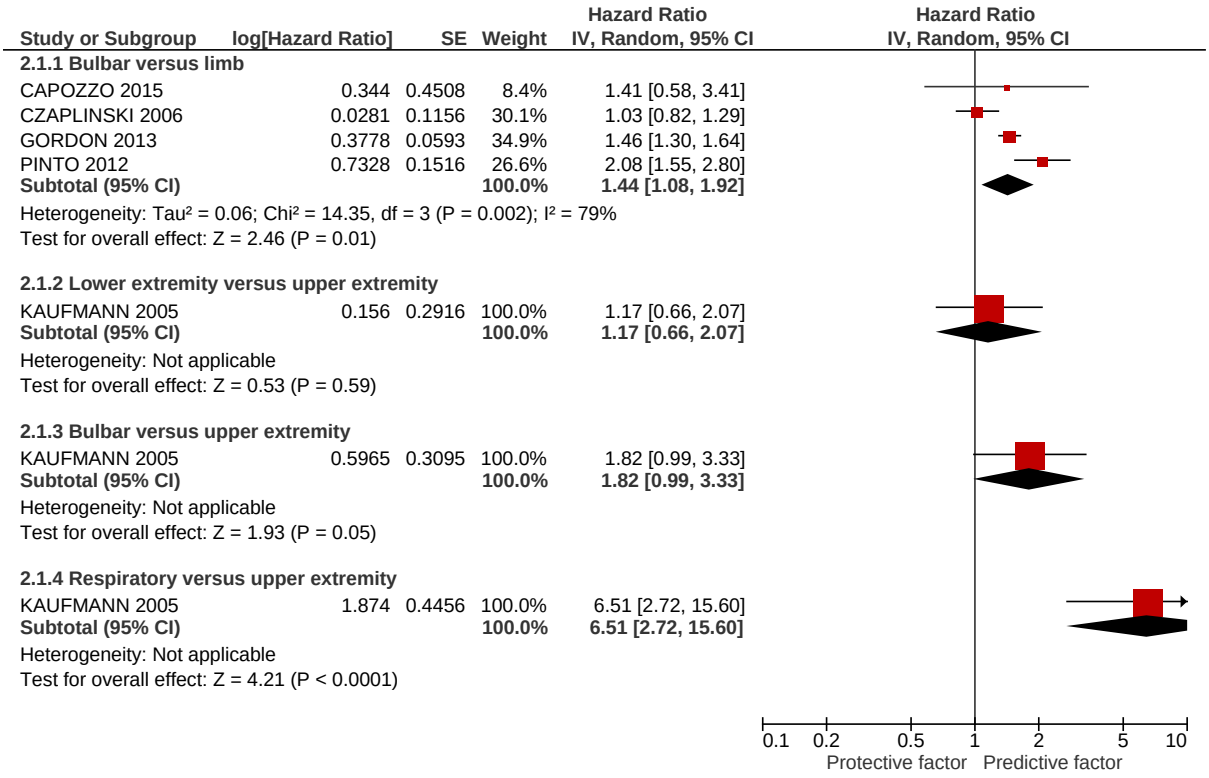
2

Figure 30: Mortality or tracheostomy (all participants had non-invasive ventilation from the beginning of the study)



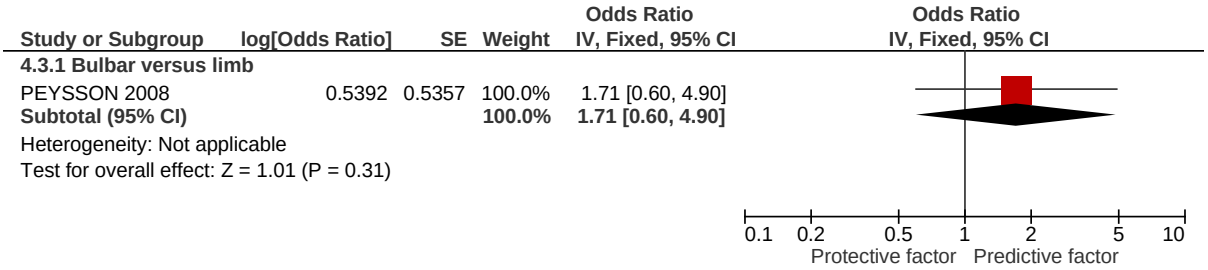
1 **Site of onset**

Figure 31: Mortality/mortality or tracheostomy (time to event)



2

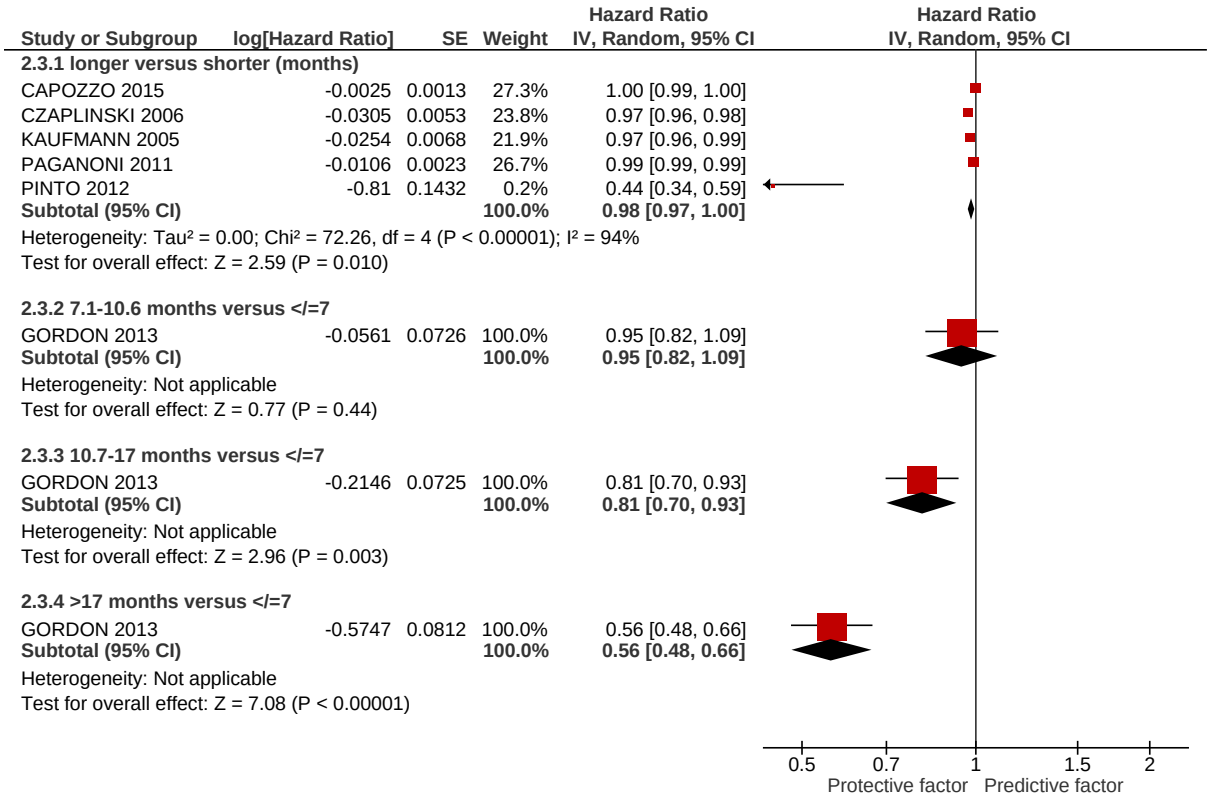
Figure 32: Mortality or tracheostomy (all participants had non-invasive ventilation from the beginning of the study)



3

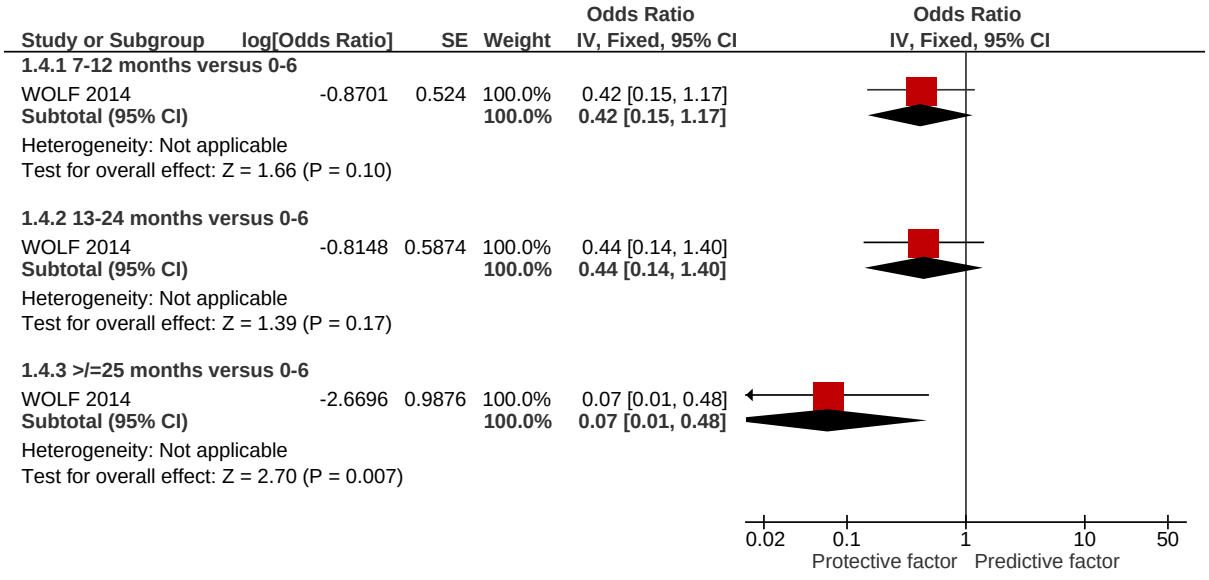
1 **Diagnostic delay**

Figure 33: Mortality/mortality or tracheostomy (time to event)



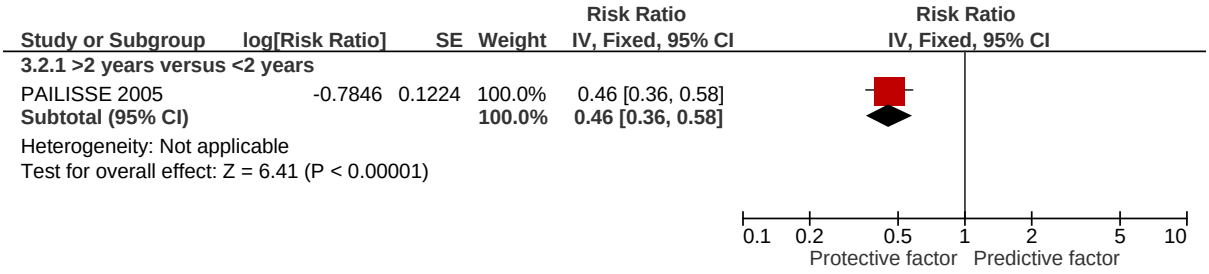
2

Figure 34: One year mortality



3

Figure 35: Mortality



1

2 J.2 Organisation of care

3 MDT plus case management versus MDT alone - RCT

Figure 36: MDT and case management versus MDT alone: ALSAQ-40 Emotional functioning

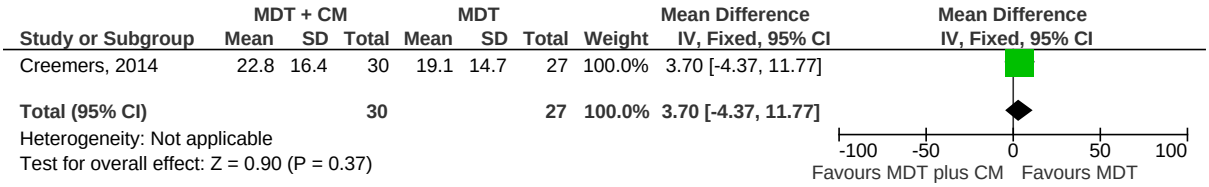
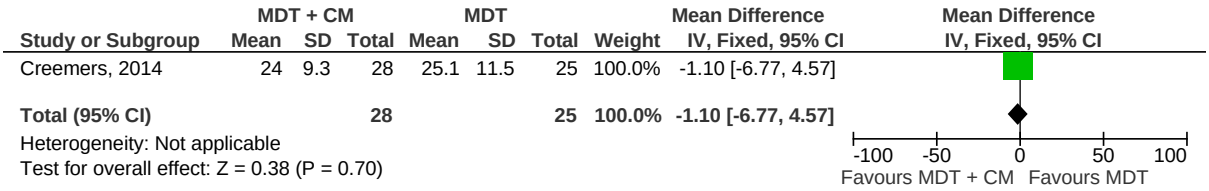
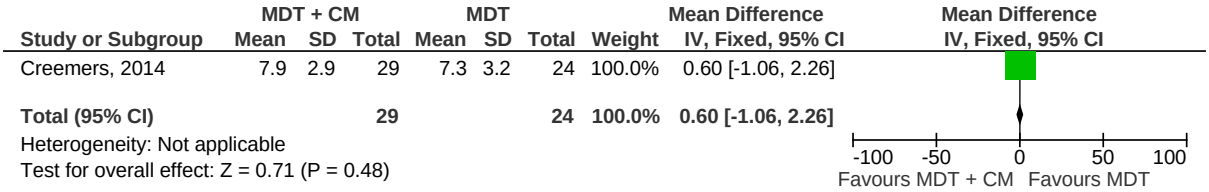


Figure 37: MDT plus case management versus MDT alone: ALSFRS-R



4

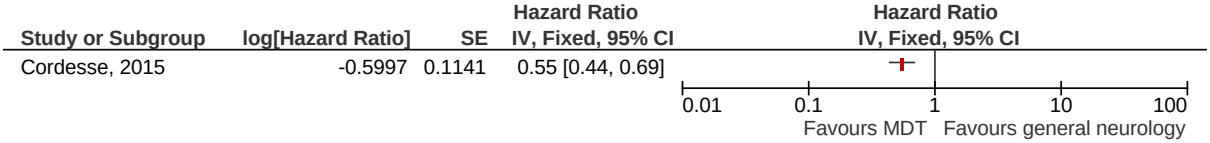
Figure 38: MDT plus case management versus MDT alone: CSI



5

MDT plus co-ordinator versus MDT alone – before and after study

Figure 39: MDT plus co-ordinator versus MDT alone: survival



MDT versus general neurology – cohort studies

Figure 40: Survival time from onset of symptoms

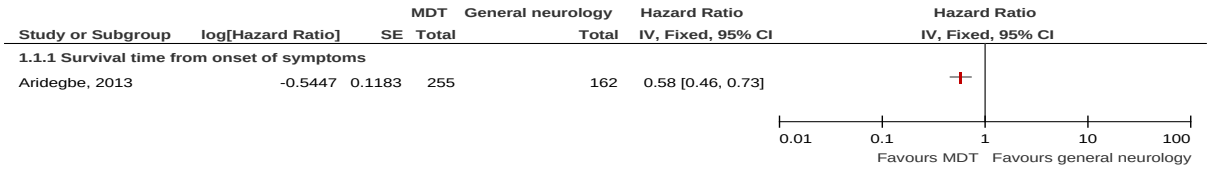


Figure 41: Survival time from diagnosis

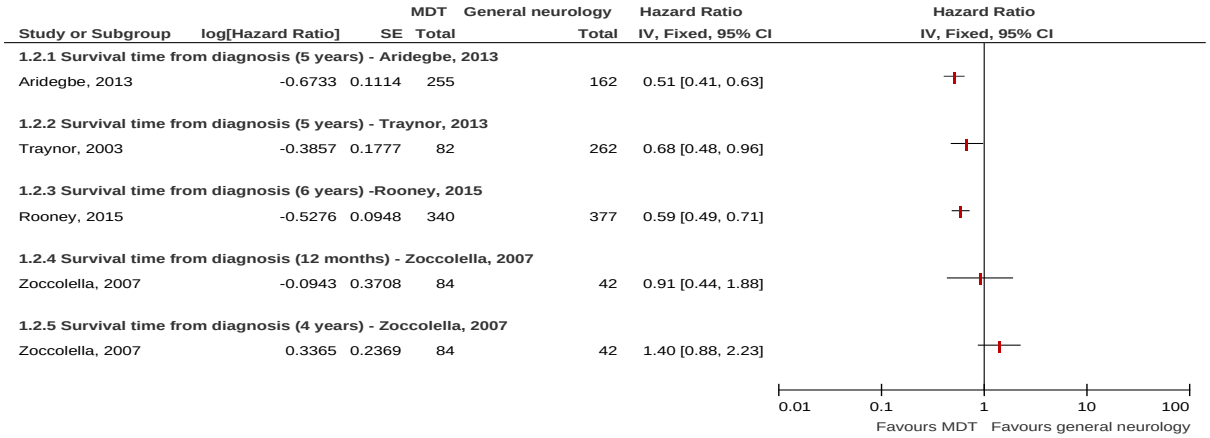
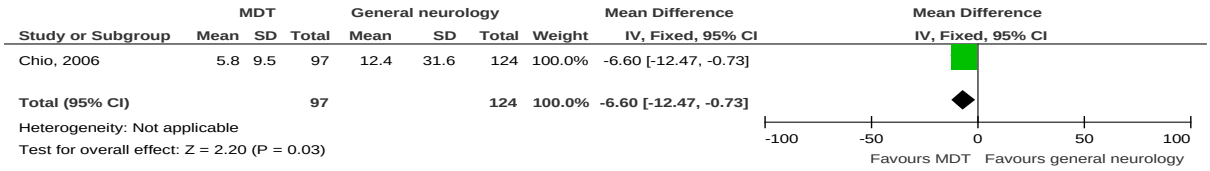


Figure 42: Mean duration of hospital stay



J.3 Pharmacological treatment for muscle problems

Memantine versus placebo

Figure 43: Memantine versus placebo: SF36

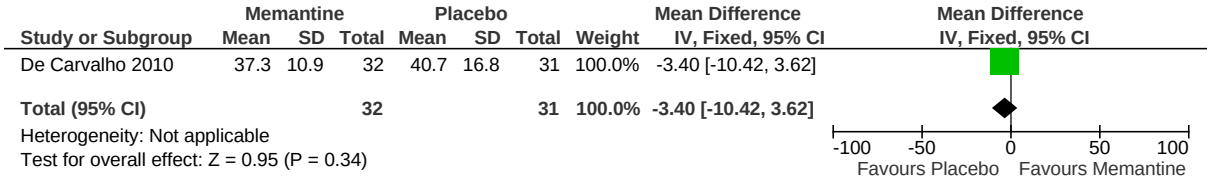


Figure 44: Memantine versus placebo: MRC (muscle strength)

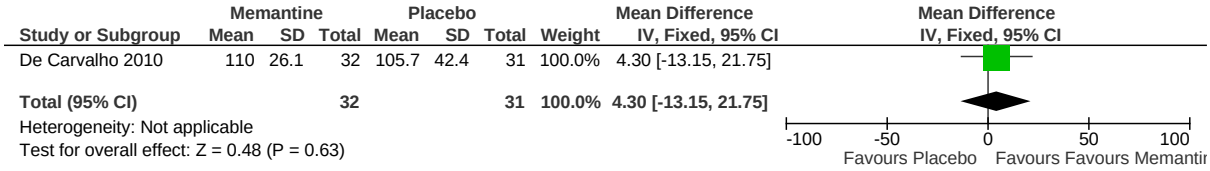
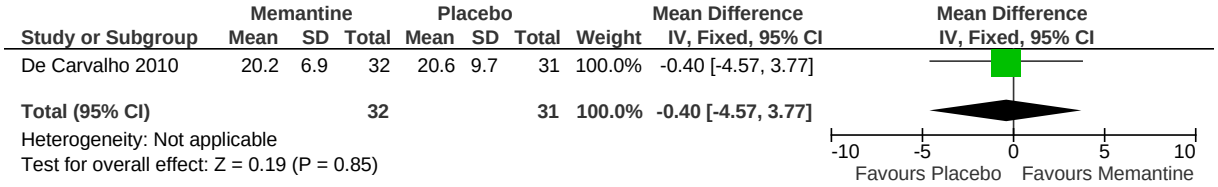


Figure 45: Memantine versus placebo: ALSFRS



Gabapentin versus placebo

Figure 46: Gabapentin versus placebo: drowsiness

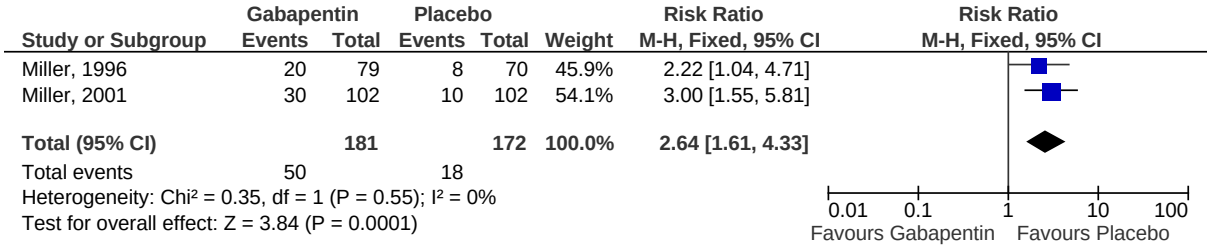
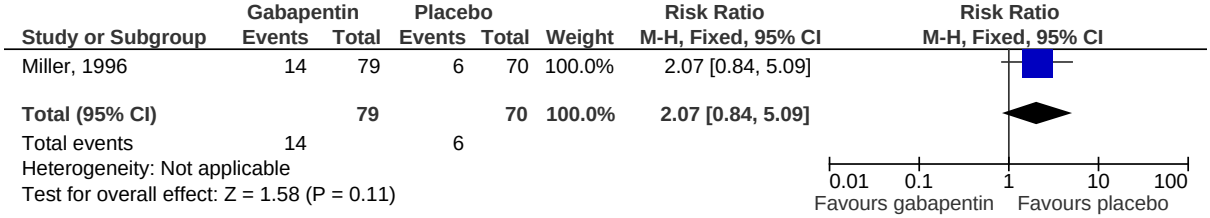
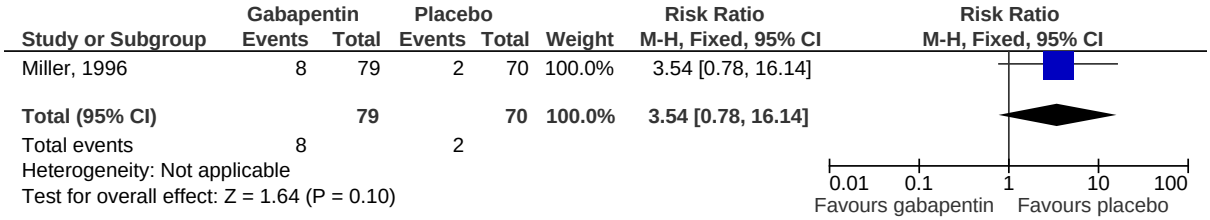


Figure 47: Gabapentin versus placebo: weakness



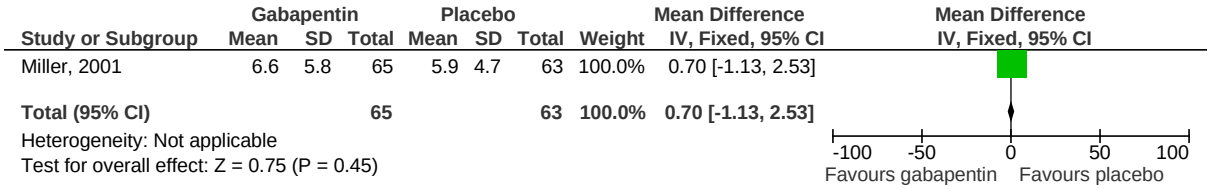
1

Figure 48: Gabapentin versus placebo: cramps



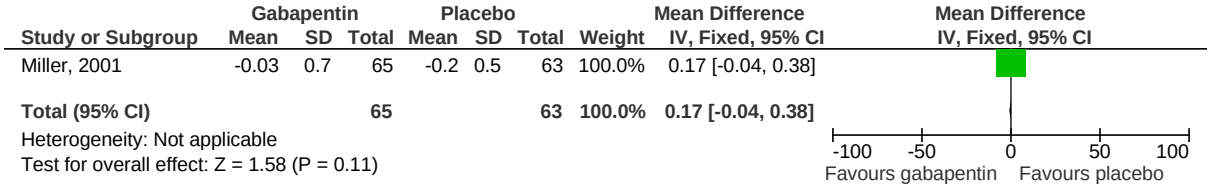
2

Figure 49: Gabapentin versus placebo: ALSFRS



3

Figure 50: Gabapentin versus placebo: SF-12



J.4 Non-pharmacological management of muscle problems

Resistance exercise versus usual care

Figure 51: SF-36 physical function at 6 months

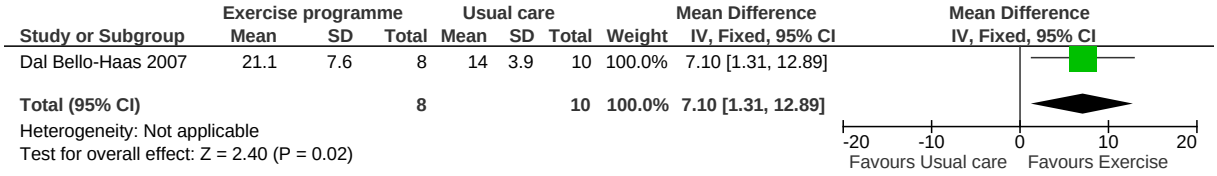


Figure 52: SF-36 physical role at 6 months

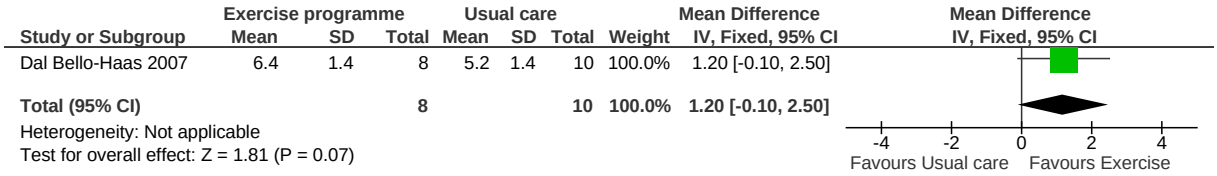


Figure 53: SF-36 pain at 6 months

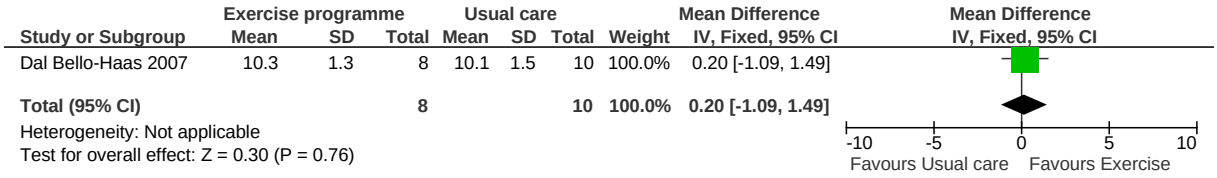


Figure 54: SF-36 general health at 6 months

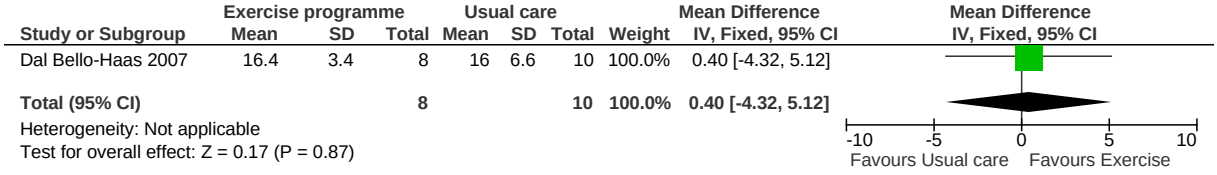


Figure 55: SF-36 vitality at 6 months

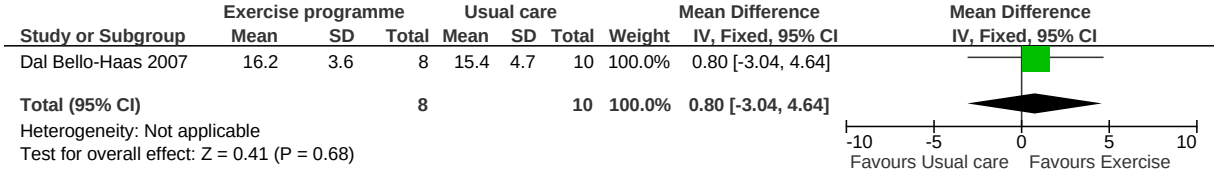


Figure 56: SF-36 social function at 6 months

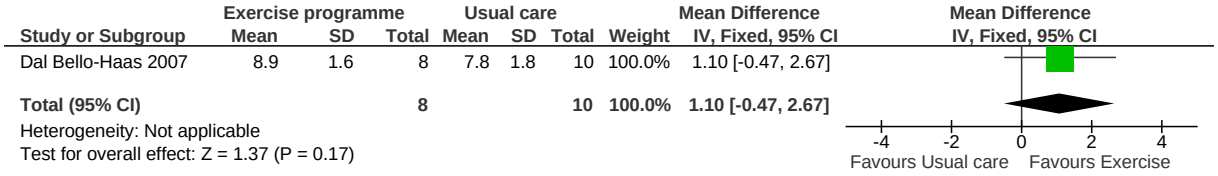


Figure 57: SF-36 emotional state at 6 months

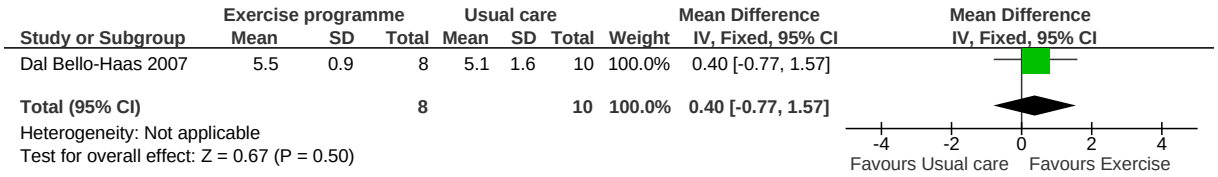


Figure 58: SF-36 mental health at 6 months

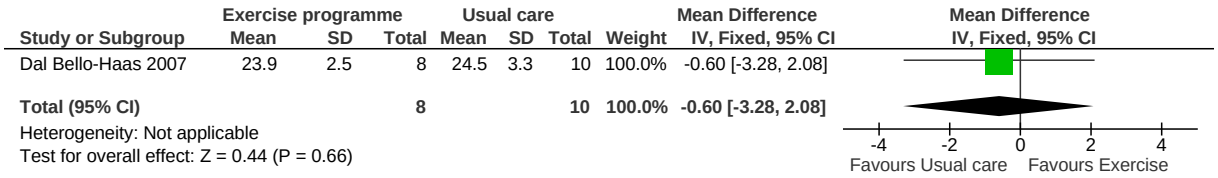


Figure 59: ALSFRS at 6 months

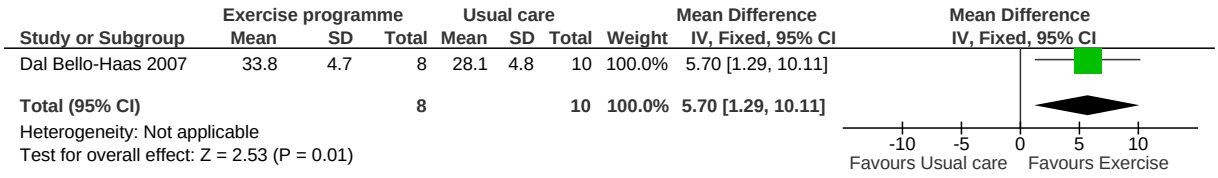


Figure 60: FSS at 6 months

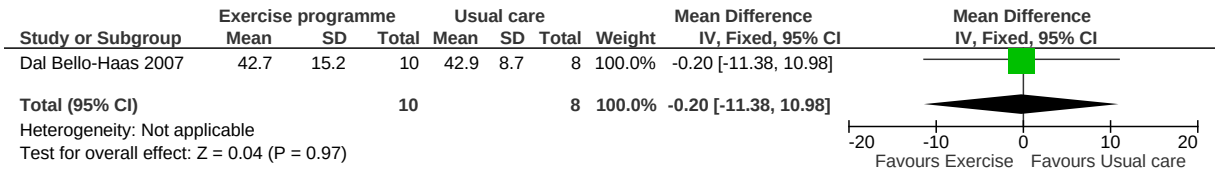
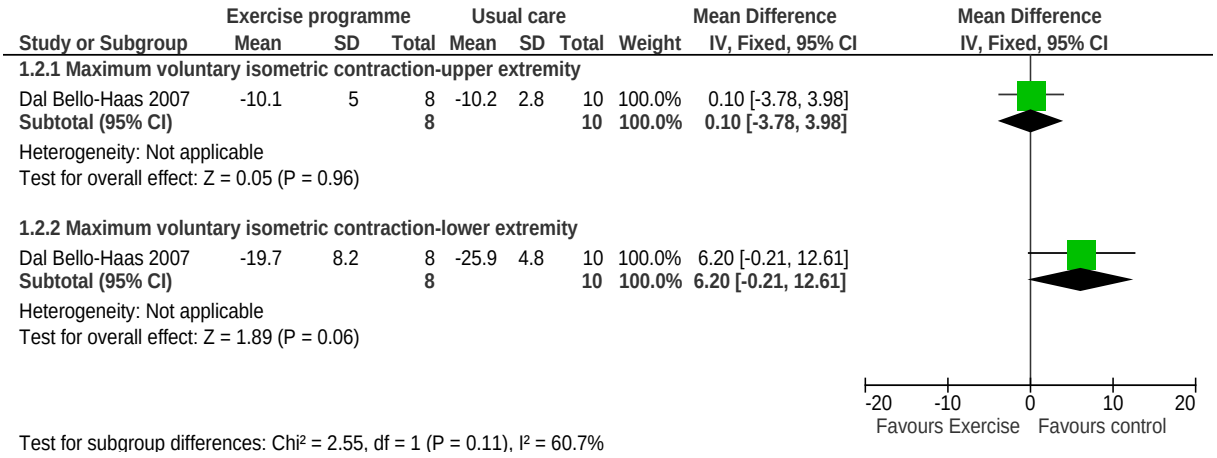


Figure 61: Maximum voluntary isometric contraction-upper extremity and lower extremity



Test for subgroup differences: $Chi^2 = 2.55$, df = 1 (P = 0.11), $I^2 = 60.7\%$

J.4.1.1 Range of motion versus usual care

Figure 62: SF-36 at 3 months

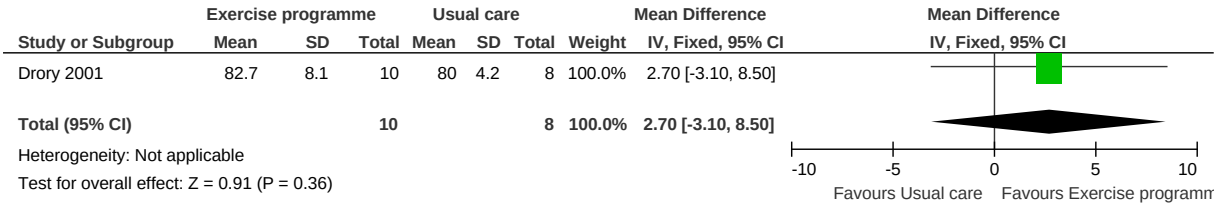


Figure 63: MRC (muscle strength) at 3 months

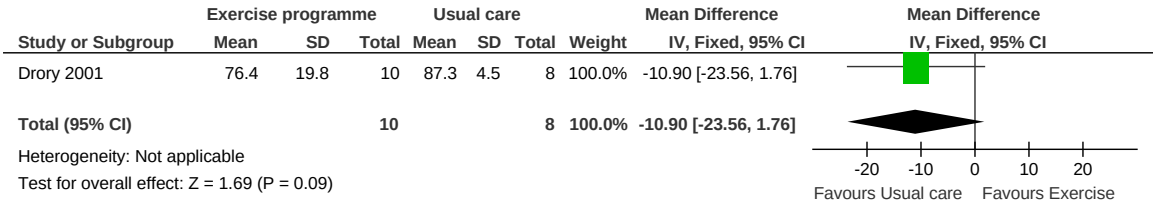


Figure 64: Ashworth scale at 3 months

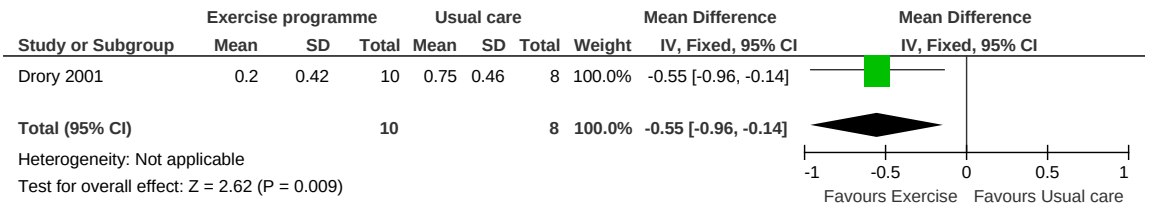


Figure 65: ALSFRS at 3 months

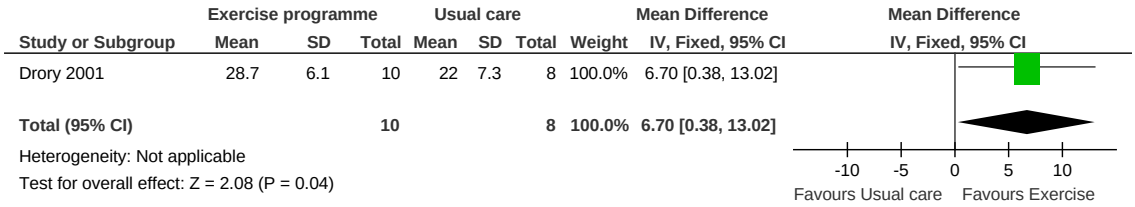


Figure 66: FSS at 3 months

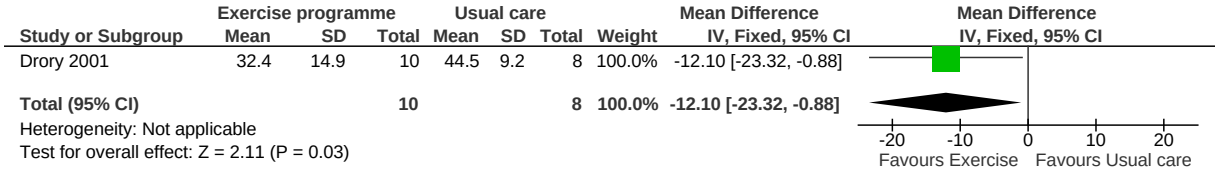
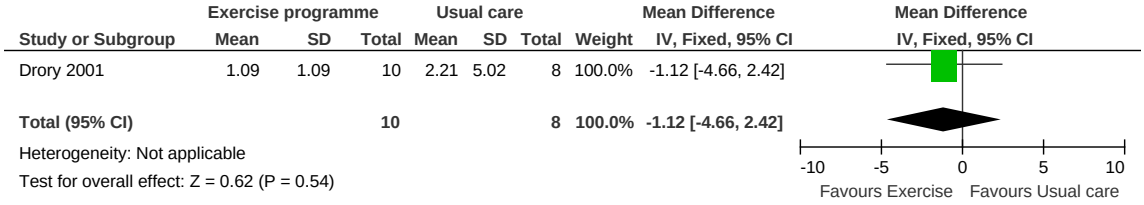


Figure 67: VAS for pain at 3 months



J.4.1.2 TMS versus placebo

Figure 68: MRC (muscle strength) at 12 months

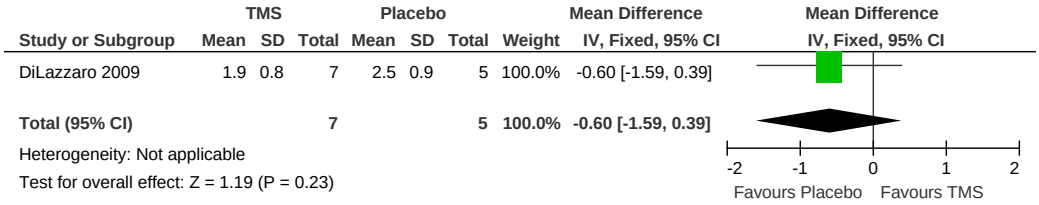
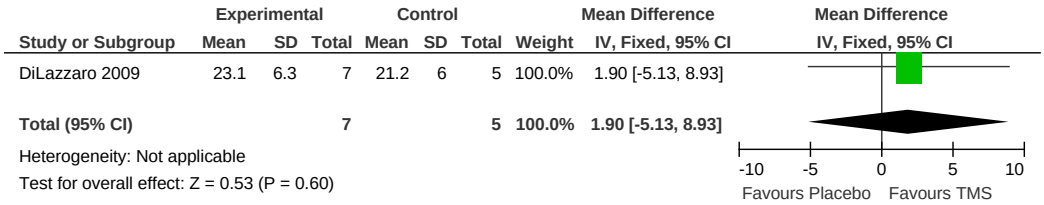


Figure 69: ALSFRS-R at 12 months



J.5 Saliva management

J.5.1.1 Botulinum toxin versus placebo in patients with MND

Figure 70: Health related quality of life SEIQOL-DW (0-100)

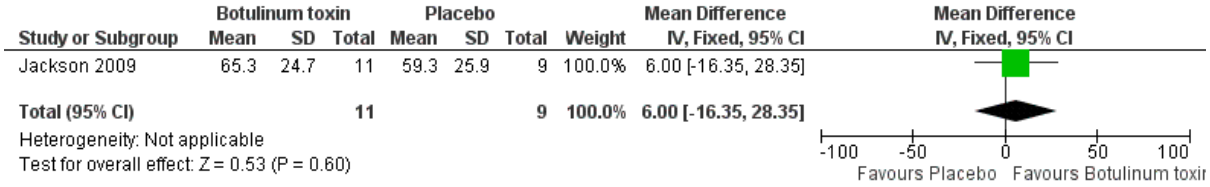


Figure 71: Patient assessment of severity of sialorrhoea

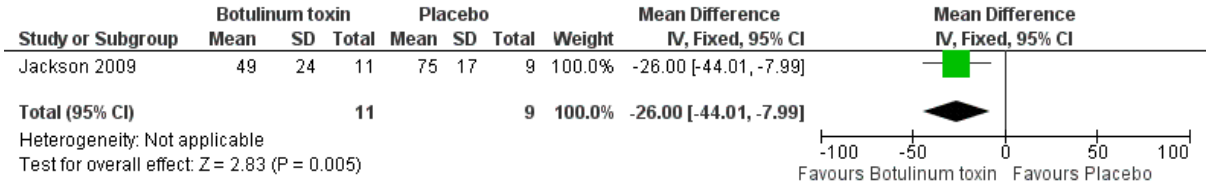


Figure 72: Patient assessment of saliva thickness

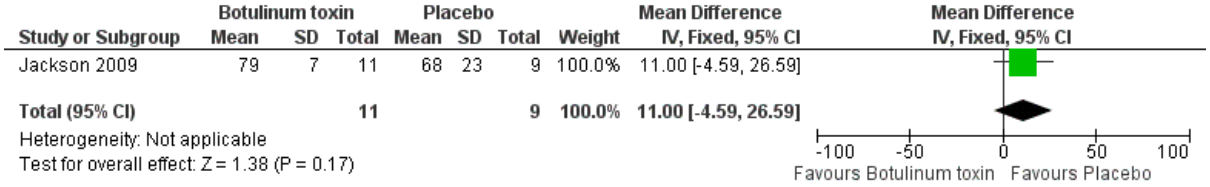


Figure 73: Caregiver assessment of severity of sialorrhoea

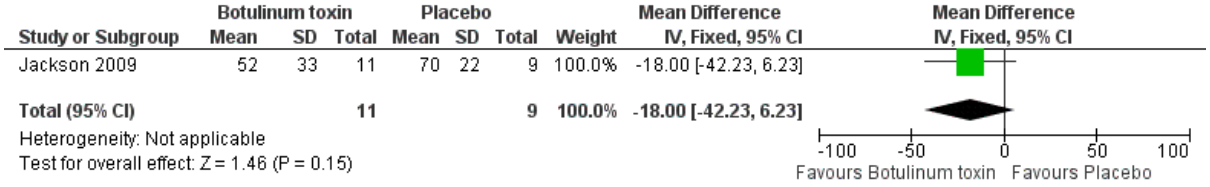


Figure 74: Caregiver assessment of saliva thickness

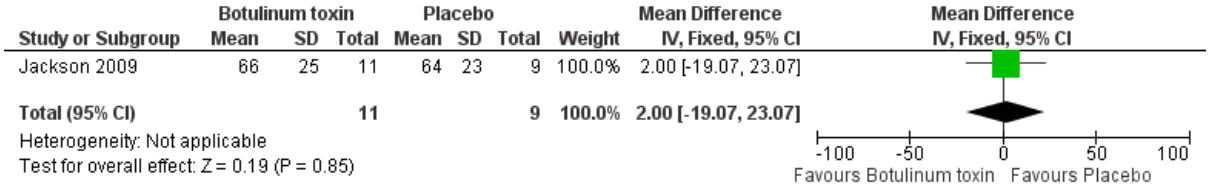
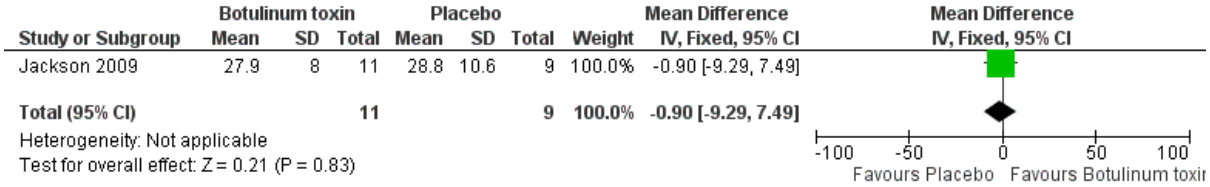
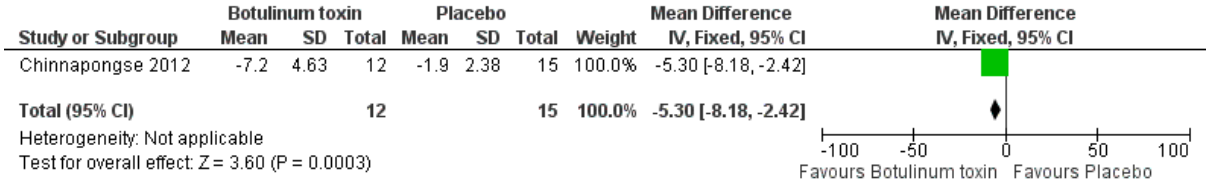


Figure 75: Function (ALSFRS-R; 0-48)



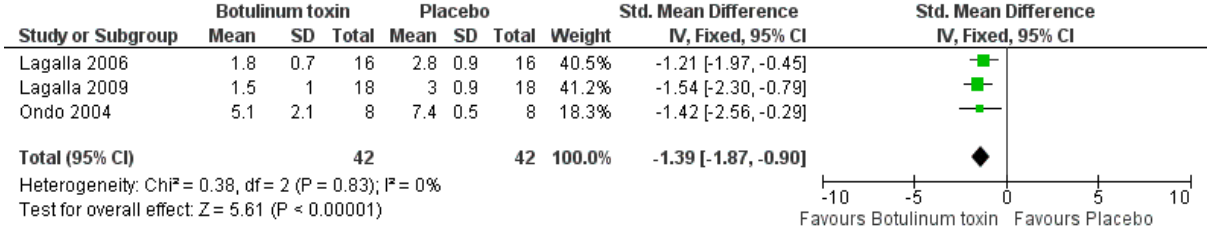
1 **J.5.1.2 Botulinum toxin versus placebo for patients in indirect populations**

Figure 76: Change in impact of drooling on daily activities



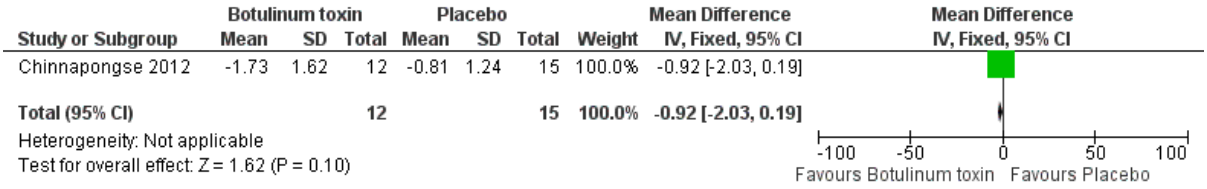
2

Figure 77: Patient assessment of severity of sialorrhoea



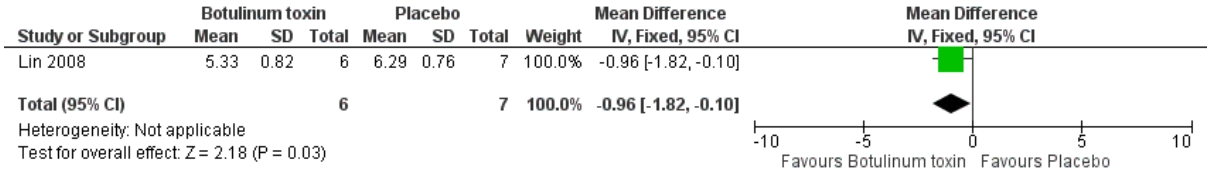
3

Figure 78: Patient reported change in symptom severity



4

Figure 79: Frequency and severity of drooling



5

Figure 80: Patient satisfaction

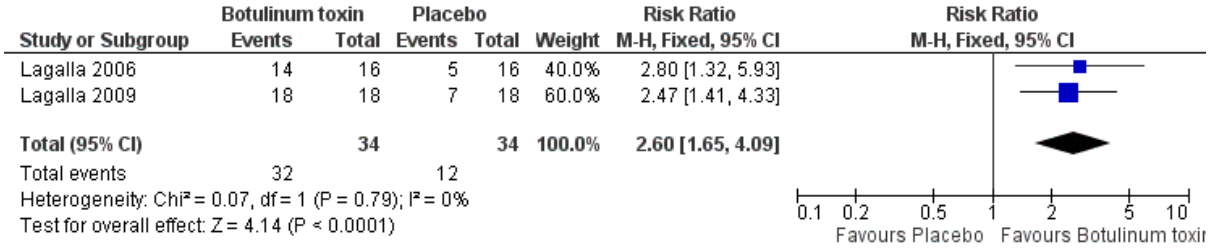
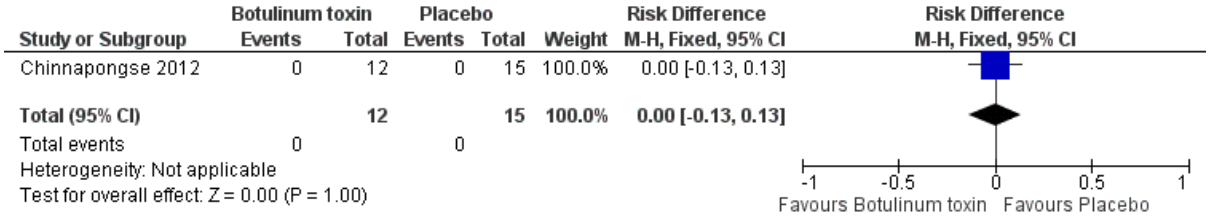
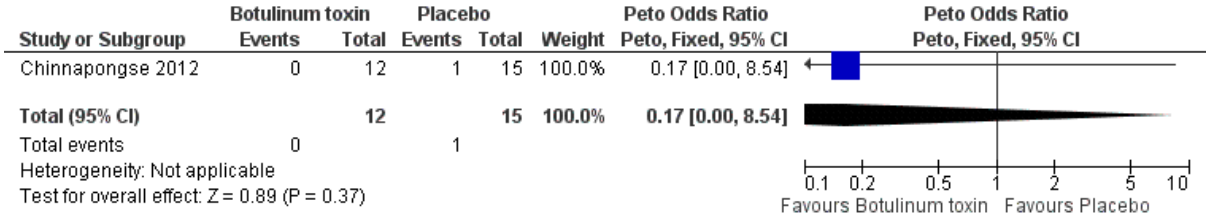


Figure 81: Aspiration pneumonia



1

Figure 82: Discontinuation of study medication due to side effects



2 **J.5.1.3 Botulinum toxin versus no treatment for patients in indirect populations**

Figure 83: Caregiver assessment of severity of sialorrhoea

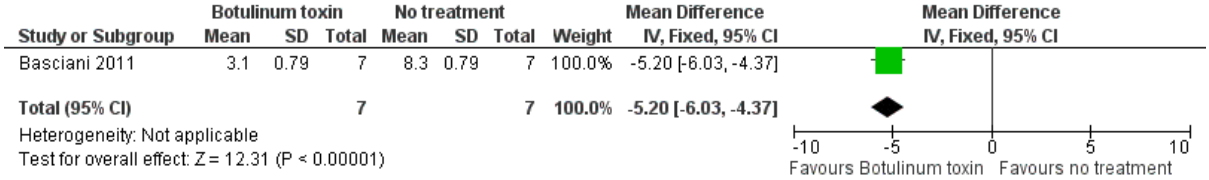
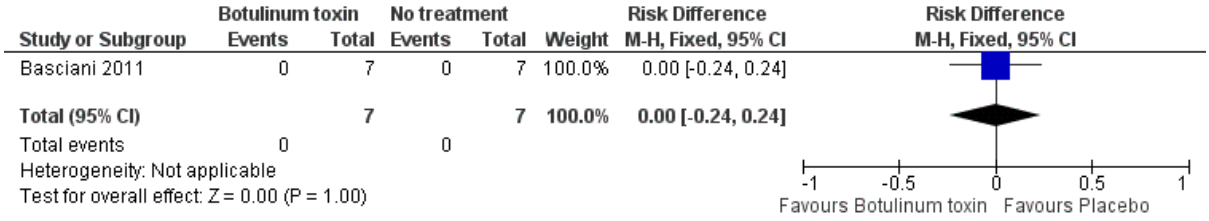
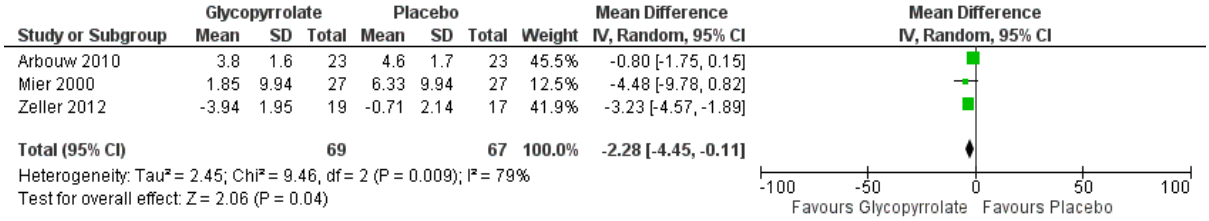


Figure 84: Muscle weakness



1 **J.5.1.4 Glycopyrrolate versus placebo for patients in indirect populations**

Figure 85: Caregiver assessment of severity of sialorrhoea



2

Figure 86: Caregiver satisfaction with medication

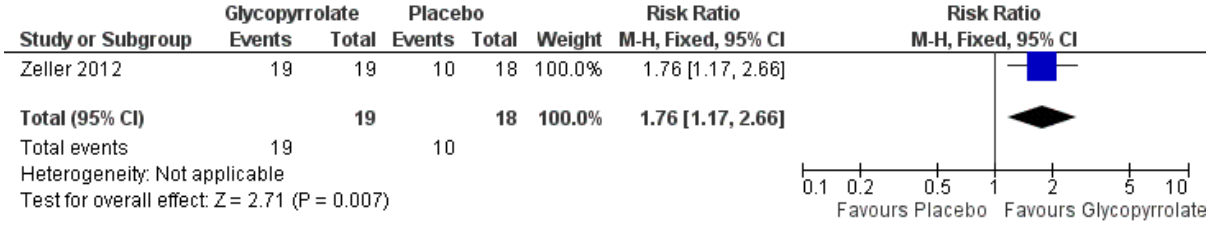


Figure 87: Change in motor symptoms

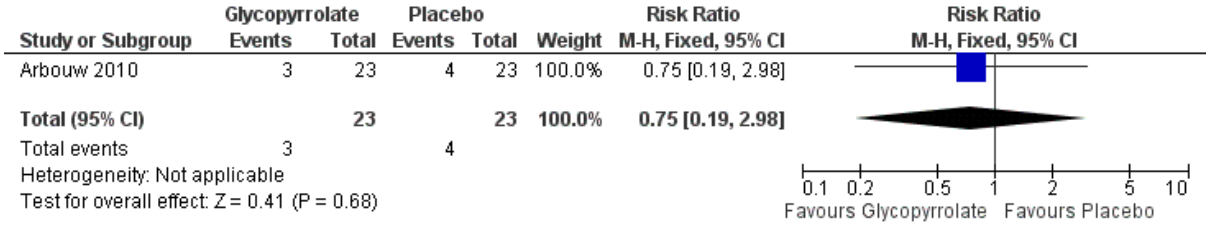
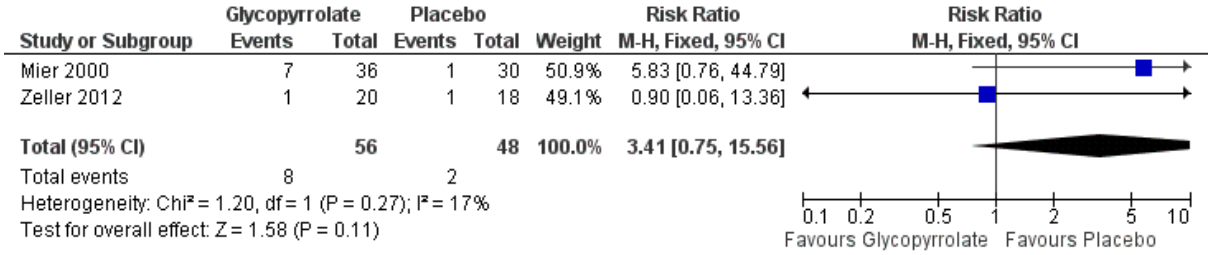
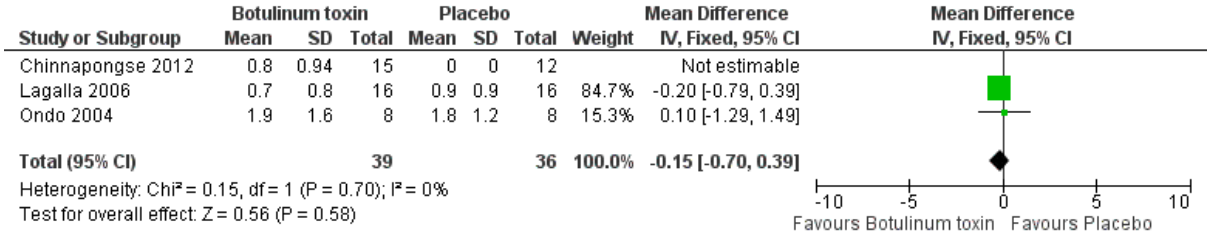


Figure 88: Discontinuation of medication due to side effects



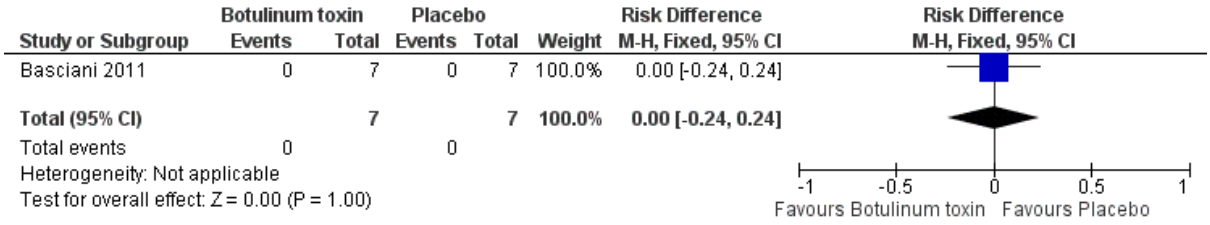
1

Figure 89: Dysphagia



2

Figure 90: Dysphagia



3 **J.5.1.5 Benztropine versus placebo for patients in indirect populations**

Figure 91: Drooling severity

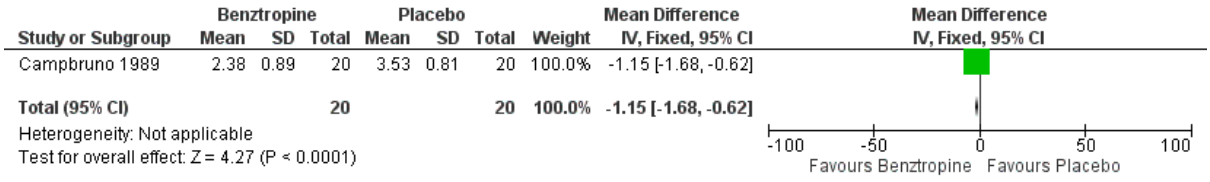
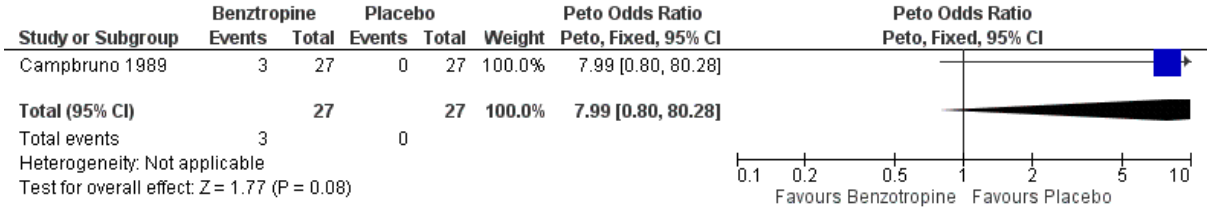


Figure 92: Adverse effects



J.6 Nutrition

J.6.1.1 High fat content versus high carbohydrate content

Figure 93: High fat content versus high carbohydrate content – weight gain

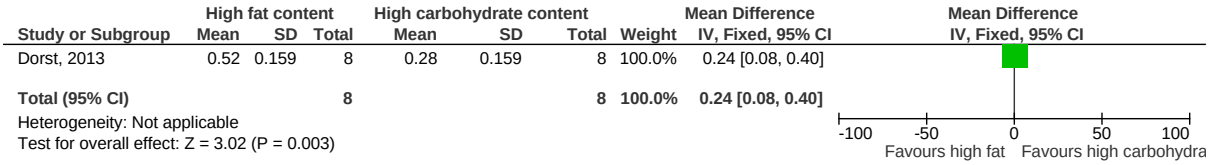


Figure 94: High fat content versus high carbohydrate content –change in BMI

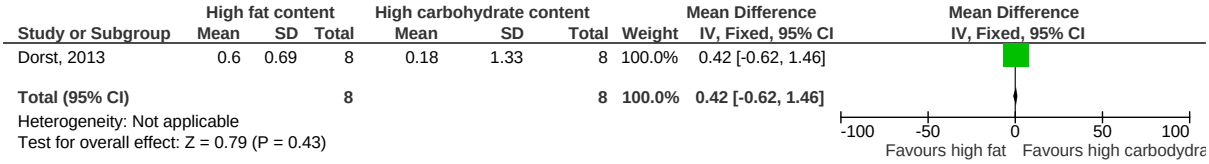
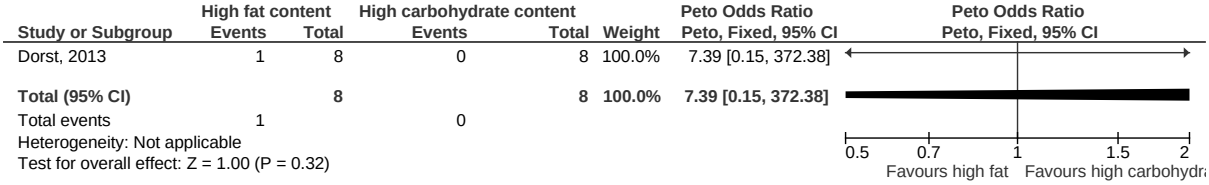


Figure 95: High fat content versus high carbohydrate content –diarrhoea



J.7 Cough effectiveness

Peak cough flow

Figure 96: MI-E versus exsufflation in people with ALS

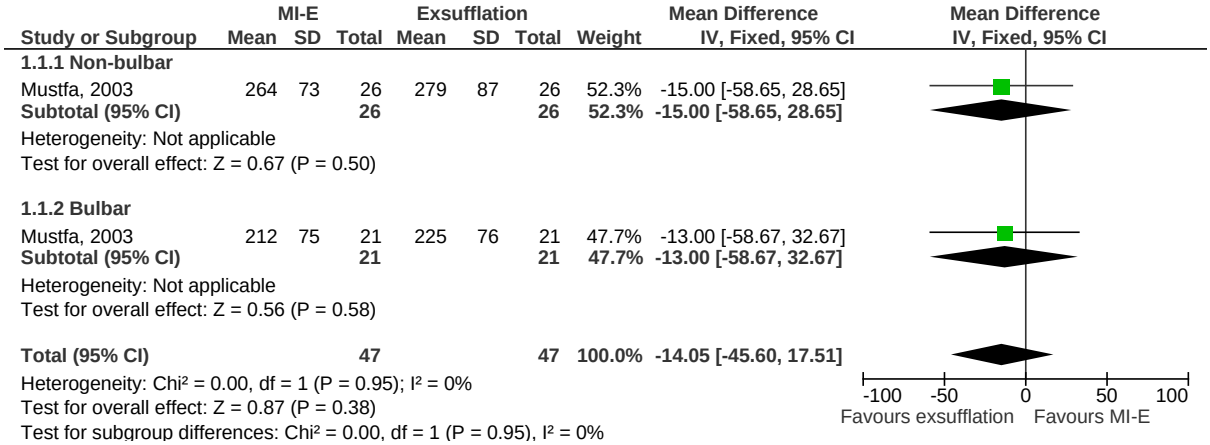


Figure 97: MI-E versus insufflation in people with ALS

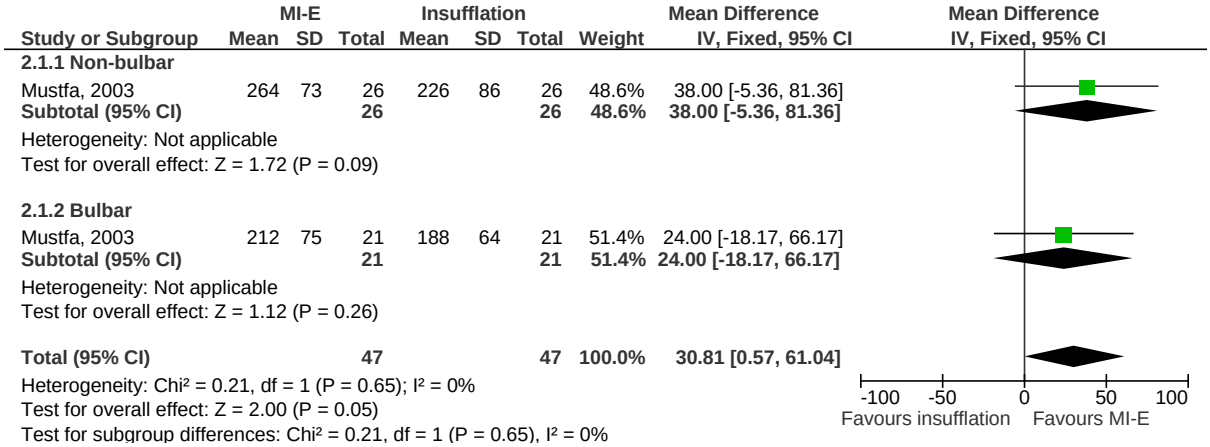
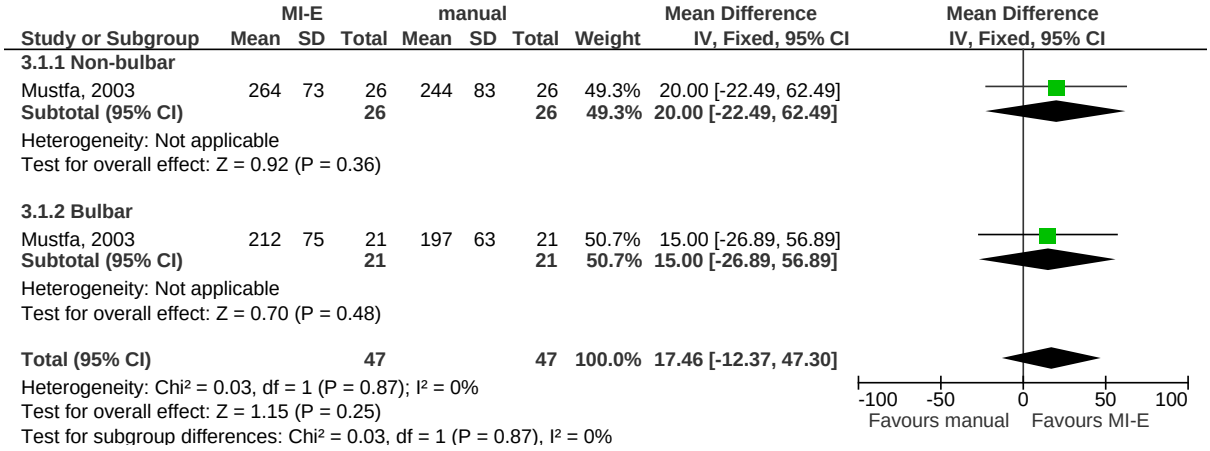
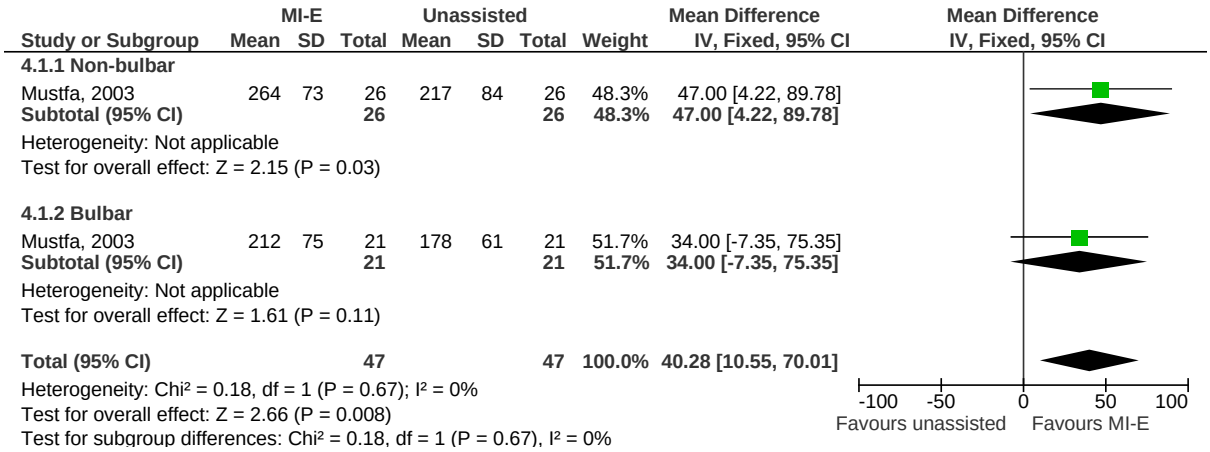


Figure 98: MI-E versus manual in people with ALS



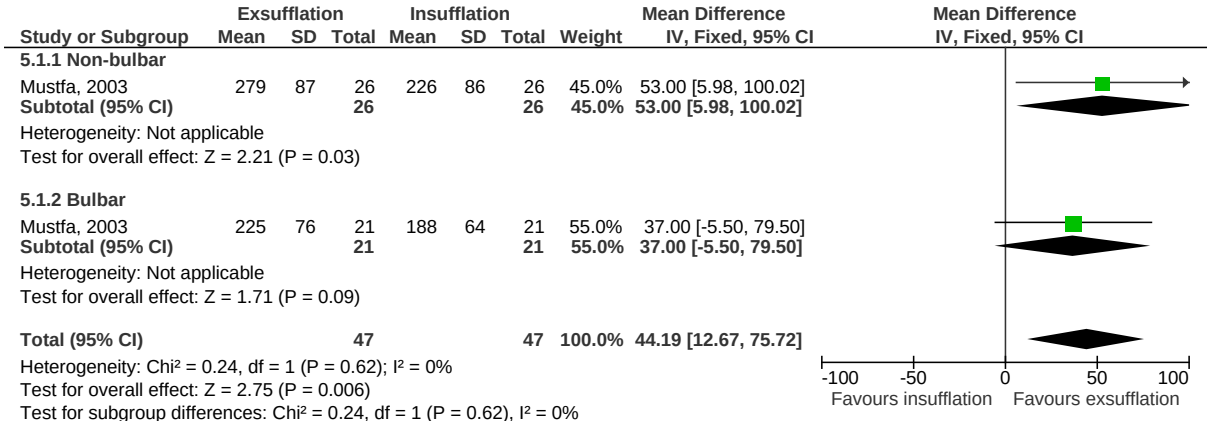
1

Figure 99: MI-E versus unassisted in people with ALS



2

Figure 100: Exsufflation versus insufflation in people with ALS



3

Figure 101: Exsufflation versus manual in people with ALS

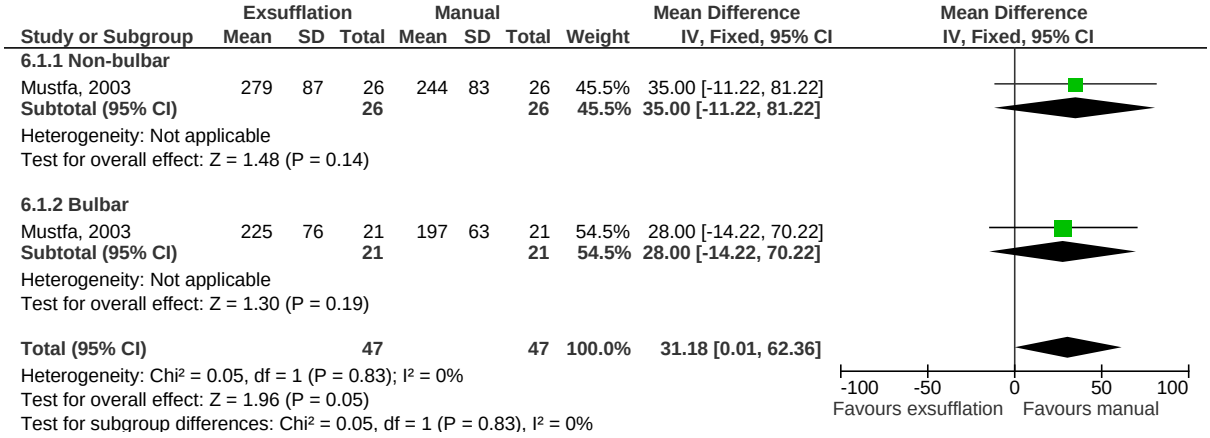
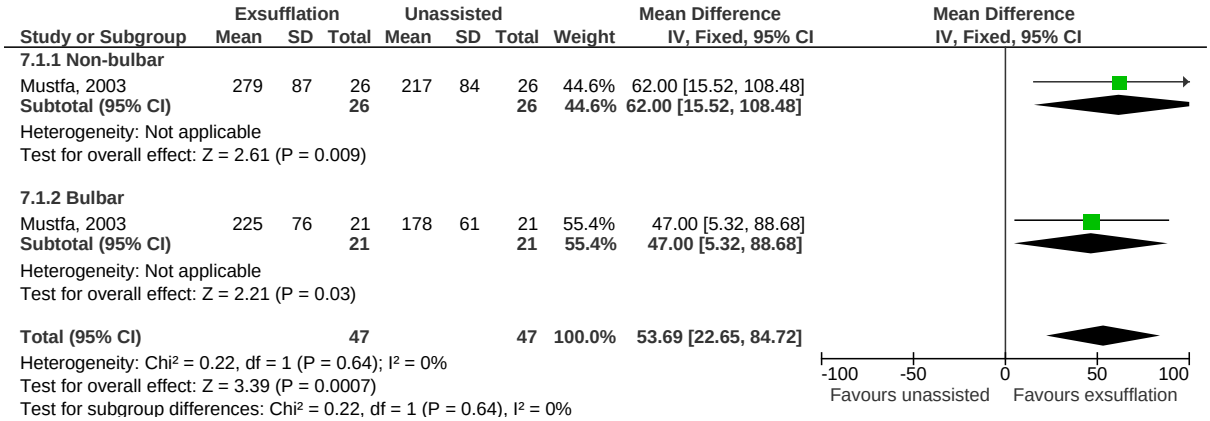
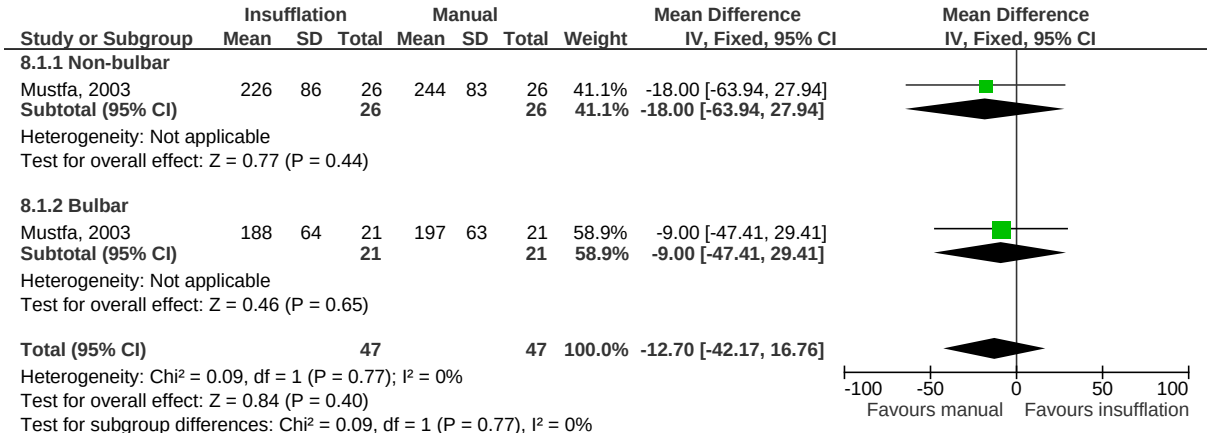


Figure 102: Exsufflation versus unassisted in people with ALS



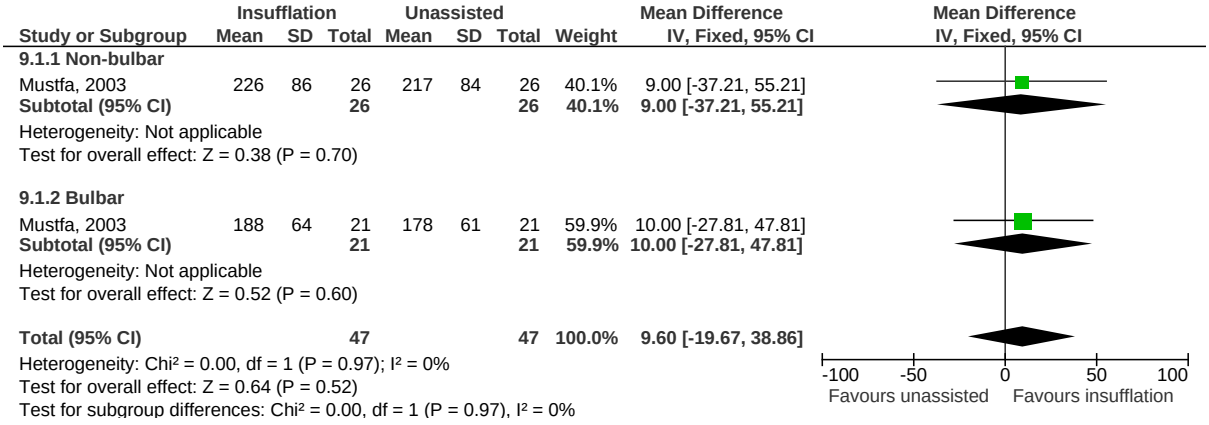
1

Figure 103: Insufflation versus manual in people with ALS



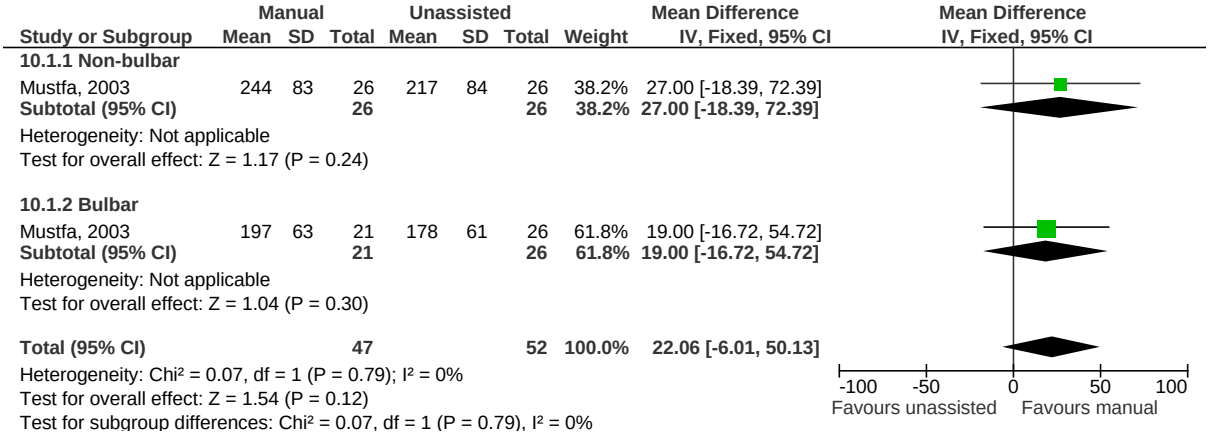
2

Figure 104: Insufflation versus unassisted in people with ALS



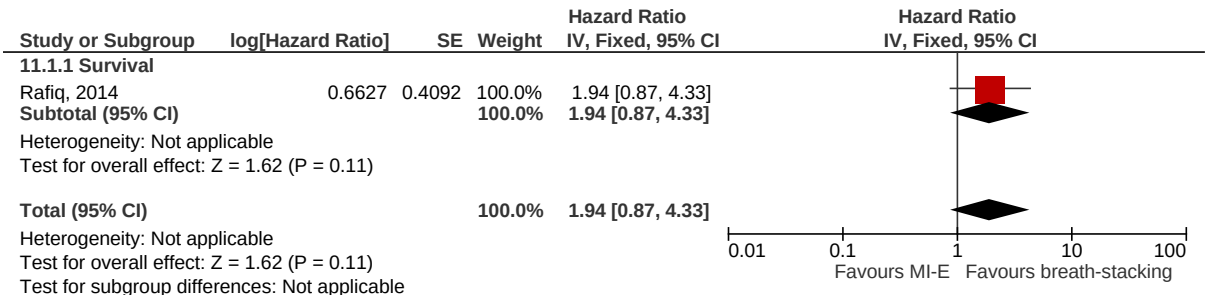
1

Figure 105: Manual versus unassisted in people with ALS



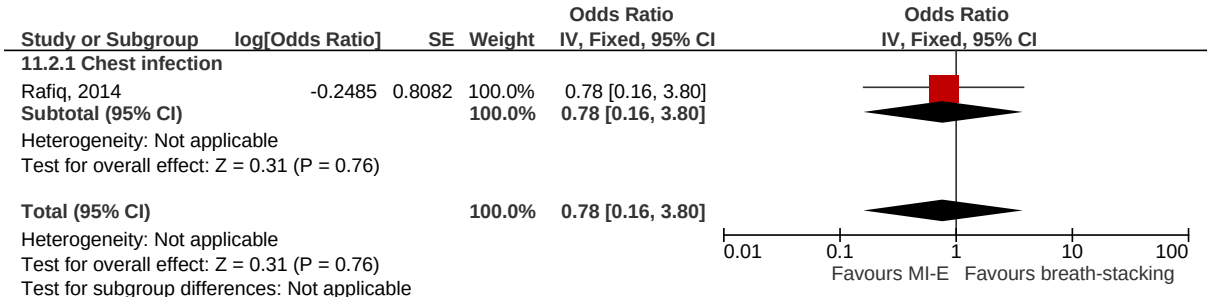
2

Figure 106: MI-E versus breath-stacking: survival



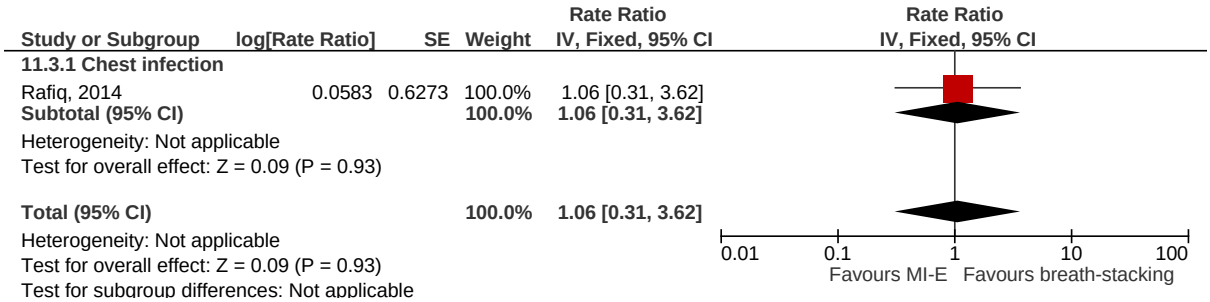
3

Figure 107: MI-E versus breath-stacking: number of patients with at least one chest infection



1

Figure 108: MI-E versus breath-stacking: total number of chest infections



2

Figure 109: MI-E versus breath-stacking: number of patients with any hospitalisation

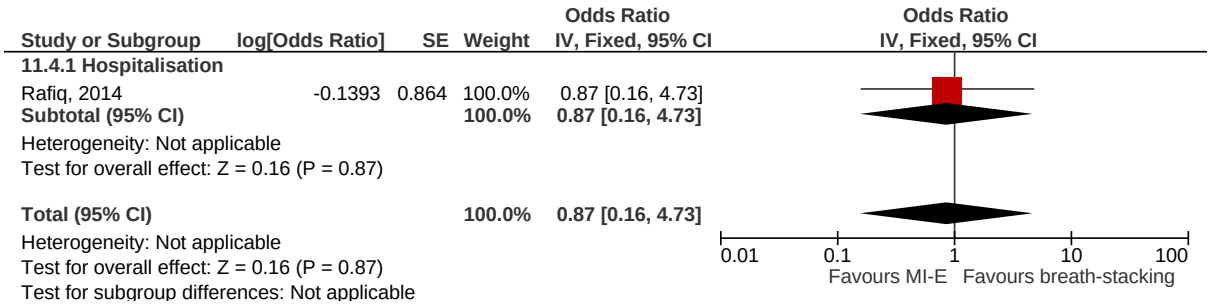
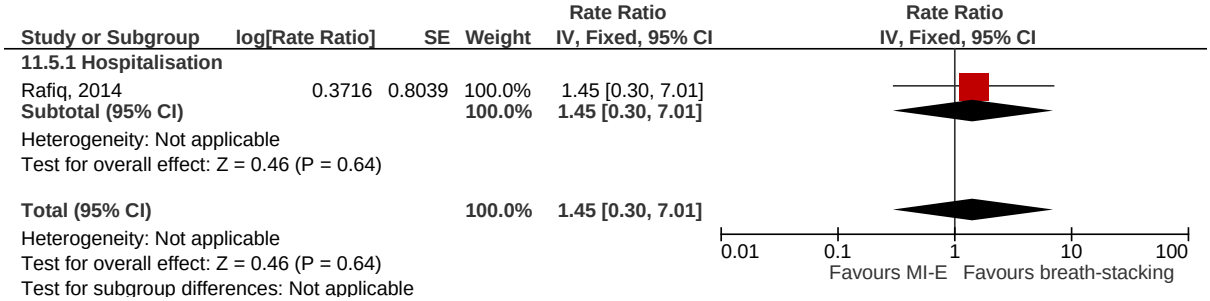


Figure 110: MI-E versus breath-stacking: total number of hospitalisations



3

Appendix K: Excluded clinical studies

K.1 Recognition and referral

Table 60: Studies excluded from the clinical review

Reference	Reason for exclusion
Beisecker 1988[59]	Not UK (US study)
Bongioanni 2009[71,72]	Incorrect study design: protocol for a Cochrane review
Brooks 2000A[85,86]	Incorrect study design: lessons learned from a conference
Cellura 2012[108]	Retrospective analysis of diagnostic delays. Not UK (Italian study).
Donaghy 2008[187]	Prevalence study. Looked at time to diagnosis and where the delay occurred, for example which practitioner they spent time with.
Hogden 2012[277]	Not UK (Australian study).
Househam 2000[280]	Retrospective analysis of time to diagnosis using a structured interview. Looked at time to diagnosis and where the delay occurred, for example which practitioner they spent time with.
Iwasaki 2001[287,287]	Incorrect study design: case series
Kano 2013[312]	Retrospective study, comparing type of physician first consulted by an ALS patient and time elapsed until diagnosis. Not UK (Japanese study).
Peters 2013A[460]	Cross-sectional survey of patients' experiences, not specifically timeliness of diagnosis. Only gives time to diagnosis.
Rocchetti 2012[490]	Modelling delay to diagnosis. Not UK (Italian study).
Sathasivam 2008[507]	Prospective study of frontotemporal dementia with MND misdiagnosis.
Srinivasan 2006[528]	Retrospective analysis of inappropriate surgeries from misdiagnosis of ALS. Not UK (USA study).
Turner 2010A[558]	Retrospective analysis of time to diagnosis.

K.2 Information and support at diagnosis

Table 61: Studies excluded from the clinical review

Reference	Reason for exclusion
Brown 2005[88]	Incorrect study design (survey)
Budych 2012[92]	Incorrect population: not MND
Carter 1998[104]	Incorrect study design (survey)
Carver 1999[105]	Incorrect study design (survey)
Chio 2008[122]	Incorrect study design (survey)
Foley 2012[216]	Incorrect study designs (literature review)
Foley 2014[220]	Not relevant to question
Foley 2014B[219]	Not relevant to question
Foley 2014D[218]	Not relevant to question
Gelinas 1997[237]	Incorrect study design (non-qualitative)
Gelinas 1998[236]	Incorrect study design (survey)
Hugel 2010[282]	Incorrect study design (survey)
Johnston 1996[303]	Incorrect study design (survey)

Reference	Reason for exclusion
Li 1991[353]	Incorrect study design (survey)
McCluskey 2004[382]	Incorrect study design (survey)
Mistry 2013[398]	Not relevant to question
Morris 2013[413]	Mixed population, not just MND
Moss 1993[414]	Not relevant to question
Pongratz 1999[468]	Incorrect study design (survey)
Rowland 1998[497]	Incorrect study design (literature review)
Schellenberg 2014[509]	Incorrect study design (non-qualitative study)
Silverstein 1991[522]	Incorrect study design (survey)
Vanteijlingen 2001[566]	Incorrect study design (survey)
Wicks 2008[578]	Incorrect study design (survey)
Young 1998[587]	Not relevant to question

K.3 Cognitive assessments

Table 62: Studies excluded from the clinical review

Reference	Reason for exclusion
Abrahams 1997[3]	Study not relevant to review (prevalence of cognitive dysfunction in patients with ALS versus healthy controls)
Abrahams 2004[4]	Study not relevant to review (prevalence of word retrieval deficit in patients with ALS versus healthy controls)
Abrahams 2005[5]	Study not relevant to review (change in cognitive function in patients with ALS versus healthy controls)
Abrahams 2005a[6]	Study not relevant to review (white matter volume in patients with ALS and with/without cognitive impairment versus healthy controls)
Blain 2013[64]	Study not relevant to review (cortical communication in patients with ALS versus healthy controls)
Burrell 2011[96]	Study not relevant to review (change in cognitive function in patients with frontotemporal dementia versus patients with ALS versus healthy controls)
Canu 2013[102]	Study not relevant to review (change in cognitive function and white matter damage in patients with PLS versus healthy controls)
Cavallo 2011[107]	Study not relevant to review (theory of mind in patients with ALS versus healthy controls)
Elamin 2011[198]	Study not relevant to review (executive dysfunction as a prognostic factor for survival in patients with ALS)
Elamin 2013[199]	Study not relevant to review (change in cognitive function as a prognostic factor for functional decline in patients with ALS)
Ji 2012[300]	Study not relevant to review (evaluating methods of identifying cognitive impairment in patients with ALS)
Olm 2014[443]	Study not relevant to review (grey matter change in patients with ALS versus healthy controls)
Rippon 2006[485]	Study not relevant to review (prevalence of cognitive dysfunction in patients with ALS versus healthy controls)
Rusina 2010[498]	Study not relevant to review (cognitive impairment as a prognostic factor for survival in patients with ALS)
Sarro 2011[506]	Study not relevant to review (ability of DT MR imaging to identify

Reference	Reason for exclusion
	cognitive dysfunction in patients with ALS)

K.4 Prognostic factors

Table 63: Studies excluded from the clinical review

Reference	Reason for exclusion
Agosta 2010[11]	Study did not account for all prognostic variables
Agosto 2010A[10]	Outcome is not survival
Agosto 2012[12]	Outcome is not survival
Ahn 2011[13]	Study did not account for all prognostic variables
Aksoy 2014[15]	Study did not account for all prognostic variables
Armon 1998[33]	Study does not account for prognostic variable diagnostic delay
Armon 2000[32]	Study does not account for prognostic variable diagnostic delay
Atassi 2014[38]	Study did not account for all prognostic variables
Bach 1995[46]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Baumann 2010[53]	Multivariable analysis does not account for weight loss or time to symptom onset
Bede 2013[57]	Study did not account for all prognostic variables
Boylan 2013[77]	Study did not account for all prognostic variables
Brettschneider 2006[82]	Outcome is not survival
Bromberg 1993[84]	Study did not account for all prognostic variables
Burrell 2013[95]	Study did not account for all prognostic variables
Byrne 2013[97]	Study did not account for all prognostic variables
Chancellor 1993[110]	Study did not account for all prognostic variables
Chaudri 2002[111]	Study did not account for all prognostic variables
Cheah 2011[114]	Study did not account for all prognostic variables
Chio 1985[117]	Study did not account for all prognostic variables
Chio 1999[118]	Neither multivariable model accounts for all prognostic factors
Chio 2002A[123]	Study did not account for all prognostic variables
Chio 2004[120]	Incorrect outcome: quality of life
Christensen 1990[132]	Study did not account for all prognostic variables
Chung 2004[133]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Ciccarelli 2009[134]	Study did not account for all prognostic variables
Clavelou 2013[137]	Model does not account for all prognostic factors
Coon 2011[144]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Czaplinski 2006A[157]	The analyses undertaken did not account for weight loss
Czaplinski 2006B[156]	Not primary research
de Carvalho 2006[170]	Outcome is not survival
Decarvalho 2005[169]	Outcome is not survival
De Groot 2006[173]	Outcome is not survival
De Groot 2007[172]	Incorrect outcome: quality of life

Reference	Reason for exclusion
Delaguila 2003[174]	Multivariable analysis does not account for respiratory function
Desport 2000[178]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Desport 2008[182]	Not data presented for prognostic variables of interest in the multivariable analysis. Results presented do not meet variables specified in protocol.
Elamin 2011[198]	No results presented for relevant prognostic factors in multivariate analysis
Fini 2014[209]	Study did not account for all prognostic variables
Forbes 2004[222]	Study did not account for all prognostic variables
Gallo 2013[230]	Multivariable analysis does not account for respiratory function
Gay 1991[235]	The analyses undertaken did not account for weight loss
Grosskreutz 2006[258]	Study did not account for all prognostic variables
Haverkamp 1995[267]	Study did not account for all prognostic variables
Higo 2004[272]	Study did not account for all prognostic variables
Jablecki 1989[288]	Study did not account for all prognostic variables
Javad Mousavi 2014[291]	Multivariable analysis does not account for weight loss
Jawaid 2010[292]	Multivariable analysis does not account for respiratory function
Johnston 1999[302]	Study did not account for all prognostic variables
Kihira 2008[321]	Multivariable analysis does not account for weight loss or respiratory function
Kimura 2006[323]	Study does not account for prognostic variable site of symptom onset
Kollewe 2008[328]	The various multivariable analyses undertaken did not account for time to symptom onset and relevant prognostic factors within the same model
Kosticdedic 2012[331]	Study did not combine relevant prognostic factors in a multivariable analysis
Krampe 2008[332]	Outcome is not survival
Kurtzke 1991[339]	Paper investigates risk factors for ALS itself
Lee 1995[348]	Study did not account for all prognostic variables
Lee 2013[347]	Study did not account for all prognostic variables
Leonardis 2012[350]	Study does not account for prognostic variable weight loss
Limousin 2010[357]	Study does not account for respiratory function
Liu 2009[362]	Outcome is not survival
Lo Coco 2007[363]	Incorrect population: all participants have tracheostomy
Louwerse 1997[368]	Multivariable analysis does not account for weight loss or respiratory function
Lyall 2001[372]	Outcome is ventilatory failure rather than survival
Mandrioli 2006[374]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Menke 2012[392]	Study did not account for all prognostic variables
Mohammadi 2011[406]	Study did not account for all prognostic variables
Morgan 2005[410]	Study does not account for prognostic variable diagnostic delay
Pastula 2009[456]	Study did not account for all prognostic variables
Preux 1996[470]	Study did not account for all prognostic variables
Raaphorst 2013A[471]	Outcome is not survival

Reference	Reason for exclusion
Rio 2010[483]	Multivariable analysis does not account for respiratory function
Roccatagliata 2009[489]	Not a prognostic study
Rooney 2013[494]	Multivariable analysis does not account for weight loss or respiratory function
Rutkove 2014[500]	Outcome is not survival
Schmidt 2006[510]	Analysis does not account for weight loss
Scotton 2012[511]	Study did not account for weight loss or respiratory function
Shimizu 2012[518]	Study did not account for all prognostic variables
Shimizu 2014[517]	Study did not account for all prognostic variables
Silva 2008[521]	Outcome is not survival
Stagg 2013[529]	Study did not account for all prognostic variables
Stambler 1998[530]	Multivariable analysis results not fully presented and supplemental data could not be acquired
Stoppel 2014[536]	Study did not account for all prognostic variables
Takeuchi 2008[542]	Study did not account for all prognostic variables
Testa 2004[546]	Study did not account for all prognostic variables
Thijs 2000[547]	The analyses undertaken did not account for weight loss
Turner 2002[556]	Study did not account for all prognostic variables
Tysnes 1994[560]	Study did not account for all prognostic variables
Vender 2007[567]	Study did not use multivariable analysis to find the independent effects of prognostic variables
Visser 2007[571]	Multivariable analysis not linked to survival outcome
Vitacca 1997[572]	Multivariable analysis does not account for respiratory function
Yuen 1997[588]	Study did not account for all prognostic variables
Zhang 2011[592]	Study did not account for all prognostic variables

K.5 Organisation of care

Table 64: Studies excluded from the clinical review

Study	Reason for exclusion
Arbesman 2014[29]	Systematic review: study designs inappropriate, quality assessment is inadequate
Borasio 2001[73]	Incorrect study design: cross-sectional study
Brewah 2013[83]	Incorrect study design: review
Chakraborty 2008[109]	Incorrect study design, not review population, not guideline condition
Chio 2001[124]	Incorrect study design: audit of service provision
Connolly 2015[143]	No clinical data
Creemers 2011[148]	Abstract: have full paper (see Creemers 2014)
Jefferies 2012[293]	Incorrect study design: cross-sectional study
Kang 2013[311]	Incorrect study design: case series
Lima 2011[356]	Incorrect study design: cross-sectional study
Miller 2009[394]	Systematic review: study designs inappropriate
Rodriguez de rivera 2011[492]	Inappropriate comparison, incorrect interventions

Van den berg 2003[563]	Incorrect study design: audit of care
Van den berg 2005[562]	Incorrect study design: cross-sectional study
Van der steen 2009[564]	Incorrect study design: cross-sectional study
Vitacca 2010[573]	Incorrect study design: non-comparative review of tele-health service
Wicks 2010[579]	Incorrect study design: cross-sectional study

K.6 Frequency of assessment

Table 65: Studies excluded from the clinical review

Reference	Reason for exclusion
De Carvalho 2005A[169]	Not comparing different frequencies of assessment
De Groot 2006[173]	Not comparing different frequencies of assessment
Rutkove 2012[499]	Not comparing different frequencies of assessment
Wang 2002[574]	Not comparing different frequencies of assessment

K.7 Psychological support

Table 66: Studies excluded from the clinical review

Reference	Reason for exclusion
Akiyama 2006[14]	Very specific to Japan. The withdrawal of NIV in Japan differs and the study themes related to this.
Atassi 2011A[37]	Survey
Atkins 2010[40]	Interview using questionnaires
Averill 2007[44,44]	Incorrect study design: abstract of a randomised controlled trial
Averill 2013[43,44]	Incorrect study design: randomised controlled trial
Boerner 2012[67]	Survey
Borasio 2001[73]	Survey
Bremer 2004[81]	Survey
Brown 1970[90]	Case study of 4 patients
Bungener 2005[93]	Interview using questionnaires
Carter 1998[104]	Survey
Chio 2005[119]	Interview using questionnaires
Chio 2008[122]	Interview using questionnaires
Chio 2010[125]	Interview using questionnaires
Clarke 2001[136]	Survey
Cobb 1986[140]	Case study of 2 patients
Cox 1992[146]	Interviews using questionnaires
Fegg 2005[207]	Survey and interview using questionnaires
Flaherty 2011[210]	Not relevant. Cognitive assessment. Case-control study
Foley 2006[211]	Abstract
Foley 2012A[217]	Review of qualitative studies and questionnaires
Ganzini 2008[231]	Survey
Gauthier 2007[234]	Interview using questionnaires

Reference	Reason for exclusion
Gelinas 1998[236]	Survey
Goldstein 1998[243]	Survey
Goldstein 1999[247]	Literature review
Goldstein 2002[246]	Survey
Goldstein 2006[245]	Interview using questionnaires
Goldstein 2006A[244]	Survey
Grehl 2011[257]	Survey
Hecht 2002[268]	Standardised interview with a questionnaire and self-rating depression scale
Hugel 2010[282]	Semi-structured interview using questionnaires
Hughes 2004A[283]	Abstract
Hunter 1993[285]	Interview using questionnaires
Jelsone-Swain 2012[294]	Survey
Jenkinson 2000B[295]	Survey
Rabkin 2005[472]	Semi-structured interviews and survey results not separated
Krivickas 1997[335]	Survey
Kubler 2005[336]	Survey
Kurt 2007[338]	Review of various types of studies
Lemoignan 2010[349]	Not relevant – about how patients decide whether to have NIV
Lerum 2015[351,351]	Not relevant – meaning of chronicity and terminality
Locock 2012[365]	Re-analysis of data, looking at metaphoric language and articulation of emotions. Study that original data comes from is included in the review.
Lillo 2011[355]	Survey
Lillo 2012[354]	Survey
Love 2005[370]	Survey
Mannino 2007[375]	Not relevant. Verifying if ALSFRS is able to be used over the phone.
Mayer 1990[380]	Interviews and questionnaires – results not separated and only brief summary (2-3 words) reported
McElhiney 2009[386]	Survey
McLeod 2007A[389]	Review of various types of studies
Miyashita 2009[402]	Survey
Mock 2005[403]	Abstract of a survey
Mockford 2006[404]	Review of various types of studies, mainly quantitative
Mockford 2009[405]	Not relevant. Development of a questionnaire.
Moore 1998[408]	Survey
Ng 2011A[426]	Interviews using questionnaires
Ng 2011c[425]	Survey
O'Connor 2011[436]	Survey
Oh 2011B[440,440]	Incorrect study design: dissertation; associated published papers included in the review
Olsson 2010[446]	Survey
Pagnini 2011[450]	Survey
Rabkin 2005[472,473]	Survey
Roach 2009[488]	Survey

Reference	Reason for exclusion
Sebring 1987[512]	Survey and interview; findings not separated
Taylor 2010[545]	Survey
Trail 2004[550]	Survey
Wasner 2004[575]	Survey
Wicks 2007[577]	Survey
Williams 2008[580]	Concept mapping – mixed methods, using qualitative and quantitative data; needs of caregivers were sorted into a hierarchy of needs to form a concept map, rather than qualitative themes.

K.8 Social care support

Table 67: Studies excluded from the clinical review

Reference	Reason for exclusion
Atassi 2011A[37]	Survey
Boerner 2012[67]	Survey
Borasio 2001[73]	Survey
Bremer 2004[81]	Survey
Brown 1970[90]	Case study of 4 patients
Bungener 2005[93]	Survey
Carter 1998[104]	Survey
Chio 2005[119]	Survey
Chio 2008[122]	Survey
Chio 2010[125]	Survey
Clarke 2001[136]	Survey
Cobb 1986[140]	Case study of 2 patients
Cox 1992[146]	Interview using questionnaire and open questions, not separated, quantitatively analysed
Fegg 2005[207]	Survey
Flaherty 2011[210]	Not relevant: cognitive assessment, case-control study
Foley 2006[211]	Abstract
Foley 2012[216]	Review of qualitative studies and questionnaires
Ganzini 2008[231]	Survey
Gauthier 2007[234]	Survey
Gelinas 1998[236]	Survey
Goldstein 1998[243]	Survey
Goldstein 1999[247]	Literature review
Goldstein 2002[246]	Survey
Goldstein 2006[245]	Survey
Goldstein 2006A[244]	Survey
Grehl 2011[257]	Survey
Hecht 2002[268]	Standardised interview with a questionnaire and self-rating depression scale
Hugel 2010[282]	Semi-structured interview using questionnaires
Hughes 2004A[283]	Abstract

Reference	Reason for exclusion
Hunter 1993[285]	Survey
Jelsone-Swain 2012[294]	Survey
Jenkinson 2000B[295]	Survey
Krivickas 1997[335]	Survey
Kubler 2005[336]	Survey
Kurt 2007[338]	Review of various types of studies
Lemoignan 2010[349]	Not relevant: how patients decide whether to have NIV
Lillo 2011[355]	Survey
Lillo 2012[354]	Survey
Locock 2012[365]	Re-analysis of data looking at metaphoric language and articulation of emotions. Study containing the original data is included in the review.
Love 2005[370]	Survey
Mannino 2007[375]	Not relevant: verifying if ALSFRS is able to be used over the phone
Mayer 1990[380]	Interviews and questionnaires: results not separated and only brief summary (2-3 words) reported
Mcelhiney 2009[386]	Survey
McLeod 2007A[389]	Review of various types of studies
Miyashita 2009[402]	Survey
Mock 2005[403]	Abstract of a survey
Mockford 2006[404]	Review of various types of studies, mainly quantitative
Mockford 2009[405]	Not relevant: development of a questionnaire
Moore 1998[408]	Survey
Ng 2011A[426]	Survey
Ng 2011C[425]	Survey
O'Connor 2011[436]	Survey
Olsson 2010[446]	Survey
Pagnini 2011[450]	Survey
Rabkin 2005[473]	Semi-structured interviews and survey results not separated
Ray 2006[479]	Study not relevant
Roach 2009[488]	Survey
Sebring 1987[512]	Inappropriate study design: does not stratify findings between survey and qualitative data
Trail 2004[550]	Survey
Wasner 2004[575]	Survey
Wicks 2007[577]	Survey
Williams 2008[580]	Concept mapping: use of qualitative and quantitative data

K.9 Planning for end of life

Table 68: Studies excluded from the clinical review

Reference	Reason for exclusion
Achille 2003[7]	Inappropriate study design: survey
Adelman 2004[8]	Inappropriate study design: survey
Albert 2009[17]	Inappropriate study design: survey

Reference	Reason for exclusion
Aoun 2010[25]	Inappropriate study design: survey
Aoun 2013[26]	Inappropriate study design: literature review
Baxter 2013a[55]	Inappropriate population: themes do not distinguish between views of health professionals and patients/carers
Bentley 2012[60,60]	Inappropriate study design: survey
Brownlee 2012[91]	Inappropriate study design: survey
Connolly 2015A[142,143]	Inappropriate study design: literature review
Dawson 2003[164]	Inappropriate population: themes do not distinguish between views of carers of patients with MND and muscular dystrophy
Fanos 2008[205]	Not relevant to review topic
Foley 2011[212]	Inappropriate study design: conference abstract
Foley 2013[213]	Inappropriate study design: conference abstract
Foley 2014c[214]	Inappropriate study design: conference abstract
Freer 2010[226]	Inappropriate study design: conference abstract
Ganzini 2002a[232]	Inappropriate study design: survey
Gelinas 1997[237]	Inappropriate study design: commentary
Gredal 2012[254]	Inappropriate study design: conference abstract
Hecht 2003[269]	Inappropriate study design: survey
Hughes 2005[284]	Inappropriate population: themes do not distinguish between views of health professionals and patients/carers
Johnson 2007[301]	Not relevant to review topic
Kristjanson 2006[334]	Inappropriate population: themes do not distinguish between views of patients with MND and other neurodegenerative disorders
Martin 2001[377]	Inappropriate study design: survey
Neudert 2001[424,424]	Inappropriate study design: survey
O'Brien 2004a[432]	Not relevant to review topic
O'Brien 2012[435]	Not relevant to review topic
O'Brien 2012b[433]	Not relevant to review topic
Oyebode 2013[448]	Not relevant to review topic
Palmer 2012[453]	Inappropriate study design: conference abstract
Rosengren 2015[496,496]	Inappropriate study design: 4 written biographies.
Stutzki 2014[537,537]	Inappropriate study design: survey
Trail 2003[422]	Inappropriate study design: survey
Ushikubo 2013[561,561]	Inappropriate study design: retrospective case study
Veronese 2012[568]	Inappropriate study design: conference abstract
Veronese 2014[569]	Does not address communication and support to help MND patients, their families and carers anticipate and prepare for end of life

K.10 Pharmacological treatment for muscle problems

Table 69: Studies excluded from the clinical review

Study	Reason for exclusion
Apaydin 2011[28]	Population not MND
Armon 2008[34]	Correspondence

Study	Reason for exclusion
Baba 2004[45]	Narrative review
Berry 2013[61]	Wrong intervention
Bethoux 2013[62,62]	Incorrect study design: cohort study not an RCT
Borg 2011[74]	Population not MND
Boxer 2013[76]	MND-FTD data not reported separately
Bradley 1990[79]	Narrative review
Brooks 1987[86]	Wrong intervention
Burrell 2011A[94,96]	Wrong intervention
Chou 2004[130]	Not MND population
Chow 2013[131]	Wrong population (population <20)
Cocchiarella 1967[141]	Majority population not MND
Deltombe 2008[175,175]	Not MND population
Diana 2006[185]	Protocol, no further review found
Duning 2011[193]	Wrong intervention
Engel 1983[202,202]	Incorrect study design: case series
Esquenazi 2013[203]	Systematic review, included studies not MND
Francisco 2004[223]	Systematic review, no information on MND in included studies
Fryda-kaurimsky 1981[227]	Population not MND
Gooch 2014[248,249]	Not relevant: a technology and literature review of motor unit number estimation
Gracies 2004[253]	Narrative review
Hennies 1981[270]	Population not MND
Kissel 2014[325,325]	Population not MND
Lataste 1994[345]	Population not MND
Levine 2010[352]	Monitoring of disease progression
Louwerse 1995[369]	Wrong intervention
Mazzini 1998[381]	Wrong comparison: gabapentin 500mg/day versus 1000mg/day
Mondrup 1984[407]	Wrong intervention: progabide
Mueller 1997[415]	Population not MND
Norris 1979[430]	Dosages not relevant to current practice
Penn 1997[459]	Wrong intervention
Shakespeare 2003[514]	Indirect population: multiple sclerosis
Sheean 2006[516]	Narrative review
Turhanoglu 2002[555]	Population not MND, only 1 intervention, no comparator
Wissel 2009[583]	Systematic review, included studies not MND

K.11 Non-pharmacological management of muscle problems

Table 70: Studies excluded from the clinical review

Study	Reason for exclusion
Ansari 2007[23]	Population not MND
Arts 2011[35]	Incorrect study design

Study	Reason for exclusion
Ashraf 2009[36]	Population not MND
Attarian 2005[42]	Diagnostic study
Bakheit 2005[50]	Population not MND
Bizovicar 2012[63]	Not symptom management
Boyraz 2009[78]	Population not MND
Chow 2013[131]	Population not MND
Cup 2007[151]	Not Cochrane review, Drory 2001 already included
De carvalho 1999[165]	Cohort study, sample size small n=11, not symptom management
De carvalho 2002[167]	TMS as a diagnostic tool to monitor disease progression
De carvalho 2005[166]	Narrative review
De carvalho 2010[171]	Cross-sectional study
Di Lazzaro 2006[183]	RCT, unclear intervention
Dooley 1977[188]	Case study
Eisen 1996[196]	Prognostic study
Elsworth 2009[201]	Incorrect study design
Fimland 2010[208]	Population not MND
Galinsky-malaguti 1996[229]	Narrative review
Guo 2011[261]	Protocol
Handa 1995[264]	Incorrect study design: case study
Hashizume 2012[266]	Monitoring disease progression
Hobson-webb 2013[273]	Review-diagnosis
Ingram 1987[286]	Cohort study, n=12
Kaufmann 2004[318]	Diagnostic study
Keenan 1999[319]	Population not MND
Khedr 2011[320]	Case-control study
Kloos 2004[327]	Diagnostic study
Krampfl 2004[333]	Diagnostic study
Levine 2010[352]	Population not MND
Lin 2010[358]	Population not MND
Lui 2009[371]	Systematic review, included RCT in review
Mills 2003[397]	Diagnostic study
Mitsumoto 2007[401]	Diagnostic markers for motor neurone dysfunction
Morris 2006[412]	Systematic review, included RCT used for review
Nakajima 1997[418]	Not symptom management
Oates 2010[439]	Population not MND
Rochester 2001[491]	Population not MND, n=17
Solomon 2010[525]	Not symptom management, n=13
Turner 2005[557]	Not symptom management
Van groenestijn 2011[565]	Protocol
Zanette 2008[590]	Incorrect study design: this is a non-randomised pilot study

K.12 Saliva management

Table 71: Studies excluded from the clinical review

Study	Reason for exclusion
Andersen 2001[20]	Incorrect study design (case series)
Bachrach 1998[48]	Incorrect study design (cross-sectional design)
Castelnovo 2013[106]	Abstract only
Chnag 2012[127]	Abstract only
Chou 2007[129]	Systematic review included studies not relevant to review question
Dogu 2004[186]	Inappropriate comparison (guided versus unguided administration of botulinum toxin)
Eiland 2012[195]	Systematic review included studies not relevant to review question
Ellenbogen 2013[200]	Abstract only
Evangelos 2013[204]	Inappropriate comparison (dose ranging study)
Fraraccio 2013[224]	Inappropriate comparison (parotid versus submandibular gland administration of botulinum toxin)
Fuster torres 2007[228]	Systematic review is not relevant to review question or unclear PICO
Garnock-Jones 2012[233]	Systematic review included studies not relevant to review question
Guidubaldi 2011[260]	Inappropriate comparison (botulinum toxin A versus botulinum toxin B)
Jongerius 2004[305]	Incorrect study design (crossover no randomisation)
Jongerius 2004[306]	Incorrect study design (crossover no randomisation)
Kalf 2007[308]	Inappropriate comparison (parotid versus submandibular gland administration of botulinum toxin)
Lakraj 2013[343]	Systematic review included studies not relevant to review question
Lipp 2003[360]	Inappropriate comparison (dose ranging study)
Little 2009[361]	Systematic review is not relevant to review question or unclear PICO
Mato 2010[378]	Mixed indirect population (<80% included population; 36.7% cerebral palsy)
Neppelberg 2007[423]	Incorrect study design (case series)
Nordgarden 2012[429]	Inappropriate comparison (parotid and submandibular gland administration versus submandibular gland administration of botulinum toxin)

Reid 2008[480]	Mixed population (<80% included population; 65% cerebral palsy)
Restivo 2013[481]	Inappropriate comparison (botulinum toxin in patients with lower motor neurone impairment versus patients without lower motor neurone impairment)
Rodwell 2012[493]	Systematic review included studies not relevant to review question
Scheffer 2010[508]	Incorrect study design (cohort study)
Sigan 2013[519]	Inappropriate intervention (complex intervention for the improvement of oral motor function in children with cerebral palsy; judged by GDG to not be relevant be this review)
Squires 2014[527,527]	Systematic review included studies not relevant to review question
Steinlechner 2010[533]	Mixed indirect population (<80% included population; 50% Parkinson's disease; 50% schizophrenia)
Stokholm 2013[534]	Systematic review: study designs inappropriate
Stone 2009[535]	Systematic review: study designs inappropriate
Thomsen 2007[548]	Incorrect intervention (ipratropium bromide)
Truong 2008[552]	Systematic review included studies not relevant to review question
Tscheng 2002[553]	Systematic review included studies not relevant to review question
Tysnes 2008[559]	Systematic review is not relevant to review question or unclear PICO

K.13 Equipment and adaptations to aid activities of daily living and mobility

Table 72: Studies excluded from the clinical review

Reference	Reason for exclusion
Aoun 2006[24]	Not able to obtain
Brown 2005[88]	Delays in obtaining equipment rather than what equipment patients required
Brownlee 2012[91]	What patients thought of augmentative and alternative communication rather than what equipment patients required
Creemers 2014[149]	Procurement of equipment; specific to Netherlands.
Foley 2007[215]	Perceptions of quality of life rather than what equipment patients required
Foley 2011[212]	Abstract of service users' perceptions of services and decision making
Gruis 2010[259]	Abstract of Gruis 2011 paper
Hughes 2005[284]	Experiences of living with MND rather than what equipment patients required
King 2009[324]	Experiences of living with MND rather than what equipment patients required

Reference	Reason for exclusion
Lima 2011[356]	Not qualitative study of what equipment patients required
McDonald 1996[385]	Prescription of environmental control systems rather than what equipment patients required
McNaughton 2001[390]	What patients thought of augmentative and alternative communication rather than what equipment patients required
Sakellariou 2013[501]	Experiences of living with MND rather than what equipment patients required

K.14 Nutrition

Table 73: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelnour 2011[1]	Incorrect study design (not an RCT: case study)
Attanasio 2009[41]	Incorrect population (only 3 patients had ALS; enteral nutrition)
Bae 2012[49]	Incorrect study design (not an RCT: descriptive study)
Clavelou 2013[137]	Incorrect study design (not an RCT: cohort study which did not compare different nutritional or weight management strategies)
Desport 2000[179 178]	Incorrect study design (not an RCT: review)
Desport 2001[179 177]	Incorrect intervention: assessment of nutritional status
Desport 2003[179 180]	Incorrect intervention: assessment of nutritional status
Fondell 2014[221,221]	Not relevant: looking dietary fibre intake and the risk of ALS
Freedman 2013C[225]	Incorrect study design (not an RCT); vitamin E used as prevention for ALS
Good 2014[250,250]	Corhrane review with no included studies
Hubbard 1992[281]	Incorrect study design (not an RCT). Case control with 11 patients looking at plasma glucagon level abnormality.
Jesus 2012[299]	Incorrect intervention: describing nutritional status
Karam 2013[314 313]	Incorrect study design (not an RCT); incorrect intervention (vitamin D as treatment for those with low vitamin D levels)
Kasarskis 2004[316 315]	Incorrect study design (not an RCT: report)
Korner 2013[329 330]	Incorrect study design (not an RCT: case series)
Morassutti 2012[409]	Incorrect study design (not an RCT). Incorrect intervention: monitored with a precise nutritional intervention protocol compared to monitoring before applying the protocol. Incorrect population: a high percentage had enteral nutrition.
Morozova 2008[411]	Incorrect intervention: study looking at associations between consumption of certain foods and ALS
O'Reilly 2013[438]	Incorrect intervention: pre-MND BMI as predictor of late MND onset
Payne 2012[457]	Cochrane review where no studies related to our protocol
Shimizu 2012[518]	Incorrect intervention: nutritional status as predictor of survival
Wills 2014[581]	Incorrect population: patients with enteral nutrition

K.15 Gastrostomy

Table 74: Studies excluded from the clinical review

Reference	Reason for exclusion
Adler 2014[9]	Inappropriate study design: conference abstract
Albert 1999[16,16]	Not relevant to review question: patient preferences to treatment
Allen 2013[18]	No account of confounding
Atassi 2011[39]	Inappropriate comparisons: gastrostomy versus no gastrostomy
Beggs 2010[58]	Not relevant to review question: no relevant outcomes
Blondet 2010[65]	Results not reported in full (p-value only)
Bodger 2010[66]	Not relevant to review question: not guideline population
Braksick 2014[80]	Inappropriate study design: conference abstract
Calver 2009[99]	Not relevant to review question: not guideline population
Chavada 2010[112]	Not relevant to review question: comparison of types of gastrostomy
Chio 1999[118]	No account of confounding
Chio 2004a[120]	No account of confounding
Chio 2012[121]	Results not reported
Czell 2013[161]	No account of confounding
Desport 2005[181]	Not relevant to review question: comparison of types of gastrostomy
Forbes 2004A[222]	Systematic review: no relevant studies
Gledhill 2011[241]	Not relevant to review question. Inappropriate study design: conference abstract.
Gregory 2002[256]	No account of confounding
Janes 2005[290]	Not relevant to review question: not guideline population
Kasarskis 1999[316]	No account of confounding
Labra 2011[340]	Inappropriate study design: conference abstract
Lee 2013[346]	Not relevant to review question: not guideline population
Mitchell 2000[399]	Systematic review: no relevant studies
Mitsumoto2003[400]	Inappropriate study design: conference abstract
Park 2009[454]	Inappropriate study design: conference abstract
Park 2010[455]	Inappropriate study design: conference abstract

Reference	Reason for exclusion
Pena 2012[458]	No account of confounding
Rampoldi 2012[477]	Inappropriate study design: conference abstract
Rio 2005[484]	Not relevant to review question: comparison of types of gastrostomy
Rio 2010[483]	No account of confounding
Sarfaty 2013[505]	No account of confounding
Shaw 2006[515]	No account of confounding
Spataro 2011[526]	No account of confounding
Stanich 2011[531]	Inappropriate study design: conference abstract
Stavroulakis 2013[532,532]	Inappropriate study design for timing of gastrostomy: survey
Thornton 2002[549]	Inappropriate study design: conference abstract
Tsou 2012[554]	Inappropriate study design: conference abstract
Verschueren 2009[570]	No account of confounding

K.16 Communication

Table 75: Studies excluded from the clinical review

Reference	Reason for exclusion
Caligari 2013[98,98]	Incorrect study design (not an RCT or cohort study)
Duffy 2006[192]	Incorrect study design (not an RCT or cohort study)
Kageyama 2014[307,307]	Incorrect study design (not an RCT or cohort study)
Mefferd 2012[391]	Incorrect study design (not an RCT or cohort study)
Riccio 2012[482]	Incorrect study design (systematic review but not of RCTs)
Yunusova 2011[589]	Incorrect study design (not an RCT or cohort study)

K.17 Cough effectiveness

Table 76: Studies excluded from the clinical review

Reference	Reason for exclusion
Aboussouan 1997[2]	Incorrect study design (not an RCT): cohort study of NIV Not patients with ineffective cough
Anderson 2005[21]	Population does not match protocol (neuromuscular diseases); systematic review of controlled trials
Annane 2007[22,22]	Population does not match protocol (neuromuscular diseases and chest wall disorders); nocturnal mechanical ventilation
Bach 2002[47]	Incorrect study design (not an RCT): retrospective review of NIV. Not patients with ineffective cough
Bourke 2006[75]	Incorrect intervention: NIV but not for ineffective cough
Cheagh 2009[113]	Population does not match protocol (not ineffective cough)
Choi 2012[128]	Incorrect study design (not an RCT or cohort study)
Cleary 2013[138]	Incorrect study design (not an RCT): non-randomised crossover study comparing lung volume recruitment to no lung volume recruitment

Reference	Reason for exclusion
Eidenberger[194,194]	Population does not match protocol (not ineffective cough); systematic review
Hadjikoutis 1989[262]	Incorrect study design (narrative review)
Hannan 2014[265]	Systematic review on NIV but not for ineffective cough
Kang 2000[309]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)
Kang 2000A[310]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)
Kim 2011[322]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)
Kleopa 1999[326]	Incorrect study design (not an RCT) of BiPAP >4 hours per day, BIPAP <4 hours per day and no BiPAP
Lange 2006[344]	Population does not match protocol (not ineffective cough)
Matsumura 2012[379]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)
McDermott 2012[384]	On-going study
Pallero 2014[452,452]	Not relevant
Pinto 1999[464]	Incorrect study design (not an RCT); not ineffective cough
Pinto 2004[463]	Incorrect study design: letter to the editor
Pinto 2012[466]	Population does not match protocol (not ineffective cough)
Polkey 1998[467]	Incorrect study design (not an RCT or cohort study); not ineffective cough
Radunovic, 2013[474]	Incorrect intervention: non-invasive ventilation but not for ineffective cough
Rafiq 2014[475,476]	Incorrect study design: abstract and have full paper for this study
Sancho 2003[502]	Incorrect study design (not an RCT), non-randomised crossover study
Sancho 2004[504]	Incorrect study design (not an RCT or cohort study)
Sancho 2010[503]	Incorrect study design (not an RCT or cohort study)
Smith 1998[524]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)
Suleman 2003[539]	Incorrect study design (abstract); no data provided for outcomes
Suleman 2004[538]	Incorrect study design (not an RCT or cohort study); MND patients versus those without MND
Winck 2004[582]	Incorrect study design (not an RCT or cohort study); population does not match protocol (neuromuscular diseases)

K.18 Pharmacological management of breathing difficulties

Table 77: Studies excluded from the clinical review

Study	Reason for exclusion
Barnes 2014[51]	Inappropriate study design (Cochrane review protocol)
Bausewein 2013[54]	Systematic review (no meta-analysis)
Clemens 2008[139]	Incorrect study design. Sample size <20 (n=6).
Cranston 2013[147]	Paper withdrawn
Currow 2007[153]	Inappropriate population
Currow 2011[152]	Inappropriate population

Hosaka 1996[279]	Article not in English (Chinese)
Jennings 2002[296]	Systematic review is not relevant to review question or unclear PICO
Jennings 2012[297]	Paper withdrawn
Noseda 1997[431]	Inappropriate population
Peterson 1996[461]	Inappropriate population
Simon 2010[523]	Systematic review: study designs inappropriate
Yi 2012[586]	Inappropriate study design (Cochrane review protocol)

K.19 Experience of discontinuation of NIV

Table 78: Studies excluded from the clinical review

Reference	Reason for exclusion
Kuhnlein 2008[337]	Quantitative and qualitative study on the process of dying. Non-UK study (Germany).
Ritsma 2010[486]	Not looking at discontinuation of NIV. Non-UK study (Canada).
Goldblatt 1989[242]	Descriptive study of 3 cases. Non-UK study (USA).
Nolan 2008[428]	Quantitative and qualitative study on decision making and self-efficacy at the end of life. Not looking at discontinuation of NIV. Non-UK study (USA).
Sundling 2009[540]	Not looking at discontinuation of NIV
O'Neill 2012[437]	Not looking at discontinuation of NIV
Swash 2012A[541]	Not looking at discontinuation of NIV
McKim 2012[388]	Not looking at discontinuation of NIV

K.20 Management of discontinuation of NIV

Table 79: Studies excluded from the clinical review

Study	Reason for exclusion
Dreyer 2012[190]	Not review population: people with invasive ventilation

Appendix L: Excluded economic studies

None

Appendix M: Cost-effectiveness analysis: Multi-disciplinary care

M.1 Introduction

Motor neurone disease (MND) is a neurological condition that causes neurodegeneration, thus limiting the individual's ability to walk, speak and eventually breathe. There is no known cure for MND so treatment focuses mainly on the control of symptoms as the disease progresses. As MND affects many different aspects of the body (such as speech, swallowing, breathing and mobility) treating MND requires the involvement of many different specialities including, but not limited to: neurologists, physiotherapists, specialist nurses, social workers and dieticians. Over time there has been a trend towards multi-disciplinary care for individuals living with MND. Multi-disciplinary teams (MDTs) combine the expertise across a range of specialities that are involved in the MND treatment. Therefore rather than just see a neurologist and other specialties when needed, as part of the MDT care, the individual with MND will regularly be assessed by a group of specialists who could therefore be in a better position to pre-empt treatments and provide more timely and efficient care. Although the efficacy of MDTs has been well documented in the literature in terms of survival[31,116,495,551] there have been no formal cost-effectiveness analyses of MDTs. The following analysis will weigh up the additional costs associated with providing MDT care against the additional QALY gain from improved survival.

The economic literature review found no studies that formally assessed the cost-effectiveness of MDT care. One cost-comparison study by Van der-Steen[564,564] compared the cost of MDT care in the Netherlands against 'general care'. They found that the cost to the health service of MDT care relative to general care was higher but not of statistical significance. However this finding was limited by the fact it was derived from a non-UK study, thus making the result less generalizable and it did not assess the cost-effectiveness of the intervention.

M.2 Methods

M.2.1 Model overview

M.2.1.1 Comparators

Only two comparators were considered in this economic evaluation:

- General care – currently when an individual is diagnosed with MND the majority of individuals will continue to be reviewed in a general neurology clinic. The neurologist running this clinic would usually have a primary interest that was not MND. The individual would likely be reviewed once or twice a year where monitoring and discussion of future interventions would be discussed.
- MDT care – another type of care that some individuals with MND receive at diagnosis is delivered by a specialist MDT clinic. These clinics comprise of an extended team of specialists whose primary interest is MND. The individual will be regularly reviewed and monitored by this team.

Although the composition of specialist that an MDT comprises of could vary, there was no clinical evidence that specifically evaluated the increased effectiveness of each additional specialist in an MDT. Therefore the MDT composition in the model was the same as what was used in the clinical studies.

M.2.1.2 Population

The population of interest are individuals who have just been diagnosed with MND. It is at this point that the care plan for the individual will be agreed.

M.2.1.3 Time horizon, perspective, discount rates used

The analysis will follow the standard assumptions of the reference case including taking on an NHS/PSS perspective and discounting at 3.5% for costs and health effects. A sensitivity analysis using a discount rate of 1.5% for both costs and health benefits is conducted. A lifetime time horizon has been implemented.

M.2.1.4 Deviations from NICE reference case

There are no deviations from the NICE reference case.

M.2.2 Approach to modelling

The cost-effectiveness of MDT care was evaluated with the use of a discrete event simulation (DES) model.

DESs treat time as a continuous variable and track costs and health outcomes over the course of a simulation. Within this simulation the individual will be exposed to a series of events that can occur at any timepoint throughout the simulation. These events will influence costs and health outcomes and might be re-occurring or only happen once (for example death). The simulation ends once the individual has died or the model has reached its set time horizon. Time-to-event is the key parameter in DESs and these values are often characterised using exponential or Weibull distributions. This is further elaborated on in section M.2.3.

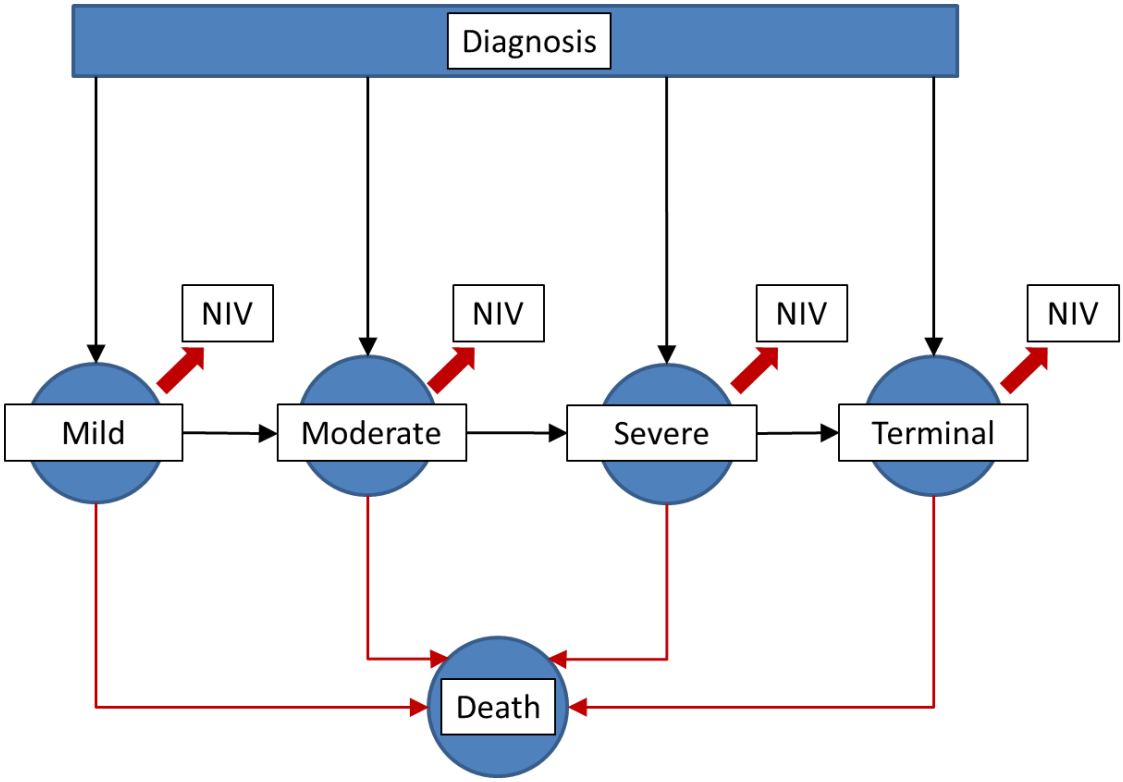
A DES simulation was chosen as the main parameter that informs the clinical effectiveness of MDTs is given as time to event data, in the form of a survival curve. DES can incorporate this statistic more accuraelty into a model than a Markov model, as a Markov model imposes an assumption that the probability of an event occurring remains fixed for a given cycle length.

M.2.2.1 Model structure

Within the model there are three types of event that can occur to the individual with MND: disease progression, non-invasive ventilation (NIV) use and death.

Conceptual design of the model

Figure 111: diagram of DES model



The model starts when the individual is diagnosed with MND. At this point they will either be diagnosed with mild, moderate, severe or terminal MND as defined by Riviere. As time progresses the individual's MND progresses and moves through the states, each state with its own associated cost and health outcomes. At any point the individual can also die and enter the death state, the likelihood of this occurring is influenced by whether or not the individual recieves MDT care and the state they are diagnosed in. Finally at any point of the simulation the individual may receive NIV impacting cost and health outcomes. Transition arrows highlighted in red represent events that are influenced by receiving MDT care. Each of these events that can occur is described in more detail below.

Disease progression

The first subgroup of events concerns disease progression. From symptom onset as time progresses the individual will slowly lose function of several areas including speech, arms and legs. Therefore as the disease progresses the individual's quality of life will also decrease. Likewise costs to the NHS will change as the individual will require differing levels of assessments and support based on what symptoms they have. The progression through these disease states has been captured in the model by implementing a staging system. In the model there are four disease states that the individual could be in at any point in time, including at diagnosis. These have been defined by Rivere[487] as:

- State 1 (mild): mild deficit in only 1 of 3 regions (ie speech, arm and leg); and functionally independent in speech, upper extremity activities of daily living, and ambulation.
- State 2 (moderate): mild deficit in all 3 regions or moderate to severe deficit in 1 region, while the other 2 regions are normal or mildly affected.

- State 3 (severe): needs assistance in 2 or 3 regions; speech is dysarthic and/or patient needs assistance to walk and/or needs assistance with upper extremity activities of daily living.
- State 4 (terminal): non-functional use of at least 2 regions and moderate or non-functional use of the third region.

In the model progression from one disease state to the next is treated as an event. When this event occurs the individual will receive a lower quality of life and likewise the cost of treating the individual will also change, the values associated with each disease state are discussed in sections M.2.3.5 and M.2.3.6. A few things to note, firstly an individual cannot return to a previous state and they can only move to the state immediately following the current one (ie they cannot 'skip' a state). Secondly as there is a delay from symptom onset to diagnosis not all individuals will start in state 1, some will start in state 2 or 3 and a minority will start in state 4. The same study by Rivere et al[487] used for the state definitions also informed the time to progression data, more detail of which is provided in section M.2.3.3. This study also details the proportion of individuals starting in each state.

NIV use

A prominent treatment that is offered to individuals with MND is non-invasive ventilation (NIV). The clinical evidence found that although the timing of when this treatment is offered was the same regardless of what care the individual received (9.5 months for MDT care compared with 10.1 months for general care)[495], the up-take of this treatment was higher for individuals who received MDT care (5% vs 29%, as reported by Aridegbe et al).[31] This could be because the MDT is more likely to offer NIV to patients or because the improved survival in the MDT care group increases the likelihood of surviving long enough for NIV to become an appropriate intervention to consider.

In the model the time when NIV is used is the same for both MDT and general care. However, when this event is due to happen, there is a probability that the individual will eventually receive NIV or not. This probability reflects that individuals as part of the MDT are more likely to be offered NIV at this point in time. This probability is adjusted to account for the improved survival in the MDT arm. To do this the model was run 10,000 times and the overall probability of an individual surviving until the point where NIV is offered was calculated in both the MDT and usual care arms. We then calculated what proportion of individuals who survived would need to receive NIV to be in line with the values estimated in the clinical evidence (29% and 5% for MDT and usual care respectively).

When the individual receives NIV there will be an on-going cost and quality of life increase that lasts until the individual dies (see sections M.2.3.5 and M.2.3.6 for further details). Although use of these treatments in the model will not affect disease progression, any effects on survival will be captured as discussed below.

Death

The final type of event that can occur in the model is death. The evidence identified from the clinical review showed that there was a survival benefit for individuals that receive MDT care.

Time to death throughout the model was dependent on the intervention received and on the initial disease stage when the individual entered the model. For example, if the individual entered the model at the mild MND stage, the time to death associated with the mild stage was applied throughout their time spent in the model, also after they progressed to other stages. This is because the survival for individuals starting in a specific stage already takes into account the possible disease progression throughout time. Details on what data were used and how it was extrapolated is reported in section M.2.3.2 below.

M.2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; the model is then run for 10,000 trials using these values. Mean costs and mean QALYs were then calculated. The model was run repeatedly – model inputs were sampled 5,000 times and for each of these samples the model underwent 10,000 trials.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 80 and in the relevant input summary tables in Section M.2.3.1. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 80: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = $Alpha \times [(1-mean)/mean]$
Hazard ratio	Beta	Bounded between 0 and 1. Although a hazard ratio could go beyond 1, there is no logical reasoning as to why MDT care would increase the chance of death, therefore a beta distribution was deemed most appropriate. Alpha and Beta values were calculated as follows: Alpha = $mean^2 \times [(1-mean)/SE^2] - mean$ Beta = $Alpha \times [(1-mean)/mean]$
Probabilities and proportions	Beta	Bounded between 0 and 1. Derived using event data given in the clinical studies. Alpha and Beta values were calculated as follows: Alpha = (number of events) Beta = (sample size) – (number of events)
Costs of NIV	Gamma	Bounded at 0, positively skewed. Derived from mean and its standard deviation. Alpha and Beta values were calculated as follows: Alpha = $(Mean^2/SD^2)$ Lambda = $(Mean/SD^2)$
Cost of MND care	Lognormal	Where appropriate, the lognormal distribution may provide a better fit than the gamma distribution for costs. The natural log of the mean was calculated as follows: Mean = ln(mean cost) − $SE^2/2$ Where the natural log of the standard error was calculated by: SE = [ln(upper 95% CI) − ln(lower 95% CI)]/(1.96×2)

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE),
- the resource, including cost of staff, required to implement each strategy (assumed to be fixed according to national pay scales and programme content)
- the distribution around survival, as the main variable of interest is the difference in survival between the two interventions, which is varied probabilistically using the hazard ratio.

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

M.2.3 Model inputs

M.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the GDG. A summary of the model inputs used in the base-case (primary) analysis is provided in **Table 81** below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 81: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Events				
Median time to disease progression from mild to moderate (months)	3.29	Weibull	Shape=0.8 Scale=5.1	Rivere et al[487]
Median time to disease progression from moderate to severe (months)	8.25	Weibull	Shape=1.14 Scale=10.76	Rivere et al[487]
Median time to disease progression from severe to terminal (months)	6.33	Weibull	Shape=1.51 Scale=8.34	Rivere et al[487]
Median time to death for mild severity (months)	22.91	Weibull	Shape=0.82 Scale=34.91	Rivere et al[487]
Relative risk of death for moderate severity MND	1.2	-	-	Rivere et al[487]; GDG opinion
Relative risk of death for severe severity MND	1.68	-	-	Rivere[487]; GDG opinion
Relative risk of death for terminal severity MND	4.18	-	-	Rivere et al[487]; GDG opinion
Hazard ratio of survival for MDT relative to general care	0.51	Beta	α=36.51, β=35.08	Aridegbe et al[31]
Median time to being offered NIV (months)	10.1	Weibull	Shape=8.38 Scale=11.63	Rooney et al[495]; GDG opinion
Quality of life				

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Mild severity MND	0.63	Beta	α=30.32, β=17.81	Green et al[255]
Moderate severity MND	0.56	Beta	α=33.36, β=26.21	Green et al[255]
Severe severity MND	0.41	Beta	α=31.14, β=69.31	Jones et al[304]
Terminal severity MND	0.27	Beta	α=57.79, β=204.89	Jones et al[304]
Cost (annual in £)				
Mild severity MND	1978	Lognormal	meanlog=7.59, sdlog=0.05	Munsat et al[416]
Moderate severity MND	1212	Lognormal	meanlog=7.10, sdlog=0.05	Munsat et al[416]
Severe severity MND	2671	Lognormal	meanlog=7.89, sdlog=0.04	Munsat et al[416]
Terminal severity MND	5160	Lognormal	meanlog=8.55, sdlog=0.33	Munsat et al[416]
NIV	3149	Gamma	Mean=3149, SE=1334	NICE NIV guideline CG105[420]
MDT	1275	lognormal	meanlog=7.0, sdlog=0.50	Aridegbe et al[31], GDG opinion, PSSRU[154]
General care	352	-	-	Aridegbe et al[31], NHS reference cost[176]
Riluzole	445	-	-	NHS drug tariff[427]f
Probabilities				
Proportion of individuals receiving NIV - MDT group	0.29	Beta	R=73, N=255	Aridegbe et al[31]
Proportion of individuals receiving NIV - usual care group	0.05	Beta	R=8, N=162	Aridegbe et al[31]
Proportion of extra individuals receiving Riluzole - MDT group	0.89	Beta	R=222, N=255	Aridegbe et al[31]
Proportion of extra individuals receiving Riluzole - usual care group	0.55	Beta	R=88, N=162	Aridegbe et al[31]
Probability of having mild severity MND at diagnosis	0.19	Beta	R=183, N=954	Rivere et al[487]
Probability of having moderate severity MND at diagnosis	0.67	Beta	R=642, N=954	Rivere et al[487]
Probability of having severe severity MND at diagnosis	0.13	Beta	R=120, N=954	Rivere et al[487]
Probability of having terminal severity MND at diagnosis	0.01	Beta	R=9, N=954	Rivere et al[487]

Abbreviations: MDT: multi-disciplinary team; MND: motor neurone disease; NIV: non-invasive ventilation

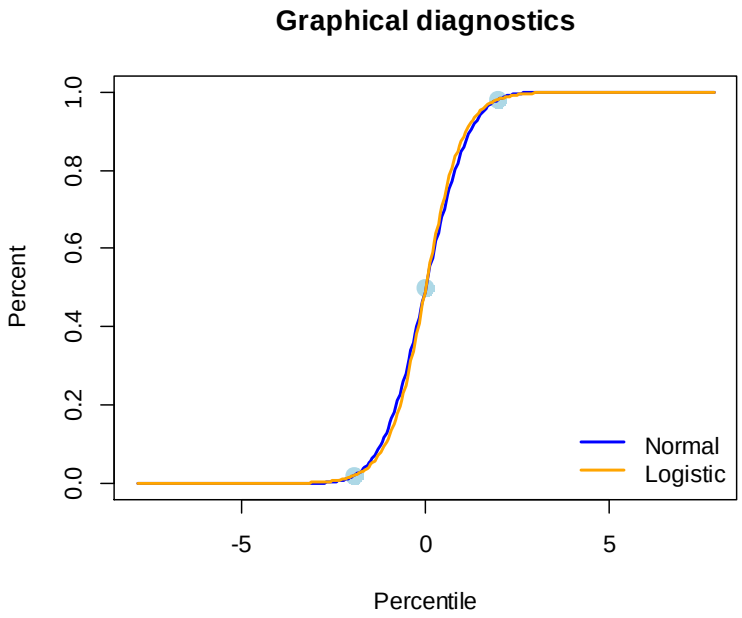
M.2.3.2 Building Weibull distributions using R

To characterise the likelihood of an event occurring over time, Weibull distributions were attached to the clinical data using the package RriskDistributions in R software. The package builds a distribution when you specify what values occur at known quantiles such as the median.

For example if you specify the known quantiles:

(0.02, 0.5, 0.98) = (-1.96, 0, 1.96)

Then the software will fit a distribution that best matches that data set. The data above perfectly reflects a normal distribution and this distribution is fitted as shown in the graph below using the three specified data points:



The outputs from R (R_lambda and R_shape) were used in the model by creating the scale and shape parameters of Weibull distributions as follows:

$Scale_x$ = (1/(R_lambda_x ^ R_shape_x)

$Shape_x$ = R_shape_x

Where R_lambda_x and R_shape_x were the parameters obtained in R for each event in the model (death, disease progression, and NIV use).

In the paragraph below we explain what data were used to inform the Weibull distributions definition for each of these events; the Weibull parameters values derived from this data are reported in Table 81.

M.2.3.3 Data used to build Weibull distributions

Disease progression

For the progression of disease the data on length of time spent in each state is given as a median along with its inter-quartile range in Rivere et al.

Table 82: Time to event for disease progression (months)

	Median	Lower quartile	Upper quartile
Progression to moderate from mild	3.29	1.05	7.59
Progression to severe from moderate	8.25	3.25	14.55
Progression to terminal from severe	6.34	3.71	11

Note: In the study, data is given separately for Riluzole and non-Riluzole users. The weighted average between the two groups was chosen as there appeared to be no statistically significant difference for disease progression between the two.

Therefore the progression to each disease state was characterised by a Weibull distribution using the three point estimates given above. For example a Weibull distribution characterising disease progression from mild to moderate was determined using the following input data:

(0.25, 0.5, 0.75) = (1.05, 3.29, 7.59)

NIV use

The only data point from the clinical evidence given for when NIV is offered was taken from Rooney et al. It was stated that the median time of which NIV is offered is 10.1 months. To turn this into a Weibull distribution the GDG elicited a range to place around this value noting that 95% of cases would occur between 7 and 14 months of diagnosis.

Death

A Weibull distribution was extrapolated from the survival curve for individuals that received MDT care and a hazard ratio was applied to this distribution to reflect survival for individuals that received general care. In the base case the survival curve and hazard ratio were taken from Aridegbe et al.[31] Other survival curves and hazard ratios were explored in sensitivity analyses, more details of which can be found in section M.2.3.4 below.

The survival curve for individuals receiving MDT care is unadjusted for NIV and Riluzole use and therefore any benefits these treatments contribute to survival will have been captured. The survival curve also represents an average survival curve across all disease states. Therefore the Weibull distribution attached to survival was manipulated to allow for differing survival lengths between disease states.

From the study by Riviere et al[487] it was identified what the 'relative risk' of death was for each disease state relative to the mild disease state. This was achieved by calculating how long it would take an individual to reach the death state from mild and comparing this to the time taken from moderate, severe and terminal. For these 'relative risks' to apply the 'average' survival curve needed to be manipulated to represent the survival for an individual who is diagnosed in the mild state. A relative risk ratio was needed that represented the relative risk of death for the average population compared to those with the least severe 'mild' disease. To do this an assumption was first made that the starting composition of disease states is the same in the Aridegbe study identified in the clinical review as it is in the Rivere paper.

Table 83: Data used to calculate the relative risk of death for those with 'mild' MND relative to the general MND population

State	Mild	Moderate	Severe	Terminal
Proportion starting in this state	19%	67%	13%	1%
Relative risk of death compared to mild state	1	1.20	1.68	4.18

Source: Riviere[487]

Using the data in Table 83 above the relative risk of death for an individual who starts the disease as mild can be calculated relative to the average MND population.

$$RR(average_{mild}) = \Pr(starting\ mild) * RR(mild_{mild}) + \Pr(starting\ moderate) * RR(moderate_{mild}) + \Pr(starting\ severe) * RR(severe_{mild}) + \Pr(starting\ terminal) * RR(terminal_{mild})$$

Where Pr is the proportion of patients starting in the indicated state and RR is the relative risk of death of the indicated state compared to the mild state.

Once this value is calculated, the survival in the mild state can be obtained as:

$Survival_{mild} = Survival_{average} / RR(average_{mild})$

Once the survival curve for mild has been established this can be adjusted for disease state by using the relative risks shown in **Table 83** above.

- $Survival_{moderate} = Survival_{mild} * RR(moderate_{mild})$
- $Survival_{severe} = Survival_{mild} * RR(severe_{mild})$
- $Survival_{terminal} = Survival_{mild} * RR(terminal_{mild})$

Therefore those who have a mild form of the disease have the longest survival and this shortens for each step down the disease states. Depending on which disease state the individual starts in determines which survival curve they will start on, this survival curve remains un-altered throughout the simulation and is therefore unaffected by the events such as disease progression and NIV insertion as this has already been incorporated into the survival estimate. The survival benefit derived from MDT care, characterised by the hazard ratio, affects each disease state the same.

M.2.3.4 Effectiveness data on survival

Five retrospective cohort studies were identified in the clinical review conducted for this guideline which calculated the survival benefit derived from MDT care.[31,116,495,551,593] The hazard ratios of mortality in the MDT group compared to usual care identified in three of the studies y Aridgbe, Rooney and Traynor were 0.51, 0.59 and 0.68 respectively. One Italian study by Zoccolella identified the hazard ratio as being 0.91 therefore conferring little benefit.[593] The final study by Chio did not report a hazard ratio but concluded that individuals receiving MDT care survived an additional 305 days, on average, compared to general care.

These studies were not meta-analysed as they were retrospective cohort studies that were influenced by different confounders such as Riluzole, PEG and NIV use. For example in one study by Zoccolella[593], NIV use was not different between the general care and MDT interventions whereas in Aridegbe[31] NIV use was significantly different. The model did not use the adjusted hazard ratios that singled out the survival benefit of just MDT care adjusting for the increased use of NIV and Riluzole

use because MDT care increases the use of these interventions and therefore the costs and health benefits from this need to be captured. Therefore we decided to select one of the studies for the base case and use the others in a sensitivity analysis.

Of these five papers only one was analysed in a UK setting, Aridegbe.[31] Therefore this study was deemed the most appropriate to represent NHS care. The other hazard ratios identified were implemented in a sensitivity analysis. The baseline mortality was estimated for the MDT group as reported in the paragraph above according to the MND stage at diagnosis. In the usual care group the baseline mortality was adjusted by the HR of 0.51 reported in Aridegbe et al at every time point of the model.

M.2.3.5 Utilities

In the model there are four health states the individual could be in and each one has its own associated utility. A systematic search of the literature was conducted to identify studies that measured the utility in people with MND in accordance with the NICE reference case. Three studies were identified that measured EQ-5D in an MND cohort.[100,100,255,255,304]

The first study by Green et al[255] measured EQ-5D in a cohort of individuals sub-grouped by what stage of the disease they were in. The results are shown below:

Table 84: Results from Green et al

Disease state	Mean utility value	Patient reported utility (SG)
Mild	0.63	0.79
Moderate	0.56	0.67
Severe	0.27	0.71
Terminal	-0.01	0.45

Although at first this paper seemed preferable the GDG noted that the data was gathered in 1999. Since then there have been technological advancements that have allowed individuals with MND to live a better quality of life. For example Alternative and Augmentative Communication (AAC) devices have made it easier for individuals with MND to communicate and these have become more sophisticated and widespread. The GDG noted that such interventions would be more widely used for individuals with the severe and terminal states of the disease however quality of life for those with mild and moderate forms of the disease may have remained unchanged. The GDG noted that there was a considerable divergence between patient reported values and values elicited using 'general population' elicited methods, especially in the more severe forms of the disease. This could be partially due to adaptation, whereby the patient becomes more accepting of their illness. However this divergence could also represent an element of quality of life that has been inadequately captured by EQ-5D.

The second study by Calvert et al[100] measured EQ-5D in a German MND cohort more recently in 2009 but did not subgroup by disease state. However it was noted in the paper, due to selection bias, individuals who participated in the study were more likely to have a more severe form of the disease. In fact, in this study 50% of the population were unable to complete daily activities and 95% had at least some problems walking. Only one individual had no problems performing usual activities (1.75%). Therefore the GDG agreed that this cohort mainly comprised of individuals with severe and terminal forms of the illness. The study found that the mean utility value for these individuals was 0.33 with a 95% confidence interval of: (0.22 – 0.4). This value is therefore likely to represent the average utility for the severe state; the lower end of the 95% confidence interval (0.22) could be interpreted as a proxy for the utility of the terminal state.

The third study by Jones et al[304] took EQ-5D values from a randomised controlled trial and extrapolated them to fit disease states in a staging system they produced. The results are shown below:

Table 85: Results from Jones et al[304]

Disease state	Mean utility value	Patient reported values (VAS)
Diagnosis	0.65	0.7165
Stage 2: Involvement of second region	0.53	0.6707
Stage 3: Involvement of third region	0.41	0.5976
Stage 4: Need for intervention (gastrostomy/NIV)	0.27	0.5675

Both diagnosis and stage 2 produce utility values very similar to Green et al. However stage 3 and stage 4 have quite different values. The first thing to note is that we are assuming that stage 3 and the 'severe' disease state are describing the same patient, likewise for stage 4 and 'terminal'. The GDG felt based on the description of the states the quality of life values were likely to be similar. The main reason for this divergence in quality of life could be explained through quality of life improvements for individuals living with MND since 1999 when the Green et al data was gathered.

Therefore considering the improvement in the QoL in the more severe stages since the publication of Green et al the GDG agreed it would be sensible to use the quality of life estimates for severe (stage 3) and terminal (stage 4) from the Jones study. Therefore an assumption imposed here is that stage 3 and stage 4 as described in Table 85 can be seen as a proxy for severe and terminal as described by Riviere et al.[487]

Finally it was noted that patient reported utilities, using standard gamble and VAS methods, were significantly higher than general population elicited methods across all studies. For example in Green et al[255] the quality of life for terminal as valued by the general population methods was -0.01. The same disease state was valued at 0.45 using the patient elicited methods. One reason why this could be is because EQ-5D potentially downgrades the quality of life due to its limited option of answers. For example an individual in a wheelchair is neither 'confined to bed' nor 'has some problems walking about'. However they are more likely to put themselves in the latter category. An MND patient would therefore interpret this aspect of their disease differently than those who are just viewing the disease state as 'confined to bed'. Therefore it was acknowledged that quality of life measurements using EQ-5D were likely to underestimate the quality of life of individuals living with MND.

A utility improvement was given to individuals who received NIV. This value was calculated by observing the SF-6D quality of life data taken from Bourke et al[75] and how this data was interpreted in the model built for the NICE NIV guideline.[420] It was noted that quality of life mainly affected the mental wellbeing aspect of quality of life. Looking at the EQ-5D tariff a one-step improvement from some problems to no problems in anxiety/depression improves quality of life by 0.07. A two-step improvement from severe problems to no problems improves quality of life by 0.236. Due to the large amount of uncertainty surrounding this value a conservative 0.05 improvement in quality of life was chosen for individuals who received NIV in the model.

No disutility or additional QoL values were used for other events in the model and no QoL improvement due to MDT care were assigned to that group. This assumption was addressed in a sensitivity analysis.

M.2.3.6 Resource use and costs

Health states

In the model there are four defined disease states, each with its own resource implications. A systematic search of the literature identified six studies that measured the costs of MND care to the health service in an OECD non-US setting.[126,298,367,416,564] Table 86 below shows the results from the review. A study by Collony et al[143] is presented separately in Table 87 as they give a full resource breakdown that has been cost using UK sources.

The drug cost in each study has been removed as these studies were assessed prior to Riluzole's patent expiring meaning it is now significantly cheaper. Although this means the cost of drugs other than Riluzole would also have been excluded, these costs would likely make up a small portion of the total cost. This process was not conducted in Munsat as Riluzole was not in widespread use in 1996 when the costs were gathered so the cost of other drugs will have been included in this cost. The cost of Riluzole is considered in the model and adjusted to account for the difference in usage between MDT and general care.

In the table below all costs for non-UK studies were converted into GBP using the OECD purchasing power parities (PPPs). This adjusts currencies for purchasing power as well as exchange rate. Finally all costs have been inflated to 2014 using healthcare specific inflation indices taken from the PSSRU publication Unit costs for health and social care. This process has been conducted to make the costs as comparable as can be.

Table 86: Cost of MND care

	Disease state, cost per year (2014 GBP)				
Study (setting, date when costs were gathered)	**Mild**	**Moderate**	**Severe**	**Terminal**	**Details**
Chiò (Italy, 2003)	£799	£2,196	£3,494	£5,041-£5,291	This study attaches costs to its own 5 stage staging system. The cost of each of these stages has been placed in the most appropriate stage used in the Riviere staging system. The final two stages have both been placed in terminal.
Van de-Steen (Netherlands, 2003)	£4,685				This study only reports a mean cost for general care for all individuals with MND. The cost of appliances which was cost at £19,340 per year has been excluded as it is unclear whether this is a one-off or recurring cost. The exclusion of appliance costs is discussed below.
Jenum (Denmark, 2009)	£9,456				This study only reports a mean cost for general care for all individuals with MND. This cost was mostly comprised of inpatient treatment, which accounted for £7,904 of the cost. This is significantly more than any other study. It is worth noting this cost includes non-MND related inpatient costs, however this still does not explain the large difference.
Lopez (Spain, 2003)	£2,433		£3,980		This study subgroups the cost of MND care into 'low severity' (not needing any additional support) and 'high severity' (defined as

	Disease state, cost per year (2014 GBP)				
					whether they need caregiver support to perform daily activities).
Munsat, (UK, 1996)	£1,978	£1212	£2,671	£5,160	This is the only UK study and the only study to subgroup costs according to stage as defined in Riviere et al. This is the only study where drug costs have not been excluded as Riluzole was not in widespread use. The cost of medication for the mild state was £98 going up to £272 for the terminal state. The study notes that costs decrease for the moderate state as there will be more screening examinations and monitoring reviews in the individuals first year since diagnosis.

A recent study by Collony et al[143] measured resource use of individuals with MND in Ireland. They separated out costs that are incurred by the MDT. The breakdown of resource use associated with care that occurs outside of the MDT is given below along with the associated UK cost.

Table 87: resource use and costs associated with treating MND across an individual's lifetime, excluding MDT costs.

Resource	Units	Unit cost	Total cost (unit * unit cost)	Source
GP visits	7	£37	£259	PSSRU[155]
Physiotherapist visits	12	£52	£624	NHS reference costs 2013-14[176]
Public health nurse visits	24	£43	£1,032	PSSRU[155]
Occupational therapist visits	6	£74	£444	NHS reference costs 2013-14[176]
Speech therapist visits	6	£84	£504	NHS reference costs 2013-14[176]
Dietitian	1	£80	£80	NHS reference costs 2013-14[176]
Number of home care hours funded by NHS[(a)]	122-486	£24	£2,916 - £11,664	PSSRU[155]
Number of palliative care hours	174	£30	£5,220	PSSRU[155]
Number of outpatient appointments	3	£174	£522	NHS reference costs 2013-14[176]
Number of accident and emergency visits	1	£135	£135	NHS reference costs 2013-14[176]
Number of inpatient admissions	1	£2,706	£2,706	NHS reference costs 2013-14[176]
		Total (lifetime)	£14,442 - £23,190	
		Total (per year)[(b)]	£4,951 - £7,950	
		Total (per year, excluding palliative care)	£3,160 - £6,161	

a) The GDG noted that not all individuals with MND would receive NHS funded home care. In some instances individuals will fund this themselves or a personal carer will forefill this role. In other cirsumtances this care will be funded by a third party such a charity. The GDG noted that the NHS could fund this care as low as 25% of the time thus representing the range of values used here.

b) The study stated that the mean life expectancy was 2.9 years hence the yearly cost is the total cost divided by 2.9

The first thing to note is that palliative care costs are only incurred once in the last phase of the individual's life. The rest of these costs are recurring and can occur from the beginning of the disease onset right up until death. As palliative care costs are a one-off cost that are incurred regardless of how long the individual survives for they will be the same for both MDT care and general care and therefore can be excluded for this analysis. The range of costs calculated in Table 87 as £3,160 - £6,161 is unadjusted for disease severity and simply represents a mean annual cost. Regardless, this mean cost falls within the same ranges shown in Table 86.

As the study by Munsat was the only UK study and also measured costs according to the models defined disease states, the GDG acknowledged they were the most appropriate costs to use. It was also noted that apart from the study by Jenum, costs were not too dissimilar across the studies therefore justifying the use of the Munsat figures. The study also gave a minimum and maximum cost for each disease state. This range was used to form a lognormal distribution using the Rriskdistribution package mentioned above.

The GDG noted that resource use associated with equipment use is likely to be much higher now. However this would be a one-off non-recurring cost that could apply equally to MDT and general care. Although there are arguments that MDT care would lead to higher equipment use there is no data to accurately account for this in the model. Firstly costing equipment is difficult as there is a variety of differing types of equipment that range vastly in cost with each piece of equipment individualised to the person with MND. Some individuals may receive an advanced costly piece of equipment whilst others may receive a much simpler and cheaper device as it is more appropriate for the individual. Secondly equipment can be used multiple times lowering the cost per patient. Finally differential equipment use would also likely lead to differing quality of life between the two types of care and this has not been captured in the model.

The clinical reviews did find a significant difference between NIV and Riluzole use between the two types of care and these additional costs have been considered in the model as mentioned above. The cost of Riluzole was taken from the NHS drug tariff while the annual cost of NIV was taken from the NICE guideline on NIV use from 2010. See also **Table 81**.

Incremental cost of MDT care vs cost of usual care

In addition to the MND stage-specific costs, which are assumed to be representing the cost of usual care, the additional cost of MDT was added to this group.

The cost of MDT care was cost by the GDG using expert consensus. The MDT was cost to match the professional composition in the Abridge study used from the clinical review, as this formed the clinical evidence of the model and also represented current NHS care. The GDG identified two components of the MDT that required healthcare professional's time. Firstly there was the time associated with keeping up to date with patient records that were part of the MDT. Secondly there was a dedicated time spent with the patient. The timings dedicated to each activity are given below.

Table 88: Cost of MDT clinic

Healthcare professional	Cost per hour[(a)]	Minutes spent outside of patient contact, dedicated to MDT per 9 weeks [(b)] (range)	Minutes spent at dedicated MDT patient meetings per 9 weeks [(b)] (range)
Neurologist	£101.00	3 (0 – 10)	20 (10 - 30)

Healthcare professional	Cost per hour[(a)]	Minutes spent outside of patient contact, dedicated to MDT per 9 weeks [(b)] (range)	Minutes spent at dedicated MDT patient meetings per 9 weeks [(b)] (range)
Specialist nurse	£42.00	6 (5 - 30)	20 (10 - 30)
Physio (hospital)	£32.00	2 (1 - 10)	20 (10 - 30)
Occupational therapist	£32.00	2 (1 - 10)	20 (10 - 30)
Speech/language therapist	£32.00	2 (1 - 10)	20 (10 - 30)
Respiratory physiologist	£94.00	2 (1 - 10)	20 (10 - 30)
Dietitian (hospital)	£31.00	2 (1 – 10)	5 (2 - 10)
Social worker	£40.00	2 (1 - 10)	5 (2 - 15)
TOTAL (annual)		£101.01	£634.59

(a) Source: PSSRU
(b) Source: GDG expert opinion

On top of the costs associated with the MDT clinic the GDG noted that the cost of an extended outreach team would also need to be considered. The extended outreach team would visit the individual with MND in between clinic visits.

Table 89: Cost of MDT extended outreach team

Healthcare professional	Cost per hour(a)	Hours spent in between clinic visits (range)	Number of MDT visits per year
Community outreach staff[(a)]	£30.00	3 (1 - 8)	6
TOTAL (annual)			£540

(a) It was noted that this could include a variety of community staff such as an occupational therapist
(b) Source: PSSRU, GDG opinion

Therefore the total cost of MDT care combining the costs in Table 88 and Table 89 is £1,275.61

A gamma distribution was attached to this value using maximum and minimum ranges around the point estimate derived above. This range was estimated to be £547 - £2888. This was derived by estimating the cost using all the lowest point estimates and then again using all the highest point estimates. A lognormal distribution was built using Rriskdistributions and assuming this range covered the 95% confidence interval around the mean.

The GDG agreed that if the individual was not part of an MDT the individual would likely receive two neurological outpatient visits per year which were cost at £176 per visit in the NHS reference costs. This was the level of care that was apparent in the 'general care' arm of the Aridegbe study. Therefore the incremental cost of receiving MDT care is £923.61.

It is worth noting that a study by Van de Steer[564] found the incremental cost of MDTs, relative to general care, to be on average £573 more per year. This cost takes into account any changes in healthcare professional time outside of the MDT and any differences in unscheduled healthcare utilisation. Therefore our estimates fall within a sensible range.

M.2.4 Computations

The model was constructed in TreeAge 2015 and was evaluated by micro-simulation. DES functionality is only usable in the most recent version of TreeAge pro 2015.

Costs and outcomes were adjusted by the time unit defined by the time to event data; as event occurrence was defined in terms of months, annual costs and utility values were divided by 12.

The QALY is calculated by taking into account how long an individual spends in each health state before they die. The length of time they spend in each state is then weighted by the corresponding utility value. For example half a year spent in the mild state with a utility of 0.63 is 0.315 QALYs. QALYs were then discounted to reflect time preference (discount rate 3.5%). The total discounted QALYs were the sum of the discounted QALYs per time period spent in each state.

Costs were calculated in the same way as QALYs. The time spent in each state was weighted by the corresponding annual cost. The cost of MDT care is constant throughout the model. Costs were discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$$

Where:
r=discount rate per annum
n=time (years)

M.2.5 Sensitivity analyses

Table 90: sensitivity analyses

Analysis	Parameter	Description	Values	Comment
S1	Hazard ratio, NIV use, Riluzole use	Another study by Rooney, identified in the clinical review, found that the survival benefit from MDT care was slightly smaller than what was used in the base case analysis. They also found the gap between NIV use and Riluzole use to be slightly smaller. Therefore the model was re-run using these values to populate the model.	Hazard ratio: 0.59 Riluzole use MDT: 90% Riluzole use 'general care': 80% NIV use MDT: 31% NIV use 'general care': 15%	Unlike the values used for the base case analysis the cohort of individuals with MND was taken from the same time therefore temporal changes that may affect mortality will not impact the results.
S2	Hazard ratio, NIV use, Riluzole use	Another study by Zoccolella, identified in the clinical review, found that the survival benefit from MDT care was much smaller than what was used in the base case analysis. They also found there was no gap between NIV use between the two types of care and the proportion of individuals on Riluzole was much smaller.	Hazard ratio: 0.91 Riluzole use MDT: 66% Riluzole use 'general care': 43% NIV use MDT: 2.5% NIV use 'general care': 2.5%	.
S3	Quality of life for mild, moderate, severe, terminal elicited from standard gamble techniques.	One limitation identified by the GDG was the quality of life values used for the different disease states. The use of EQ-5D has been criticised as a tool of valuing quality of life in an individual with MND. Therefore patient elicited EQ-5D values were used in this analysis.	Quality of life for: Mild: 0.79 Moderate: 0.67 Severe: 0.71 Terminal: 0.45	The GDG noted that quality of life increasing in the 'severe' state could be plausible as the individual would more likely have access to equipment that could improve their standards of

Analysis	Parameter	Description	Values	Comment
				living.
S4	Quality of life for mild, moderate, severe, terminal elicited from standard VAS.	The same study that evaluated quality of life in SA3 also measured quality of life using visual analogue scales (VAS). The model was re-run using these values.	Quality of life for: Mild: 0.74 Moderate: 0.63 Severe: 0.51 Terminal: 0.37	It is preferable in economic evaluations to use quality of life measures that have been elicited using 'preference based' measures meaning standard gamble techniques are favoured over VAS.
S5	Cost of MDT	This sensitivity analysis was constructed to see whether the cost of the MDT or the cost of prolonged survival was the main driver of cost-effectiveness.	Cost of MDT: £0	As the MDT prolongs survival, which increases costs to the NHS, this will impact the cost-effectiveness of any life extending intervention. This sensitivity analysis aims to calculate how much of an impact this will have on the model results.
S6	Cost of MDT	This sensitivity analysis increased the cost of MDT care by 50% from the base case value.	Annual cost of MDT care: £1,912	
S7	Quality of life from MDT	A study by Vandenberg et al showed that there was a quality of life impact on patients attending an MDT. The study found that MDTs had a significant impact on an individual's mental well-being. The EQ-5D tariff attaches a -0.071 reduction in quality of life for a one step decrease in anxiety and depression. Therefore a conservative 0.05 increase in quality of life from MDT care was implemented in the model.	Quality of life increase across all disease states: 0.05	
S8	Hazard ratio	Concerns were raised over the hazard ratio calculated in the Aridegbe paper due to the two cohorts being from a different time cohort. Therefore over time care might change that improves survival and therefore mortality measured in a later cohort may be lower due to reasons other than the introduction of MDT care. The	HR: 0.59	This hazard ratio assumes that interventions such as Riluzole use and NIV are the same in both types of care. However this analysis assumes that the difference in use remains the

Analysis	Parameter	Description	Values	Comment
		study runs a multivariate analysis that controls for all factors that significantly improve survival and produces a hazard ratio of MDT care that is adjusted for these variables.		same therefore the costs remain the same but the survival benefits are taken away. This will under-estimate the cost-effectiveness of MDT care.

M.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of all the model calculations.

M.2.7 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A

Cost-effective if:

- ICER < Threshold

NICE's report 'Social value judgements: principles for the development of NICE guidance'[419] sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

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

Above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of the intervention as an effective use of NHS resources will specifically take account of the following factors:

- The degree of certainty around the ICER.
- The presence of strong reasons indicating that the assessment of the change in the quality of life has been inadequately captured, and may therefore misrepresent, the health gain.
- When the intervention is an innovation that adds demonstrable and distinct substantial benefits that may not have been adequately captured in the measurement of health gain.

M.3 Results

M.3.1 Base case

The results below in Table 91 show that MDT care is not cost-effective at a £20,000 per QALY threshold. The costs associated with MDT care are significantly higher than just the cost of the MDT itself which only costs the NHS, on average, £1275 per year. This shows that the majority of the costs are due to increased survival and the increased use of Riluzole and NIV.

Table 91: Probabilistic base case results

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£4,598	0.49
MDT	£14,394	0.86
Difference	£9,796	0.37
ICER	£26,672 per QALY	

M.3.2 Sensitivity analyses

Results from SA1

The results from re-running the analysis using data from Rooney is shown in Table 92 below.

Table 92: Results from SA1: using data from Rooney et al

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£6,083	0.55
MDT	£14,269	0.84
Difference	£8,185	0.29
ICER	£28,030 per QALY	

Using data from Rooney to inform survival and NIV use has a small impact on the model results. Although a lower survival benefit will reduce the health benefits derived from MDT care, the costs associated with longer survival will also not be incurred which limits the impact of reducing this parameter. Likewise reducing the gap between NIV use reduces the cost difference between the two types of care but also reduces the QALY difference. Finally a reduced difference between Riluzole use narrows the gaps on cost but this may be the contributing factor for the smaller hazard ratio. Overall using these values makes MDT care slightly less cost-effective however this sensitivity analysis shows that the model results are robust to changes in key parameters taken from different sources.

Results from SA2

The results from re-running the analysis using data from Zoccollela is shown in Table 94 below.

Table 93: Results from SA2: using data from Zoccollela et al

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£8,904	0.76
MDT	£12,224	0.82
Difference	£3,321	0.06
ICER	£57,524 per QALY	

Using data from Zoccolella to inform survival, Riluzole and NIV use has a large impact on the model results. Zoccolella found that the survival benefit from MDT care was very small. Therefore the

additional QALYs gained from MDT care are now much smaller relative to the base case. It is worth noting that the cost differential between the two interventions is now significantly smaller as the additional costs incurred with improved survival are incurred for a much shorter length of time.

Results from SA3

The results from using patient elicited VAS quality of life scores are shown below.

Table 94: Results from SA3

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£4,500	0.59
MDT	£14,047	1.05
Difference	£9,547	0.46
ICER	£20,791 per QALY	

Using patient VAS elicited quality of life utility values from Green et al shows that MDT care is now nearly cost-effective at a £20,000 per QALY threshold. This shows that the quality of life the individual receives during the period of prolonged survival is crucial in determining the cost-effectiveness of MDT care.

Results from SA4

The results from using patient elicited standard gamble quality of life scores are shown below.

Table 95: results from SA4

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£4,629	0.71
MDT	£14,436	1.28
Difference	£9,806	0.56
ICER	£17,387 per QALY	

Using patient elicited standard gamble quality of life utility values from Green et al shows that MDT care is now a cost-effective intervention at a £20,000 per QALY threshold. This shows that the quality of life the individual receives during the period of prolonged survival is crucial in determining the cost-effectiveness of MDT care.

Results from SA5

The results from assuming that there are zero costs associated with the MDT are shown below.

Table 96: Results from SA5

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£11,762	0.50
MDT	£4,673	0.87
Difference	£7,000	0.37
ICER	£19,045 per QALY	

This result shows that even if the cost associated with the MDT were zero, this involves the MDT clinic costs and the 'extended outreach team' cost; MDT care would only just be cost-effective at a £20,000 per QALY threshold. This shows the cost of the MDT itself is a smaller driver in what is influencing the cost-effectiveness results.

Results from SA6

The results from increasing the costs associated with the MDT by 50% are shown below.

Table 97: Results from SA6

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£4,758	0.50
MDT	£16,179	0.87
Difference	£11,421	0.37
ICER	£30,828 per QALY	

This result shows that drastically increasing the cost of MDT pushes the ICER above £30,000 per QALY. However the increase in the ICER from £27,000 in the base case is not drastic, given the considerable increase in cost.

Results from SA7

The results from assuming a small quality of life increase from MDT care is shown below.

Table 98: results from SA7

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£4,600	0.49
MDT	£14,256	0.96
Difference	£9,656	0.29
ICER	£20,469 per QALY	

A small quality of life benefit has a large impact on the cost-effectiveness of MDT care. This small quality of life benefit nearly makes MDT care cost-effective at a £20,000 per QALY threshold.

Results from SA8

The results from re-running using the adjusted hazard ratio from Aridegbe are shown in Table 99 below.

Table 99: Results from SA8

Intervention	Average costs per patient	Average health outcomes (QALYs)
General care	£5,525	0.85
MDT	£14,301	0.55
Difference	£8,775	0.30
ICER	£28,876 per QALY	

When the hazard ratio is increased to 0.59 from 0.51 MDT care remains cost-effective at a £30,000 per QALY threshold. This is a highly biased sensitivity analysis as the cost differences of NIV and Riluzole remain but the survival benefit is taken away.

M.4 Discussion

M.4.1 Summary of results

The results show that although MDT care is not cost-effective at a £20,000 per QALY threshold in the base case, there is significant uncertainty surrounding this finding as detailed in the sensitivity analyses. Firstly, as discussed in section M.2.3.5, there are strong reasons to believe that the quality of life of individuals with MND has been undervalued in this model. This is demonstrated by the large

differences that arise in quality of life estimates generated by those who have MND and general public as shown in both Green and Jones. When patient elicited quality of life measures are used, as shown in sensitivity analyses 3 and 4, the ICER falls to £17,387 and £20,791 per QALY respectively. Although patient elicited quality of life measures are likely to be higher as the individual adapts to the condition, they are also fully aware of the limitations of the condition. EQ-5D is also likely to bias against the quality of life for individuals with MND due to the broadly defined categories whereby a description of the individual's health state will likely fall in all of the lowest categories whereas the individual with MND knows that they would more likely fall somewhere between the middle and lowest stage for each dimension. Therefore valuations by the general public will undervalue quality of life.

Secondly, as detailed in Vandebal, there are good reasons to believe that MDT care could also improve quality of life. When a small increase in quality of life is attatched to individuals receiving MDT care the ICER falls to £20,469 per QALY, as shown in sensitivity analysis 7. Therefore a small combined effect of improving quality of life of individuals with MND and adding a small quality of life impact of MDT care would likely cause the ICER to fall below £20,000 per QALY.

Finally, it is possible that the quality of life associated with NIV has been underestimated. Due to the lack of any robust data in the literature a conservative estimate was chosen for this parameter.

The results show that one of the main drivers of cost-effectiveness is the additional costs incurred through prolonged survival. By significantly improving survival the NHS incurs the associated costs of treating MND. Sensitivity analysis 6 showed that even if the cost of MDT was zero then it would only just be a cost-effective intervention. This issue is known as zero price cost effectiveness, whereby the costs associated with additional survival prevent the intervention from being cost-effective, even at zero cost. This issue was explored recently by Davies et al and although they conclude that these additional costs are important to consider, as they represent the true opportunity cost of the intervention, additional considerations need to take place:

"Firstly there may be a lack of evidence meeting the NICE reference case for health state utility valuations on which to base utility estimates leading to an underestimation of the direct health benefits to patients. Secondly, generic measures of health utility may fail to detect differences in quality of life that are important to patients particularly at the end of life. Thirdly, the reference case allows for all health benefits to be included whether they fall to patients or to others such as carers."

Davis (2014)[163], page 29.

As previously discussed in relation to point one there are strong reasons to believe that quality of life has been undervalued. With regards to point two, especially in the 'terminal' disease state in the model, unique benefits to end of life will have been missed in the health utility estimation used in the base case analysis. Finally with regards to point three the costs associated with MND care have significant impacts on career quality of life that is not incorporated into the analysis. Therefore taking sensitivity analyses 3 and 4 in mind along with the fact that the ICER is below £30,000 per QALY in the base case it is likely that MDT care is a cost-effective intervention, under the NICE reference case.

M.4.2 Limitations and interpretation

One limitation of the model is the observational evidence used to inform the survival and additional interventions parameters. Unlike randomised controlled trials, observational evidence is prone to selection bias. With regards to MDT care there is a concern that individuals who are more likely to survive longer will receive MDT care, therefore those with a more severe form of the condition will more likely receive general care. However this issue is less likely to be of concern in the Rooney paper as they have run a controlled experiment whereby the only difference between the cohorts is the area of Ireland in which they live. This will limit the extent to which selection bias will influence the results however all confounders cannot be controlled for. It is worth noting that across four

different studies, known confounders such as age and site-onset (such as bulbar or spinal) were not significantly different between the two cohorts. Secondly across four different populations the results were mostly the same. Although Zoccolella found that MDT care generated little survival benefit, this finding appeared to be an outlier and the GDG noted that the MDT care was significantly different from what was done in other studies. This was highlighted by the insignificant difference in NIV use which was apparent in all other studies for example. As an RCT is unlikely to ever be conducted to accurately capture this benefit, observational data is the best data available to make an informed decision over the cost-effectiveness of MDT care. The model also shows that unless survival is significantly different from what is used in the base case, MDT care remains cost-effective at a £30,000 per QALY threshold.

It is worth noting that as the hazard ratio decreases the cost between the two interventions will decrease for three reasons. The first reason is that the additional costs associated with prolonged survival become smaller. Secondly the difference between Riluzole and NIV use will likely become smaller and the finally the cost associated with the MDT itself will decrease as it is likely that the smaller the hazard ratio the more similar the level of care is between the two interventions. Therefore reducing the hazard ratio in the model, ceteris paribus, will severely underestimate the cost-effectiveness of MDT care.

The model does not attempt to account for additional costs or cost savings that arise through changes in health care professional time commitments that occur outside of the routine MDT care. First of all there is reasoning to believe that MDTs will increase the amount of time healthcare professionals spend with the patient outside of their MDT duties. For example by monitoring weight loss more extensively the individual is more likely to have early referral to a dietician and therefore spend more time with them had they not been part of an MDT. However there is also good reasoning to believe that MDTs will reduce health care professional time commitments, for example pre-empting potential problems will prevent unscheduled healthcare utilisation. A paper by Chio found that individuals who attended MDT care spent less time in the hospital. The only study to directly compare costs of MDT care to general care is by Van der Steen. The study found that MDTs cost slightly more than general care, however the difference was not of statistical significance. This suggests these additional costs and cost savings are likely to balance out and the main costs associated with MDTs are simply the direct costs of running the MDT as opposed to future downstream costs.

Finally as previously discussed it is likely that quality of life has been undervalued. Given the model incorporates the full costs incurred for treating an individual with MND this significantly biases the study as the full costs do not reflect the quality of life that is seen by both the individual with MND and the carer. This is highlighted by showing any life extending intervention is only just cost-effective at a £20,000 per QALY threshold at a zero cost.

These limitations have been tested in sensitivity analyses and show that the model's results are robust to changes that make MDT care less cost-effective, such as reducing survival from MDT care and increasing costs. Whilst the model results are robust to changes that make MDT care less cost-effective they are very sensitive to changes that make MDT care more cost-effective such as changes to quality of life. What this shows is that the base case model results can be seen as very conservative and MDT care is likely to be more cost-effective than what is described in the base case.

M.4.3 Comparisons with published studies

This is the first analysis to formally consider the cost-effectiveness of MDT care in an MND population.

M.4.4 Conclusions

The base case model results show that at a £30,000 per QALY threshold MDT can be considered a cost-effective intervention once explicit consideration is given to the undervaluation of quality of life.

M.4.5 Implications for future research

As previously discussed it is unlikely that a controlled trial will ever be conducted to determine the exact benefits MDT care provides. It is also unlikely that the results from such a study would change any conclusions drawn from the model. The main area for additional research would be to gather additional clinical evidence on the value a specialty adds to the MDT. If this evidence was gathered there would be scope to evaluate the cost-effectiveness of different compositions of MDT care.

Appendix N: Research recommendations

N.1 Cognitive assessment

Research question:

What is the impact of assessing for cognitive and behaviour change in people with MND on clinical practice, the person and their family and carers? Does repeated assessment provide more benefit than assessment at a single point at diagnosis?

Why this is important:

Clinic-based and population-based studies demonstrate that up to 15% of people with MND havefrontotemporal dementia. A further third of people with MND have changes in behaviour and cognition. These impairments are present at diagnosis. Their course during the disease has shown varying patterns between studies although several studies have shown that cognitive and behavioural impairments predict poorer survival and increased carer burden. A randomised controlled trial is needed to assess whether formal assessment at diagnosis and/or repeated assessment improves clinical practice, subsequent care of the person and quality of life for the person, their family and carers.

Criteria for selecting high-priority research recommendations:

PICO question	Population: A prospective, multi-centre trial with patients diagnosed with MND who are attending specialist MND MDT clinics, or under review by a consultant neurologist or acute admission. Intervention: Cognitive and behaviour screening at diagnosis and at repeated intervals, for example 3 or 6 months. Comparison: Comparator groups include, no screening, screening at diagnosis only, screening at repeated intervals (for example 3 months and 6 months). Outcomes: Identification of specific cognitive and behaviour impairment, effect of cognitive and behaviour impairment on daily functioning, subsequent changes in care resulting from identification of impairment, perceptions of care and quality of life of patients and carers. Identification of progression of specific cognitive and behaviour changes through repeated screening during the course of the illness, effect of impairment on daily functioning, subsequent changes in care, perceptions of care and quality of life for patients and carers resulting from further identification of cognitive and behaviour change.
Importance to patients or the population	Cognitive and behavioural impairment in MND may be hidden by severe physical disability. Early identification of these changes can ensure streamlining of care into appropriate clinical pathways. Patients, carers and clinicians can be given appropriate education on the nature of these changes and relationship to MND and on specific problems the person with MND may encounter. A more tailored patient centred approach to care can then be applied with for example adjustments made on communication aids, supporting the learning of new interventions, supporting decision making processes such as in end of life care. Support can also be provided to the carer specifically on these changes to ease burden of care.
Relevance to NICE guidance	Research in this area would inform the NICE on the most beneficial and cost effective approach for providing cognitive and behaviour screening for MND patients. The research is essential to inform future updates of key recommendations in

	the guideline.
Relevance to the NHS	Research in this area would clarify the costs and benefits of investing in NHS screening of MND patients for cognitive and behaviour change.
National priorities	No relevant national priorities
Current evidence base	There is evidence that cognitive screening is sensitive to the cognitive impairments detected through extensive neuropsychological assessment, but no evidence is available on how this may change clinical practice and the subsequent impact on the patients and carers. There is also currently no evidence on whether repeated cognitive assessment will provide further beneficial information during the course of the illness.
Equality	None identified.
Study design	Multicentre randomised control trial, on assessment of impact of screening on clinical practice, the patient and the carer, comparing patients who have undergone cognitive screening at different repeated intervals or not undergone screening. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	This proposed research should be able to be carried out within a realistic timescale and cost.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.2 Prognostic tools

Research question:

Is the ALS Prognostic Index an accurate predictor of survival in people with MND under NHS care in England and/or Wales?

Why this is important:

Accurate predictions of survival in people with MND would be of great use to clinicians and to the person with MND, their family and carers. Accurate predictions would enable people with MND to be clearer about their prognosis, make plans for the rest of their life and have a well-prepared and dignified transition into the end of life phase. Family members would similarly benefit in terms of the ability to be more aware of the likely progression and prepare themselves for the death of their loved one.

Accurate predictions of survival would enable professionals to create and deliver more effective management and care plans and access services when it is most appropriate, for example specialist palliative care.

The ALS Prognostic Index (ALS-PI) was developed in a cohort of people with ALS in the Republic of Ireland and externally validated in a cohort in Italy. However, it has not been validated in people with ALS, primary lateral sclerosis or progressive muscular atrophy in the NHS in England or Wales. The tool needs to be validated in a UK population using a simplified measure of executive function.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Newly diagnosed adults with MND under NHS care in England or Wales. Prognostic test: ALS Prognostic Index (ALS-PI). Reference standard: Survival.

	Outcomes: Accuracy of tool in predicting good or poor prognosis. Exclusions: Patients with not clearly defined / diagnosed MND/ALS. Subgroups/Stratify: Frontotemporal dementia.
Importance to patients or the population	Accurate predictions would enable people with MND to make plans for the rest of their life and aid in having a well-prepared and dignified transition into the end of life phase. Family members would similarly benefit in terms of the ability to plan better and prepare themselves for the death of their loved one.
Relevance to NICE guidance	Research in this area would support and likely modify the recommendation on monitoring disease progression within the NICE MND guideline.
Relevance to the NHS	Accurate predictions of survival would facilitate healthcare professionals and carers in creating and delivering more effective management and care plans. Plans that take into account the person with MND's disease trajectory and make the best use of resources, ensuring that the most effective equipment is provided in an appropriate way. This includes accessing services when it is most appropriate, for example, specialist palliative care.
National priorities	Accurate predictions of survival may help in enabling patients to undertake advance care planning.
Current evidence base	The ALS Prognostic Index (ALS-PI) was designed to be used in a busy clinical setting and to be employed at the first clinical consultation. The tool uses three variables: site of disease onset; ALSFRS-R slope (a measure of speed of progression); and executive dysfunction to categorise people into low, medium and high risk groups.
Equality	The tool which has been developed only applies to adults with MND, and would not be applicable to children. However MND in children is extremely rare.
Study design	This would likely be best served by a multicentre prospective cohort study. However if the correct information had already been gathered then a retrospective cohort study could be appropriate.
Feasibility	This proposed research should be feasible within a realistic timescale and cost.
Other comments	The ALS-PI development involved more extensive assessment of cognitive function than would be possible in routine clinical settings. The value of alternative simpler assessments of cognitive function need to be assessed before the tool could be used in routine practice.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.3 Saliva

Research question:

How is excessive drooling of saliva (sialorrhoea) managed in people with MND?

Why this is important:

Sialorrhoea affects up to 50% of people with MND and in 42% of these individuals the symptom is poorly controlled. There is no evidence base for clinicians to make decisions with regards to the various treatment options available. Anticholinergics are used first-line but there is no evidence to inform which anticholinergic to use and at what dose. Botulinum toxin is used second- or third-line although there is little evidence to guide dosing, which salivary glands to inject and which type of botulinum toxin to use. Currently there is no baseline information about how specialists are using these treatments and this information is required to inform comparative studies.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with MND and sialorrhoea.

	Intervention: All current treatments for sialorrhoea (registry study). Outcomes: Quality of life; patient-reported outcome measures.
Importance to patients or the population	Sialorrhoea is a distressing symptom that is poorly controlled.
Relevance to NICE guidance	Research in this area would support or appropriately modify the NICE recommendations on sialorrhoea in MND which are based on clinical principles and expert opinion due to the lack of direct evidence.
Relevance to the NHS	Would help improve patient outcomes and reduce NHS costs.
National priorities	None identified
Current evidence base	There is no evidence base for clinicians to make decisions with regards to the various treatment options available. Anticholinergics are used first-line but there is no evidence to inform which anticholinergic and at what dose. Botulinum toxin is often used third- or second-line. Again there is little evidence to guide dosing, which salivary glands to inject and which type of botulinum toxin to use.
Equality	No issues identified
Study design	A prospective cohort study is the most appropriate design given the complexities of the potential treatment options. Standardised data collection and an appropriate outcome measure for quality of life and saliva-related symptoms should be used.
Feasibility	The proposed research can be carried out in a realistic timescale and at an acceptable cost.
Other comments	None.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.4 Nutrition

Research question:

Does a high calorific diet prolong survival of people with MND if initiated following diagnosis or following initiation of feeding using a gastrostomy?

Why this is important:

There is little specific guidance on the optimal calorie intake for people with MND. There is growing evidence that people with MND have a hypercatabolic state and have high energy requirements. A large cohort study in the UK has demonstrated that nearly half of people continue to lose weight following gastrostomy and most show no improvement in their weight. A small study has demonstrated that high fat and high carbohydrate feeding may prolong survival in gastrostomy-fed people. A larger randomised trial is needed to inform clinical practice.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with ALS/MND Intervention: High-calorie diet Comparison: Current standards of care Outcomes: Survival, quality of life, BMI
Importance to patients or the population	Weight loss in people with MND is associated with poor survival. There are two key time points in the course of MND for which there is paucity of data to indicate how to nutritionally-manage patients: at the time of diagnosis when patients can still feed orally, and then later after the insertion of a gastrostomy. The literature indicates that there are potential advantages in terms of survival for patients receiving high-calorie diets and that despite insertion of gastrostomy patients still lose weight.

Relevance to NICE guidance	Research in this area would support or appropriately modify the NICE recommendations on nutrition in MND which are based on clinical principles and expert opinion due to the lack of direct evidence.
Relevance to the NHS	Research in this area would help to improve patient outcomes.
National priorities	No relevant national priorities.
Current evidence base	A large cohort study has demonstrated that patients have poor nutritional outcomes post-gastrostomy. The reasons for these outcomes are unknown. A small pilot randomised controlled trial has demonstrated improved survival in patients receiving high-fat or carbohydrate diets following gastrostomy. This has not been repeated on a larger scale or been explored as an intervention earlier in the disease process.
Equality	None identified.
Study design	• A pragmatic randomised controlled trial comparing high-calorie diet from diagnosis. • A pragmatic randomised controlled trial of high-calorie diet following insertion of a gastrostomy.
Feasibility	This proposed research should be feasible within a realistic timescale and cost.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.5 Augmentative and alternative communication

Research question:

What is the current pattern of provision and use of augmentative and alternative communication (AAC) by people with MND in England?

Why this is important:

Appropriate AAC equipment can have a significant effect on quality of life for people with MND. While the NHS has a responsibility to provide equipment and ongoing support in its use, there are no reliable data on the types of equipment found most useful at different stages of the disease process, or the number of people with MND who may benefit from AAC. A prospective census study of people with MND presenting with early onset of speech problems is needed to establish the current baseline provision and needs of this population and how best to utilise AAC equipment. The programme will begin with the collection and analysis of basic data. It will then progress to patient related outcomes.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults with MND with observable motor speech symptoms (dysarthria). Intervention: Collection of information about assessment, provision and monitoring of augmentative and alternative communication (AAC) equipment/systems by an NHS AAC hub service including hub and spoke elements of service. Outcomes: Service delivery patterns across England, quality of life and patient reported outcomes at regular stages of disease and AAC use. Exclusions: speech and/or language difficulties arising from co-morbidities such as aphasia due to stroke. Severe cognitive problems preventing engagement with consent to participate.
Importance to patients or the population	Benefits to patients will include more appropriate and equitable AAC equipment recommendations through the development of MND-AAC assessment pathways and protocols. Through the development of patient related outcomes there will

	be a much closer match between functional use requirements and what equipment is actually supplied. An England-wide study will also contribute to improving the equity of service provision across the country. Results would inform future recommendations for, or against, the use of AAC specialist hubs for people with MND-related communication needs. They would also inform more efficient service provision and more informed outcome measures.
Relevance to NICE guidance	The impact of new NHS specialist AAC hubs on the communication and quality of life of people with MND has yet to be established. The research is essential to inform future updates of key recommendations in the guideline.
Relevance to the NHS	AAC provision and support for people with MND is currently delivered by local services or in collaboration with specialist AAC hubs. Benefits to the NHS will include greater transparency of AAC equipment provision for this specific patient group and a reduction in inappropriate and untimely equipment provision through a better understanding of patient reported outcomes. The results will have relevance to strategic planning and service delivery.
National priorities	The NSF for long-term conditions (2005) clearly identified the need to provide Equipment in Quality requirement 7. QR 7 has recognised the role of electronic assistive technology in improving quality of life, enhancing independence, and in selected cases improving opportunities for employment.
Current evidence base	The current evidence base for outcomes for people with MND using AAC is very weak, based on single or small group studies. Existing UK service use/provision data are unreliable. There have been no prior prospective census studies of MND-AAC use and/or provision.
Equality	People with significant communication disabilities are often excluded from research due to the perceived challenges of participation. This research recommendation will address patient reported outcomes and experiences.
Study design	A prospective study collecting information from all 15 AAC specialised hubs to describe the current baseline for MND-AAC equipment and service provision. The data to be collected should include detailed demographics (age, symptoms at onset and assessment, speech severity/intelligibility and quality of life ratings, referral sources, referral point since onset/diagnosis), the specific equipment recommended and provided by non-specialist and specialist services and information on equipment use and returns. Data collection should be supplemented with information from patients and their carers about equipment use, including consideration of important patient outcomes.
Feasibility	There are 15 commissioned NHS specialist hubs in England. It is considered feasible to create a standard MND-AAC review and data collection system for these hubs and to collect census data over a 24-month period.
Other comments	Collaboration with third sector organisations such as the MNDA would be appropriate given their importance as a third sector provider of AAC equipment.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.6 Cough augmentation

Research question:

How does cough peak flow and the use of cough augmentation techniques to enhance cough efficacy correlate with respiratory outcomes and quality of life in people with MND?

Why this is important:

Cough is commonly impaired in people with MND due to respiratory muscle weakness. Ineffective cough can lead to problems with secretion and can contribute to morbidity and mortality in MND patients. Cough peak flow (CPF) values of greater than 160 L/min have been suggested as necessary to clear the lungs adequately and have been suggested as a value for severe cough impairment. It has been suggested that when CPF is below 270 L/min in medically-stable patients they are at risk of respiratory failure due to the inability to clear airway debris at the time of a respiratory infection. A prospective cohort study is required to examine the association between cough and respiratory and patient outcomes.

The aim would be to explore if early assessment and cough augmentation strategies (either as individual techniques or in combination) aimed at maintaining CPF above the critical values of 270 L/min and 160 L/min decreases the number of chest infections, antibiotic use, episodes of respiratory failure, delays the onset of NIV initiation, improves the patients subjective cough efficiency and improves patient and carer quality of life.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People diagnosed with MND. Intervention: Prospective collection of respiratory muscle strength (MIP, MEPS SNIP), Norris Bulbar Score, CPF, spirometry, blood gases, overnight oximetry and time from initial referral until NIV initiation will also be recorded. Patients will have baseline CPF values/ SF36 /Cough questionnaire undertaken and thereafter and on a 3 monthly basis at clinic review for the duration of the study (1 year). Outcomes: Patients will be asked to keep a diary of number of chest infections/duration of chest infections SpO2 /and cough severity/cough VAS. Carers will be asked to complete the Carer Strain Scale /Caregiver Strain Index at baseline and on a 3 monthly basis. Once CPF falls below the critical value of 270L/min then patients will be offered cough assist strategies to optimise an effective cough to CPF of greater than 270L/min as part of standard practice.
Importance to patients or the population	Evidence of usefulness of CPF as a simple measure of cough effectiveness would allow use of this tool as an indicator for the initiation of cough augmentation techniques in this population. Earlier intervention to raise CPF above threshold limits could reduce the number of respiratory infections, emergency hospital admissions and associated costs including antibiotic use and improve patient and carer quality of life.
Relevance to NICE guidance	Research in this area would inform or appropriately modify the NICE MND recommendations on cough augmentation techniques which are based on poor quality research, abstract information and clinical consensus due to the lack of direct evidence in this patient group.
Relevance to the NHS	Research in this area would clarify the costs and benefits of investing in cough augmentation strategies with probable significant reduction in overall costs.
National priorities	No relevant national priorities.
Current evidence base	There is limited validated evidence to support the use of CPF as an indicator for initiating cough augmentation techniques to be effective in reducing clinical problems and costs, specifically with the MND population. Bach (2002) demonstrated in a retrospective study that the combination of non-invasive ventilation and mechanical-assisted coughing implemented at the point when CPF reduced below the value of 270L/min in medically-stable patients improved survival and delayed the need for tracheostomy ventilation in MND patients. However, Sancho et al (2004) suggested these values should be used with caution as no prospective studies have been undertaken to support the

	retrospective work, despite these values being widely used and accepted in currently clinical practice.
Equality	None identified.
Study design	A prospective, multi-centre cohort study is required to collect this information and provide some evidence.
Feasibility	This proposed research is feasible in the UK within a realistic timescale and cost.
Other comments	The findings would inform current treatments and provide information for a subsequent randomised controlled trial.
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

N.7 Exercise programmes

Research question:

What is the clinical and cost-effectiveness of prescribing exercise in people with MND to improve their quality of life and reduce functional decline and fatigue?

Why this is important:

MND patients are often advised to avoid physical activity in order to minimise overwork muscle damage and fatigue. However deconditioning secondary to reduced activity can compound the muscle weakness, and deconditioning caused by MND impacts on independence, quality of life and carer burden. Two RCTs were appraised in a recent Cochrane (2013) meta-analysis. The studies were of low quality but indicate that both aerobic and resistance exercise programmes produced a significant mean improvement in the ALSFRS measure of function without effect on quality of life, muscle soreness or fatigue. A large randomised controlled trial is required to determine whether exercise is beneficial of harmful for people with MND.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People with MND (probable or definite diagnosis of MND). Subjects should have a FVC of 90% predicted or greater and an ALSFRS score of 30 or greater. Intervention: Individually prescribed, structured and closely monitored resistance exercise and aerobic exercise. Comparison: Current standards of rehabilitation/normal levels of daily activity. Outcomes: SF-36, ALSFRS, Fatigue Severity Scale, Pain VAS, Manual Muscle Strength Testing (0-5 Medical Research Scale/Oxford Scale). Ashworth Spasticity Scale, LFT.
Importance to patients or the population	Anecdotal evidence suggests that regular, structured exercise programmes that are non-fatiguing results in short-lived improvements in function with a positive effect on disability and quality of life with no adverse effects. Implementation of exercise in the early stage of this disease can reduce the associated complications, i.e. functional decline associated with deconditioning which may maintain mobility and functional and occupational independence for a longer period, preserving a person's quality of life and social contribution.
Relevance to NICE guidance	Research in this area would support or appropriately modify the NICE recommendations on exercise programmes. The limitations of the current body of research prevent the results being generalised to the MND population as a whole.
Relevance to the NHS	Research in this area would enhance the evidence based related to exercise therapy for patients with MND and clarify whether exercise prescription is harmful for people with MND. Such a study would determine the consequent reduction or delay in the need for assistance with (P)ADLs, adaptive equipment,

	carer burden and financial costs to health and social care.
National priorities	No relevant national priorities.
Current evidence base	Although there is some limited evidence that suggests there are benefits of regular aerobic and resistance exercise training programmes in people with MND, the findings of these studies cannot be applied to the wider MND population. Data from these studies also refute the current clinical concerns regarding the disadvantages of exercise programmes for this patient group. Conclusions from these studies cannot be generalised to the wider population due to limited research with human subjects, small sample sizes, high drop-out rates or retrospective nature of the studies.
Equality	None identified.
Study design	A multi-centre randomised controlled trial. Power calculations should be conducted to establish the required sample size of the trial. It is important that the study is adequately powered to detect a clinically important effect size.
Feasibility	This proposed research is feasible within a realistic timescale and cost. Consideration should be made to limit drop-out rates during the duration of the study. Exercise programs would have to be individually prescribed and structured and closely monitored to account for patient tolerance/limitations.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix O: How this guideline amalgamates with NICE guideline CG105

CG105 recommendations	Action	Comments
1.1.1 A multidisciplinary team should coordinate and provide ongoing management and treatment for a patient with MND, including regular respiratory assessment and provision of non-invasive ventilation. • The team should be led by a healthcare professional with a specific interest in MND. The leader should ensure that the patient's multidisciplinary care plan (see recommendation 1.1.19) is coordinated and is communicated to relevant healthcare and social care professionals, including the patient's primary care team, as well as to the patient and (where appropriate) their family and carers. • The team should include a neurologist, a respiratory physician, an MND specialist nurse, a respiratory specialist nurse, a specialist respiratory physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist (team members do not have to be at the same location). • Access to other healthcare professionals should be provided as needed. • Team members who provide non-invasive ventilation should have appropriate competencies.	Deleted. Replaced with new recommendations for MDT care.	1.5.1 Provide coordinated care for people with MND, using a clinic-based, multidisciplinary team approach. **[new 2016]** 1.5.2 The multidisciplinary team should: • include healthcare professionals and social care practitioners with expertise in MND, and staff who see people in their home • ensure effective communication between all healthcare professionals and social care practitioners involved in the person's care and their family members and/or carers (as appropriate) • carry out regular, coordinated assessments at the multidisciplinary team clinic (usually every 2–3 months) to assess people's symptoms and needs. **[new 2016]** 1.5.3 The multidisciplinary team should assess the following: • Weight, diet, nutritional intake, feeding and swallowing (see recommendations 1.10.1–1.10.10). • Muscle problems, such as weakness, stiffness, cramps (see recommendations 1.8.1–1.8.9). • Physical function, including mobility and activities of daily living (see recommendations 1.9.1–1.9.8). • Saliva problems, such as drooling of saliva (sialorrhoea) and thick, tenacious saliva (see recommendations 1.8.10–1.8.15). • Speech and communication (see recommendations 1.11.1–1.11.6).

CG105 recommendations	Action	Comments
		• Cough effectiveness (see recommendations 1.12.1–1.12.4). • Respiratory function (see section 1.13). • Pain and other symptoms, such as constipation. • Cognition and behaviour (see recommendations 1.3.1–1.3.3). • Psychological support needs (see recommendations 1.6.1–1.6.4). • Social care needs (see recommendations 1.6.5–1.6.6). • Information and support needs for the person and their family members and/or carers (as appropriate). **[new 2016]** 1.5.4 The core multidisciplinary team should consist of healthcare professionals and other professionals with expertise in MND, and should include the following: • Neurologist • Specialist nurse • Dietitian • Physiotherapist • Occupational therapist • Respiratory physiologist or a healthcare professional who can assess respiratory function • Speech and language therapist. **[new 2016]** 1.5.5 The multidisciplinary team should have access to the following services: • Clinical psychology and/or neuropsychology. • Social care. • Counselling. • Respiratory medicine • Specialist palliative care. • Gastroenterology. **[new 2016]** 1.5.6 Tailor the frequency of the multidisciplinary team assessments to the person's

CG105 recommendations	Action	Comments
		symptoms and needs, with more or less frequent assessments as needed. **[new 2016]** 1.5.7 Ensure arrangements are in place to trigger an earlier multidisciplinary team assessment if there is a significant change in symptoms identified by family members and/or carers (as appropriate), or healthcare professionals. **[new 2016]** 1.5.8 Tailor the multidisciplinary team assessment to the person's needs, for example, adjust the format if the person has cognitive or behaviour changes or difficulties with communication. **[new 2016]** 1.5.9 Inform all healthcare professionals and social care practitioners involved in the person's care about key decisions reached with the person and their family members and/or carers (as appropriate). **[new 2016]** 1.5.10 Ensure that all healthcare professionals and social care practitioners involved in the person's care are aware that MND symptoms may get worse quickly, and that people with MND will need repeated assessment. Priority should be given to ensuring continuity of care and avoidance of untimely case closure. **[new 2016]**
1.1.2 Offer to discuss the possible use of non-invasive ventilation with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times: • soon after MND is first diagnosed • when monitoring respiratory function • when respiratory function deteriorates	Unchanged	Unchanged

CG105 recommendations	Action	Comments
• if the patient asks for information.		
1.1.3 Discussions should be appropriate to the stage of the patient's illness, carried out in a sensitive manner and include information on: • the possible symptoms and signs of respiratory impairment (see table 1 in recommendation 1.1.7) • the natural progression of MND and what to expect in the future • the purpose, nature and timing of respiratory function tests, and explanations of the test results • available interventions for managing respiratory impairment, including the benefits and limitations of each intervention • accessing and using respiratory equipment, including that for non-invasive ventilation • how non-invasive ventilation (as a treatment option) can improve symptoms associated with respiratory impairment and can be life prolonging, but does not stop progression of the underlying disease • how non-invasive ventilation can be withdrawn • palliative strategies as an alternative to non-invasive ventilation.	Amended to include specific reference to non-invasive ventilation and ensure consistency with new recommendations on information about non-invasive ventilation.	1.14.2 Discussions about non-invasive ventilation should be appropriate to the stage of the person's illness, carried out in a sensitive manner and include information on: • the possible symptoms and signs of respiratory impairment (see table 1) • the purpose, nature and timing of respiratory function tests, and explanations of the test results • how non-invasive ventilation (as a treatment option) can improve symptoms associated with respiratory impairment and can be life prolonging, but does not stop progression of the underlying disease. **[2010, amended 2016]** 1.13.9 When discussing non-invasive ventilation, explain about the different ways that people can manage their breathlessness symptoms. This should include: • non-invasive ventilation, and its advantages and disadvantages • using non-invasive ventilation at different points in the course of the person's lifetime • the possibility of the person becoming dependent on non-invasive ventilation • options for treating any infections • support and information on how to recognise and cope with a distressing situation • the role of medications • psychological techniques and support. **[new 2016]** 1.13.10 Check that the person thinking about non-invasive ventilation: • understands what non-invasive ventilation is and what it can achieve

CG105 recommendations	Action	Comments
		• recognises the need for regular review • has enough information about non-invasive ventilation and other options for breathing problems to make decisions about how and when to use it. **[new 2016]** 1.13.11 Explain that non-invasive ventilation can be stopped at any time. Reassure people that they can ask for help and advice if they need it, especially if they are dependent on non-invasive ventilation for 24 hours a day, or become distressed when attempting to stop it. **[new 2016]**
1.1.4 Inform all relevant healthcare professionals about key decisions reached with the patient and their family and carers.	Deleted as similar recommendation in new guideline	1.5.9 Inform all healthcare professionals and social care practitioners involved in the person's care about key decisions reached with the person and their family members and/or carers (as appropriate). **[new 2016]**
1.1.5 Provide the patient and their family and carers with support and assistance to manage non-invasive ventilation. This should include: • training on using non-invasive ventilation and ventilator interfaces, for example: ○ emergency procedures ○ night-time assistance if the patient is unable to use the equipment independently (for example, emergency removal or replacement of interfaces) ○ how to use the equipment with a wheelchair or other mobility aids if required ○ what to do if the equipment fails • assistance with secretion management • information on general palliative strategies • an offer of ongoing emotional and psychological support[1] for the patient and their family and carers.	Amended. Footnote removed as psychological and social support are included in the new guideline.	1.14.23 Provide the person and their family and/or carers (as appropriate) with support and assistance to manage non-invasive ventilation. This should include: • training on using non-invasive ventilation and ventilator interfaces, for example: ○ emergency procedures ○ night-time assistance if the person is unable to use the equipment independently (for example, emergency removal or replacement of interfaces) ○ how to use the equipment with a wheelchair or other mobility aids if required ○ what to do if the equipment fails • assistance with secretion management • information on general palliative strategies • an offer of ongoing emotional and psychological support for

CG105 recommendations	Action	Comments
		the person and their family and carers. **[2010, amended 2016]**
1.1.6 Ensure that families and carers: • have an initial assessment if the patient they care for decides to use non-invasive ventilation, which should include: ○ their ability and willingness to assist in providing non-invasive ventilation ○ their training needs • have the opportunity to discuss any concerns they may have with members of the multidisciplinary team and/or other healthcare professionals.	Unchanged	Unchanged
1.1.7 Monitor the symptoms and signs listed in table 1 routinely to detect potential respiratory impairment.	Amended. 'Routinely' removed as new recommendations for the multidisciplinary team advise on frequency of assessment.	1.14.7 Monitor the symptoms and signs listed in table 1 to detect potential respiratory impairment. **[2010, amended 2016]**
1.1.8 As part of the initial assessment to diagnose MND, or soon after diagnosis, a healthcare professional from the multidisciplinary team who has appropriate competencies should perform the following tests (or arrange for them to be performed) to establish the patient's baseline respiratory function: • oxygen saturation measured by pulse oximetry (SpO2): ○ this should be a single measurement of SpO2 with the patient at rest and breathing room air ○ if it is not possible to perform pulse oximetry locally, refer the patient to a specialist respiratory service then one or both of the following: • forced vital capacity (FVC) or vital capacity (VC)[2] • sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP).	Unchanged	Unchanged
1.1.9 If the patient has severe bulbar impairment or severe cognitive	Unchanged	Unchanged

CG105 recommendations	Action	Comments
problems that may be related to respiratory impairment: • ensure that SpO2 is measured (at rest and breathing room air) • do not perform the other respiratory function tests (FVC, VC, SNIP and MIP) if interfaces are not suitable for the patient.		
1.1.10 A healthcare professional with appropriate competencies should perform the respiratory function tests every 3 months, although tests may be performed more or less often depending on: • whether there are any symptoms and signs of respiratory impairment (see recommendation 1.1.7) • the rate of progression of MND • the patient's preference and circumstances.	Amended. Time period removed as already included in recommendations for the multidisciplinary team.	1.14.10 A healthcare professional with appropriate competencies should perform the respiratory function tests every 2–3 months, although tests may be performed more or less often depending on: • whether there are any symptoms and signs of respiratory impairment (see table 1) • the rate of progression of MND • the person's preference and circumstances. **[2010, amended 2016]**
1.1.11 Perform arterial or capillary blood gas analysis if the patient's SpO2 (measured at rest and breathing room air): • is less than or equal to 92% if they have known lung disease • is less than or equal to 94% if they do not have lung disease. If it is not possible to perform arterial or capillary blood gas analysis locally, refer the patient to a specialist respiratory service.	Unchanged	Unchanged
1.1.12 If the patient's SpO2 (measured at rest and breathing room air) is greater than 94%, or 92% for those with lung disease, but they have sleep-related respiratory symptoms: • consider referring them to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study and • discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.	Unchanged	Unchanged
1.1.13 If the patient's arterial partial	Unchanged	Unchanged

CG105 recommendations	Action	Comments
pressure of carbon dioxide (PaCO2) is greater than 6 kPa: • refer them urgently to a specialist respiratory service (to be seen within 1 week) and • explain the reasons for and implications of the urgent referral to the patient and (if the patient agrees) their family and carers.		
1.1.14 If the patient's PaCO2 is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnoea (see recommendation 1.1.7): • refer them to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study and • discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.	Unchanged	Unchanged
1.1.15 If any of the results listed in table 2 is obtained, discuss with the patient and (if the patient agrees) their family and carers: • the impact of respiratory impairment • treatment options • possible referral to a specialist respiratory service for further assessment.	Amended. Wording changed for consistency and to emphasise patient choice for referral.	1.14.15 If any of the results listed in table 2 is obtained, discuss with the person and (if appropriate) their family and carers: • their respiratory impairment • their treatment options • possible referral to a specialist respiratory service for further assessment based on discussion with the person, and their wishes. **[2010, amended 2016]**
1.1.16 Base decisions on respiratory function tests for a patient with a diagnosis of dementia on considerations specific to their needs and circumstances, such as: • their ability to give consent[3] • their understanding of the tests • their tolerance of the tests and willingness to undertake them • the impact on their family and carers • whether they are capable of receiving non-invasive ventilation.	Amended for consistency without change in meaning. 'dementia' changed to 'frontotemporal dementia' and footnote changed to reflect Mental Capacity Act.	1.14.16 Base decisions on respiratory function tests for a person with a diagnosis of frontotemporal dementia on considerations specific to their needs and circumstances, such as: • their ability to give consent[a] • their understanding of the tests • their tolerance of the tests and willingness to undertake them • the impact on their family and carers

[a] See Mental Capacity Act 2005.

CG105 recommendations	Action	Comments
		• whether they are capable of receiving non-invasive ventilation. **[2010, amended 2016]**
1.1.17 Offer a trial of non-invasive ventilation if the patient's symptoms and signs and the results of the respiratory function tests indicate that the patient is likely to benefit from the treatment. • Discuss both the benefits and limitations of the intervention with the patient and their family and carers. • Only consider a trial of non-invasive ventilation for a patient who has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment if they may benefit from an improvement in sleep-related symptoms or correction of hypoventilation.	Amended for consistency with new recommendations. New recommendations developed for information following evidence review on stopping non-invasive ventilation.	1.14.17 Offer a trial of non-invasive ventilation if the person's symptoms and signs and the results of the respiratory function tests indicate that the person is likely to benefit from the treatment. **[2010, amended 2016]** 1.14.18 Consider a trial of non-invasive ventilation for a person who has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment only if they may benefit from an improvement in sleep-related symptoms or correction of hypoventilation. **[2010, amended 2016]** 1.13.9 When discussing non-invasive ventilation, explain about the different ways that people can manage their breathlessness symptoms. This should include: • non-invasive ventilation, and its advantages and disadvantages • using non-invasive ventilation at different points in the course of the person's lifetime • the possibility of the person becoming dependent on non-invasive ventilation • options for treating any infections • support and information on how to recognise and cope with a distressing situation • the role of medications • psychological techniques and support. **[new 2016]** 1.13.10 Check that the person thinking about non-invasive ventilation: • understands what non-invasive ventilation is and

CG105 recommendations	Action	Comments
		what it can achieve • recognises the need for regular review • has enough information about non-invasive ventilation and other options for breathing problems to make decisions about how and when to use it. **[new 2016]** 1.13.11 Explain that non-invasive ventilation can be stopped at any time. Reassure people that they can ask for help and advice if they need it, especially if they are dependent on non-invasive ventilation for 24 hours a day, or become distressed when attempting to stop it. **[new 2016]**
1.1.18 Before starting non-invasive ventilation, the multidisciplinary team should carry out and coordinate a patient-centred risk assessment, after discussion with the patient and their family and carers. This should consider: • the most appropriate type of non-invasive ventilator and interfaces, based on the patient's needs and lifestyle factors • the patient's tolerance of the treatment • the risk, and possible consequences, of ventilator failure • the power supply required, including battery back-up • how easily the patient can get to hospital • risks associated with travelling away from home (especially abroad) • whether a humidifier is required • issues relating to secretion management • the availability of carers.	Unchanged	Unchanged
1.1.19 Before starting non-invasive ventilation, the multidisciplinary team should prepare a comprehensive care plan, after discussion with the patient and their family and carers (who should be offered a copy of the plan). This	Amended. Part of last bullet point deleted as replaced by recommendations on Planning for end of life.	1.14.20 Before starting non-invasive ventilation, the multidisciplinary team should prepare a comprehensive care plan, after discussion with the person and their family and carers (who should be offered a

CG105 recommendations	Action	Comments
should cover: • long-term support provided by the multidisciplinary team • the initial frequency of respiratory function tests and monitoring of respiratory impairment • the frequency of clinical reviews of symptomatic and physiological changes • the provision of carers • arrangements for device maintenance and 24-hour emergency clinical and technical support • secretion management and respiratory physiotherapy assessment, including cough-assist therapy (if required) • training in and support for the use of non-invasive ventilation for the patient and their family and carers • regular opportunities to discuss the patient's wishes in relation to continuing or withdrawing non-invasive ventilation, and other end-of-life considerations (see also recommendations 1.1.24 and 1.1.25).		copy of the plan). This should cover: • long-term support provided by the multidisciplinary team • the initial frequency of respiratory function tests and monitoring of respiratory impairment • the frequency of clinical reviews of symptomatic and physiological changes • the provision of carers • arrangements for device maintenance and 24-hour emergency clinical and technical support • secretion management and respiratory physiotherapy assessment, including cough-assist therapy (if required) • training in and support for the use of non-invasive ventilation for the person and their family and carers • regular opportunities to discuss the person's wishes in relation to continuing or withdrawing non-invasive ventilation. **[2010, amended 2016]**
1.1.20 When starting non-invasive ventilation: • perform initial acclimatisation during the day when the patient is awake • usually start regular treatment at night, before and during sleep • gradually build up the patient's hours of use as necessary.	Unchanged	Unchanged
1.1.21 Continue non-invasive ventilation if the clinical reviews show: • symptomatic and/or physiological improvements for a patient without severe bulbar impairment and without severe cognitive problems • an improvement in sleep-related symptoms for a patient with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment.	Unchanged	Unchanged

CG105 recommendations	Action	Comments
1.1.22 Discuss all decisions to continue or withdraw non-invasive ventilation with the patient and (if the patient agrees) their family and carers.	Unchanged	Unchanged
1.1.23 Before a decision is made on the use of non-invasive ventilation for a patient with a diagnosis of dementia, the neurologist from the multidisciplinary team should carry out an assessment that includes: • the patient's capacity to make decisions and to give consent[3] • the severity of dementia and cognitive problems • whether the patient is likely to accept treatment • whether the patient is likely to achieve improvements in sleep-related symptoms and/or behavioural improvements • a discussion with the patient's family and/or carers (with the patient's consent if they have the capacity to give it).	Amended to update wording and reflect changes to law. 'dementia' changed to 'frontotemporal dementia' and footnote changed to reflect Mental Capacity Act.	1.14.25 Before a decision is made on the use of non-invasive ventilation for a person with a diagnosis of frontotemporal dementia, the multidisciplinary team should carry out an assessment that includes: • the person's capacity to make decisions and to give consent[b] • the severity of dementia and cognitive problems • whether the person is likely to accept treatment • whether the person is likely to achieve improvements in sleep-related symptoms and/or behavioural improvements • a discussion with the person's family and/or carers (with the person's consent if they have the capacity to give it). **[2010, amended 2016]**
1.1.24 Offer to discuss end-of-life care with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times: • around the time that MND is first diagnosed (but only if requested by the patient explicitly, or if the patient's clinical condition indicates that ventilator support will be needed in the immediate future) • when non-invasive ventilation is accepted or declined • when the patient is becoming increasingly dependent on non-invasive ventilation • if the patient asks for information.	Deleted and replaced with recommendations on Planning for end of life.	1.7.1 Offer the person with MND the opportunity to discuss their preferences and concerns about care at the end of life at trigger points such as: at diagnosis, if there is a significant change in respiratory function, or if interventions such as gastrostomy or non-invasive ventilation are needed. Be sensitive about the timing of discussions and take into account the person's current communication ability, cognitive status and mental capacity. **[new 2016]** 1.7.2 Think about discussing advance care planning with people at an earlier opportunity if you expect their communication ability, cognitive status or mental capacity to get worse. **[new 2016]**

[b] See Mental Capacity Act 2005.

CG105 recommendations	Action	Comments
		1.7.3 Consider an early referral to a specialist palliative care team for people with significant or complex needs, such as psychological or social distress or rapidly progressing symptoms. **[new 2016]** 1.7.4 Provide support and advice on advance care planning for end of life to the person with MND and their family members and/or carers (as appropriate). The discussion should include: • What could happen at end of life, for example how death may occur. • Providing anticipatory medicines in the home. • Advance care planning, including Advanced Decisions to Refuse Treatment (ADRT) and Do Not Attempt Resuscitation (DNACPR) orders, and Lasting Power of Attorney. • Areas that people might wish to plan for, such as: ○ what they want to happen (for example preferred place of death) ○ what they do not want to happen (for example being admitted to hospital) ○ who will represent their decisions, if necessary ○ what should happen if they develop an intercurrent illness. **[new 2016]** 1.7.5 Offer people the opportunity to talk about ADRT, DNACPR and Lasting Power of Attorney when interventions such as gastrostomy and non-invasive ventilation are planned. **[new 2016]** 1.7.6 Provide additional support as the end of life approaches, for example, additional social or nursing care to enable informal carers and family to reduce their

CG105 recommendations	Action	Comments
		carer responsibilities and spend time with the person with MND. **[new 2016]** 1.7.7 Towards the end of life, ensure there is access to the following: • An appropriate method of communication, such as an alternative and augmentative communication (AAC) system. • Holistic support. • Specialist palliative care. • Equipment, if needed, such as syringe drivers, suction machines, riser–recliner chair, hospital bed, commode, hoist. • Anticipatory medicines including opioids and benzodiazepines to treat breathlessness, and anticholinergic medicines to treat problematic saliva and respiratory secretions. **[new 2016]** 1.7.8 Offer bereavement support to family members and/or carers (as appropriate). **[new 2016]**
1.1.25 Discussions about end-of-life care should include: • planning of end-of-life care • considering advance decisions to refuse treatment • considering what to do if non-invasive ventilation fails because of either: ○ an acute, but potentially reversible, deterioration in health or ○ irreversible disease progression • strategies to withdraw non-invasive ventilation if the patient wishes • the involvement of family and carers in decision making (with the patient's consent if they have the capacity to give it).	Deleted and replaced with recommendations on: 1.Planning for end of life (section 1.7) 2. Information and support about non-invasive ventilation (recommendations 1.14.2–1.14.5) 3. Stopping non-invasive ventilation (recommendations 1.14.28–1.14.31)	

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Appendix P: NICE project team

Name	Role
Sarah Willett	Guideline Lead
Phil Alderson	Clinical Advisor
Nichole Taske	Technical Lead
Paul Crosland	Health Economist
Caroline Keir	Guideline Commissioning Manager
Margaret Ghlaimi	Guideline Coordinator
Sarah Palombella	Editor
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Appendix Q: References

1 Abdelnour-Mallet M, Verschueren A, Guy N, Soriani MH, Chalbi M, Gordon P et al. Safety of home parenteral nutrition in patients with amyotrophic lateral sclerosis: a French national survey. Amyotrophic Lateral Sclerosis. 2011; 12(3):178-184

2 Aboussouan LS, Khan SU, Meeker DP, Stelmach K, Mitsumoto H. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Annals of Internal Medicine. 1997; 127(6):450-453

3 Abrahams S, Goldstein LH, Al-Chalabi A, Pickering A, Morris RG, Passingham RE et al. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery and Psychiatry. 1997; 62(5):464-472

4 Abrahams S, Goldstein LH, Simmons A, Brammer M, Williams SCR, Giampietro V et al. Word retrieval in amyotrophic lateral sclerosis: a functional magnetic resonance imaging study. Brain. 2004; 127(Pt 7):1507-1517

5 Abrahams S, Leigh PN, Goldstein LH. Cognitive change in ALS: a prospective study. Neurology. 2005; 64(7):1222-1226

6 Abrahams S, Goldstein LH, Suckling J, Ng V, Simmons A, Chitnis X et al. Frontotemporal white matter changes in amyotrophic lateral sclerosis. Journal of Neurology. 2005; 252(3):321-331

7 Achille MA, Ogloff JRP. Attitudes toward and desire for assisted suicide among persons with amyotrophic lateral sclerosis. Omega. 2003; 48(1):1-21

8 Adelman EE, Albert SM, Rabkin JG, Del Bene ML, Tider T, O'Sullivan I. Disparities in perceptions of distress and burden in ALS patients and family caregivers. Neurology. 2004; 62(10):1766-1770

9 Adler D, Heritier A-C, Leuchter I, Genton L, Viatte V, Janssens JP et al. Respiratory failure treated by NIV is not associated with a worst outcome during peg insertion in ALS patients. Respiration. 2014; 87(6):541-542

10 Agosta F, Pagani E, Petrolini M, Caputo D, Perini M, Prelle A et al. Assessment of white matter tract damage in patients with amyotrophic lateral sclerosis: a diffusion tensor MR imaging tractography study. American Journal of Neuroradiology. 2010; 31(8):1457-1461

11 Agosta F, Pagani E, Petrolini M, Sormani MP, Caputo D, Perini M et al. MRI predictors of long-term evolution in amyotrophic lateral sclerosis. European Journal of Neuroscience. 2010; 32(9):1490-1496

12 Agosta F, Valsasina P, Riva N, Copetti M, Messina MJ, Prelle A et al. The cortical signature of amyotrophic lateral sclerosis. PloS One. 2012; 7(8):e42816

13 Ahn SW, Kim JE, Sung JJ, Lee KW, Hong YH. Asymmetry of motor unit number estimate and its rate of decline in patients with amyotrophic lateral sclerosis. Journal of Clinical Neurophysiology. 2011; 28(5):528-532

14 Akiyama MO, Kayama M, Takamura S, Kawano Y, Ohbu S, Fukuhara S. A study of the burden of caring for patients with amyotrophic lateral sclerosis (MND) in Japan. British Journal of Neuroscience Nursing. 2006; 2(1):38-43

15 Aksoy D, Cevik B, Solmaz V, Kurt SG. Clinical, demographic and prognostic features of sporadic amyotrophic lateral sclerosis in Northern Turkey. International Journal of Neuroscience. 2014; 124(1):68-73

16 Albert SM, Murphy PL, Del Bene ML, Rowland LP. A prospective study of preferences and actual treatment choices in ALS. Neurology. 1999; 53(2):278-283

17 Albert SM, Whitaker A, Rabkin JG, del Bene M, Tider T, O'Sullivan I et al. Medical and supportive care among people with ALS in the months before death or tracheostomy. Journal of Pain and Symptom Management. 2009; 38(4):546-553

18 Allen JA, Chen R, Ajroud-Driss S, Sufit RL, Heller S, Siddique T et al. Gastrostomy tube placement by endoscopy versus radiologic methods in patients with ALS: a retrospective study of complications and outcome. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(4):308-314

19 Alrefai AH, Aburahma SK, Khader YS. Treatment of sialorrhea in children with cerebral palsy: a double-blind placebo controlled trial. Clinical Neurology and Neurosurgery. 2009; 111(1):79-82

20 Andersen PM, Gronberg H, Franzen L, Funegard U. External radiation of the parotid glands significantly reduces drooling in patients with motor neurone disease with bulbar paresis. Journal of the Neurological Sciences. 2001; 191(1-2):111-114

21 Anderson JL, Hasney KM, Beaumont NE. Systematic review of techniques to enhance peak cough flow and maintain vital capacity in neuromuscular disease: the case for mechanical insufflation-exsufflation. Physical Therapy Reviews. 2005; 10(1):25-33

22 Annane D, Orlikowski D, Chevret S, Chevrolet JC, Raphaël JC. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database of Systematic Reviews. 2007; Issue 4:CD001941. DOI:10.1002/14651858.CD001941.pub2

23 Ansari NN, Naghdi S, Bagheri H, Ghassabi H. Therapeutic ultrasound in the treatment of ankle plantarflexor spasticity in a unilateral stroke population: a randomized, single-blind, placebo-controlled trial. Electromyography and Clinical Neurophysiology. 2007; 47(3):137-143

24 Aoun S, Kristjanson L, Oldham L. The challenges and unmet needs of people with neurodegenerative conditions and their carers. ACCNS Journal for Community Nurses. 2006; 11(1):17-20

25 Aoun S, McConigley R, Abernethy A, Currow DC. Caregivers of people with neurodegenerative diseases: profile and unmet needs from a population-based survey in South Australia. Journal of Palliative Medicine. 2010; 13(6):653-661

26 Aoun SM, Bentley B, Funk L, Toye C, Grande G, Stajduhar KJ. A 10-year literature review of family caregiving for motor neurone disease: Moving from caregiver burden studies to palliative care interventions. Palliative Medicine. 2013; 27(5):437-446

27 Aoun SM, Connors SL, Priddis L, Breen LJ, Colyer S. Motor Neurone Disease family carers' experiences of caring, palliative care and bereavement: An exploratory qualitative study. Palliative Medicine. 2012; 26(6):842-850

28 Apaydin Y, Erk G, Sacan O, Tiryaki C, Taspinar V. Characteristics of unilateral spinal anesthesia at different speeds of intrathecal injection. Journal of Anesthesia. 2011; 25(3):380-385

29 Arbesman M, Sheard K. Systematic review of the effectiveness of occupational therapy-related interventions for people with amyotrophic lateral sclerosis. American Journal of Occupational Therapy. 2014; 68(1):20-26

30 Arbouw MEL, Movig KLL, Koopmann M, Poels PJE, Guchelaar HJ, Egberts TCG et al. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. Neurology. 2010; 74(15):1203-1207

31 Aridegbe T, Kandler R, Walters SJ, Walsh T, Shaw PJ, McDermott CJ. The natural history of motor neuron disease: assessing the impact of specialist care. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(1):13-19

32 Armon C, Graves MC, Moses D, Forte DK, Sepulveda L, Darby SM et al. Linear estimates of disease progression predict survival in patients with amyotrophic lateral sclerosis. Muscle and Nerve. 2000; 23(6):874-882

33 Armon C, Moses D. Linear estimates of rates of disease progression as predictors of survival in patients with ALS entering clinical trials. Journal of the Neurological Sciences. 1998; 160 Suppl 1:S37-S41

34 Armon C. A randomized controlled trial of resistance exercise in individuals with ALS. Neurology. 2008; 71(11):864-866

35 Arts IMP, Overeem S, Pillen S, Schelhaas HJ, Zwarts MJ. Muscle changes in amyotrophic lateral sclerosis: a longitudinal ultrasonography study. Clinical Neurophysiology. 2011; 122(3):623-628

36 Ashraf AR, Jali R, Moghtaderi AR, Yazdani AH. Therapeutic ultrasound in the treatment of ankle plantarflexor spasticity in a unilateral stroke population: a randomized, single-blind, placebo-controlled trial. Electromyography and Clinical Neurophysiology. 2009; 49(1):3-8

37 Atassi N, Cook A, Pineda CME, Yerramilli-Rao P, Pulley D, Cudkowicz M. Depression in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2011; 12(2):109-112

38 Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E et al. The PRO-ACT database: Design, initial analyses, and predictive features. Neurology. 2014; 83(19):1719-1725

39 Atassi N, Cudkowicz ME, Schoenfeld DA. Advanced statistical methods to study the effects of gastric tube and non-invasive ventilation on functional decline and survival in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2011; 12(4):272-277

40 Atkins L, Brown RG, Leigh PN, Goldstein LH. Marital relationships in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2010; 11(4):344-350

41 Attanasio A, Bedin M, Stocco S, Negrin V, Biancon A, Cecchetto G et al. Clinical outcomes and complications of enteral nutrition among older adults. Minerva Medica. 2009; 100(2):159-166

42 Attarian S, Azulay JP, Lardillier D, Verschueren A, Pouget J. Transcranial magnetic stimulation in lower motor neuron diseases. Clinical Neurophysiology. 2005; 116(1):35-42

43 Averill AJ, Kasarskis EJ, Segerstrom SC. Expressive disclosure to improve well-being in patients with amyotrophic lateral sclerosis: a randomised, controlled trial. Psychology and Health. 2013; 28(6):701-713

44 Averill AJ. Emotional disclosure in patients with amyotrophic lateral sclerosis: A randomized, controlled trial. Dissertation Abstracts International: Section B: Sciences and Engineering. 2007; 68(4-B):2636

45 Baba MD, Osborne MD, Wszolek MD, Kwolek A, Druzbicki PD. Treatment of spasticity with botulinum toxin. Ortopedia, Traumatologia, Rehabilitacja. 2004; 6(5):665-672

46 Bach JR. Amyotrophic lateral sclerosis: predictors for prolongation of life by noninvasive respiratory aids. Archives of Physical Medicine and Rehabilitation. 1995; 76(9):828-832

47 Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AIDS. Chest. 2002; 122(1):92-98

48 Bachrach SJ, Walter RS, Trzcinski K. Use of glycopyrrolate and other anticholinergic medications for sialorrhea in children with cerebral palsy. Clinical Pediatrics. 1998; 37(8):485-490

49 Bae JS, Hong YH, Baek W, Sohn EH, Cho JY, Kim BJ et al. Current status of the diagnosis and management of amyotrophic lateral sclerosis in Korea: a multi-center cross-sectional study. Journal of Clinical Neurology. 2012; 8(4):293-300

50 Bakheit AMO, Maynard V, Shaw S. The effects of isotonic and isokinetic muscle stretch on the excitability of the spinal alpha motor neurones in patients with muscle spasticity. European Journal of Neurology. 2005; 12(9):719-724

51 Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database of Systematic Reviews. 2014; Issue 3:CD011008. DOI:10.1002/14651858.CD011008

52 Basciani M, Di Rienzo F, Fontana A, Copetti M, Pellegrini F, Intiso D. Botulinum toxin type B for sialorrhoea in children with cerebral palsy: a randomized trial comparing three doses. Developmental Medicine and Child Neurology. 2011; 53(6):559-564

53 Baumann F, Henderson RD, Morrison SC, Brown M, Hutchinson N, Douglas JA et al. Use of respiratory function tests to predict survival in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2010; 11(1-2):194-202

54 Bausewein C, Simon ST. Shortness of breath and cough in patients in palliative care. Deutsches Arzteblatt International. 2013; 110(33-34):563-572

55 Baxter SK, Baird WO, Thompson S, Bianchi SM, Walters SJ, Lee E et al. The use of non-invasive ventilation at end of life in patients with motor neurone disease: A qualitative exploration of family carer and health professional experiences. Palliative Medicine. 2013; 27(6):516-523

56 Baxter SK, Baird WO, Thompson S, Bianchi SM, Walters SJ, Lee E et al. Use of non-invasive ventilation at end of life. Palliative Medicine. 2013; 27(9):878

57 Bede P, Bokde A, Elamin M, Byrne S, McLaughlin RL, Jordan N et al. Grey matter correlates of clinical variables in amyotrophic lateral sclerosis (ALS): a neuroimaging study of ALS motor phenotype heterogeneity and cortical focality. Journal of Neurology, Neurosurgery and Psychiatry. 2013; 84(7):766-773

58 Beggs K, Choi M, Travlos A. Assessing and predicting successful tube placement outcomes in ALS patients. Amyotrophic Lateral Sclerosis. 2010; 11(1-2):203-206

59 Beisecker AE, Cobb AK, Ziegler DK. Patients' perspectives of the role of care providers in amyotrophic lateral sclerosis. Archives of Neurology. 1988; 45(5):553-556

60 Bentley B, Aoun SM, O'Connor M, Breen LJ, Chochinov HM. Is dignity therapy feasible to enhance the end of life experience for people with motor neurone disease and their family carers? BMC Palliative Care. 2012; 11:18

61 Berry JD, Shefner JM, Conwit R, Schoenfeld D, Keroack M, Felsenstein D et al. Design and initial results of a multi-phase randomized trial of ceftriaxone in amyotrophic lateral sclerosis. PloS One. 2013; 8(4):e61177

62 Bethoux F, Boulis N, McClelland S, Willis MA, Hussain M, Machado A et al. Use of intrathecal baclofen for treatment of severe spasticity in selected patients with motor neuron disease. Neurorehabilitation and Neural Repair. 2013; 27(9):828-833

63 Bizovicar N, Zidar I, Koritnik B, Zidar J. Inspiratory- and finger-flexion-related cortical potentials in patients with amyotrophic lateral sclerosis - An exploratory study. Clinical Neurology and Neurosurgery. 2012; 114(5):455-459

64 Blain-Moraes S, Mashour GA, Lee H, Huggins JE, Lee U. Altered cortical communication in amyotrophic lateral sclerosis. Neuroscience Letters. 2013; 543:172-176

65 Blondet A, Lebigot J, Nicolas G, Boursier J, Person B, Laccoureye L et al. Radiologic versus endoscopic placement of percutaneous gastrostomy in amyotrophic lateral sclerosis: multivariate analysis of tolerance, efficacy, and survival. Journal of Vascular and Interventional Radiology. 2010; 21(4):527-533

66 Bodger K, Bowering K, Thompson EB, Pearson M. All-cause mortality following Percutaneous Endoscopic Gastrostomy (PEG) in England: Analysis of hospital episode statistics linked to death registration data (2006-8). Gastroenterology. 2010; 138(5 Suppl.1):S637

67 Boerner K, Mock SE. Impact of patient suffering on caregiver well-being: the case of amyotrophic lateral sclerosis patients and their caregivers. Psychology, Health and Medicine. 2012; 17(4):457-466

68 Bolmsjo I. Existential issues in palliative care: interviews of patients with amyotrophic lateral sclerosis. Journal of Palliative Medicine. 2001; 4(4):499-505

69 Bolmsjo I, Hermeren G. Interviews with patients, family, and caregivers in amyotrophic lateral sclerosis: comparing needs. Journal of Palliative Care. 2001; 17(4):236-240

70 Bolmsjo I, Hermern G. Conflicts of Interest: experiences of close relatives of patients suffering from amyotrophic lateral sclerosis. Nursing Ethics. 2003; 10(2):186-198

71 Bongioanni P, Borasio GD, Oliver D, Tramonti F, Romagnoli A, Kapitza KP. Methods for informing people with amyotrophic lateral sclerosis/motor neuron disease of their diagnosis. Cochrane Database of Systematic Reviews. 2009; Issue 1:CD007593. DOI:10.1002/14651858.CD007593

72 Bongioanni P, Reali C, Sogos V. Ciliary neurotrophic factor (CNTF) for amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database of Systematic Reviews. 2004; Issue 3:CD004302. DOI:10.1002/14651858.CD004302.pub2

73 Borasio GD, Shaw PJ, Hardiman O, Ludolph AC, Sales Luis ML, Silani V et al. Standards of palliative care for patients with amyotrophic lateral sclerosis: results of a European survey. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2001; 2(3):159-164

74 Borg J, Ward AB, Wissel J, Kulkarni J, Sakel M, Ertzgaard P et al. Rationale and design of a multicentre, double-blind, prospective, randomized, European and Canadian study: evaluating patient outcomes and costs of managing adults with post-stroke focal spasticity. Journal of Rehabilitation Medicine. 2011; 43(1):15-22

75 Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurology. 2006; 5(2):140-147

76 Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurology. 2013; 12(2):149-156

77 Boylan KB, Glass JD, Crook JE, Yang C, Thomas CS, Desaro P et al. Phosphorylated neurofilament heavy subunit (pNF-H) in peripheral blood and CSF as a potential prognostic biomarker in amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery and Psychiatry. 2013; 84(4):467-472

78 Boyraz I, Oktay F, Celik C, Akyuz M, Uysal H. Effect of cold application and tizanidine on clonus: Clinical and electrophysiological assessment. Journal of Spinal Cord Medicine. 2009; 32(2):132-139

79 Bradley WG. Critical review of gangliosides and thyrotropin-releasing hormone in peripheral neuromuscular diseases. Muscle and Nerve. 1990; 13(9):833-842

80 Braksick S, Jones L, Mandrekar J, Hocker S. Predictors of early mortality in patients with amyotrophic lateral sclerosis undergoing elective percutaneous endoscopic gastrostomy or jejunostomy placement: The Mayo Clinic experience. Neurology. 2014; 82(10 Suppl.1)

81 Bremer BA, Simone AL, Walsh S, Simmons Z, Felgoise SH. Factors supporting quality of life over time for individuals with amyotrophic lateral sclerosis: the role of positive self-perception and religiosity. Annals of Behavioral Medicine. 2004; 28(2):119-125

82 Brettschneider J, Petzold A, Sussmuth SD, Ludolph AC, Tumani H. Axonal damage markers in cerebrospinal fluid are increased in ALS. Neurology. 2006; 66(6):852-856

83 Brewah H. Integrated health care for patients with motor neurone disease. British Journal of Nursing. 2013; 22(20):1182-1188

84 Bromberg MB, Forshew DA, Nau KL, Bromberg J, Simmons Z, Fries TJ. Motor unit number estimation, isometric strength, and electromyographic measures in amyotrophic lateral sclerosis. Muscle and Nerve. 1993; 16(11):1213-1219

85 Brooks BR. Problems in shortening the time to confirmation of ALS diagnosis: lessons from the 1st Consensus Conference, Chicago, May 1998. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2000; 1 Suppl 1:S3-S7

86 Brooks BR, Sufit RL, Montgomery GK, Beaulieu DA, Erickson LM. Intravenous thyrotropin-releasing hormone in patients with amyotrophic lateral sclerosis. Dose-response and randomized concurrent placebo-controlled pilot studies. Neurologic Clinics. 1987; 5(1):143-158

87 Brott T, Hocking C, Paddy A. Occupational disruption: Living with motor neurone disease. British Journal of Occupational Therapy. 2007; 70(1):24-31

88 Brown JB, Lattimer V, Tudball T. An investigation of patients and providers' views of services for motor neurone disease. British Journal of Neuroscience Nursing. 2005; 1(5):249-252

89 Brown J, Addington-Hall J. How people with motor neurone disease talk about living with their illness: A narrative study. Journal of Advanced Nursing. 2008; 62(2):200-208

90 Brown WA, Mueller PS. Psychological function in individuals with amyotrophic lateral sclerosis (ALS). Psychosomatic Medicine. 1970; 32(2):141-152

91 Brownlee A, Bruening L. Methods of Communication at End of Life for the Person With Amyotrophic Lateral Sclerosis. Topics in Language Disorders. 2012; 32(2):168-185

92 Budych K, Helms TM, Schultz C. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. Health Policy. 2012; 105(2-3):154-164

93 Bungener C, Piquard A, Pradat PF, Salachas F, Meininger V, Lacomblez L. Psychopathology in amyotrophic lateral sclerosis: a preliminary study with 27 ALS patients. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2005; 6(4):221-225

94 Burrell JR, Yiannikas C, Rowe D, Kiernan MC. Predicting a positive response to intravenous immunoglobulin in isolated lower motor neuron syndromes. PloS One. 2011; 6(10)

95 Burrell JR, Carpenter RHS, Hodges JR, Kiernan MC. Early saccades in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(4):294-301

96 Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor neuron dysfunction in frontotemporal dementia. Brain. 2011; 134(Pt 9):2582-2594

97 Byrne S, Heverin M, Elamin M, Bede P, Lynch C, Kenna K et al. Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis. Annals of Neurology. 2013; 74(5):699-708

98 Caligari M, Godi M, Guglielmetti S, Franchignoni F, Nardone A. Eye tracking communication devices in amyotrophic lateral sclerosis: impact on disability and quality of life. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(7-8):546-552

99 Calver J, McCaul KA, Burmas M, Horner BJ, Flicker L. Use of gastrostomy tubes in older Western Australians: a population-based study of frequency, indications and outcomes. Medical Journal of Australia. 2009; 190(7):358-361

100 Calvert M, Pall H, Hoppitt T, Eaton B, Savill E, Sackley C. Health-related quality of life and supportive care in patients with rare long-term neurological conditions. Quality of Life Research. 2013; 22(6):1231-1238

101 Camp-Bruno JA, Winsberg BG, Green-Parsons AR, Abrams JP. Efficacy of benztropine therapy for drooling. Developmental Medicine and Child Neurology. 1989; 31(3):309-319

102 Canu E, Agosta F, Galantucci S, Chio A, Riva N, Silani V et al. Extramotor damage is associated with cognition in primary lateral sclerosis patients. PloS One. 2013; 8(12):e82017

103 Capozzo R, Quaranta VN, Pellegrini F, Fontana A, Copetti M, Carratu P et al. Sniff nasal inspiratory pressure as a prognostic factor of tracheostomy or death in amyotrophic lateral sclerosis. Journal of Neurology. 2015; 262(3):593-603

104 Carter H, McKenna C, MacLeod R, Green R. Health professionals' responses to multiple sclerosis and motor neurone disease. Palliative Medicine. 1998; 12(5):383-394

105 Carver AC, Vickrey BG, Bernat JL, Keran C, Ringel SP, Foley KM. End-of-life care: A survey of US neurologists' attitudes, behavior, and knowledge. Neurology. 1999; 53(2):284-293

106 Castelnovo G, De VM, Renard D, Boudousq V, Collombier L. Comparison of different sites of injections of incobotulinumtoxin (XEOMIN) into the major salivary glands in drooling. Movement Disorders. 2013; 28(Suppl.1):S167

107 Cavallo M, Adenzato M, Macpherson SE, Karwig G, Enrici I, Abrahams S. Evidence of social understanding impairment in patients with amyotrophic lateral sclerosis. PloS One. 2011; 6(10):e25948

108 Cellura E, Spataro R, Taiello AC, La Bella V. Factors affecting the diagnostic delay in amyotrophic lateral sclerosis. Clinical Neurology and Neurosurgery. 2012; 114(6):550-554

109 Chakraborty N, Roy T, Hazra A, Biswas A, Bhattacharya K. Dysarthric Bengali speech: a neurolinguistic study. Journal of Postgraduate Medicine. 2008; 54(4):268-272

110 Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. Journal of Neurology. 1993; 240(6):339-346

111 Chaudri MB, Liu C, Hubbard R, Jefferson D, Kinnear WJ. Relationship between supramaximal flow during cough and mortality in motor neurone disease. European Respiratory Journal. 2002; 19(3):434-438

112 Chavada G, El-Nayal A, Lee F, Webber SJ, McAlindon M, Walsh T et al. Evaluation of two different methods for per-oral gastrostomy tube placement in patients with motor neuron disease (MND): PIG versus PEG procedures. Amyotrophic Lateral Sclerosis. 2010; 11(6):531-536

113 Cheah BC, Boland RA, Brodaty NE, Zoing MC, Jeffery SE, McKenzie DK et al. INSPIRATIonAL--INSPIRAtory muscle training in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2009; 10(5-6):384-392

114 Cheah BC, Vucic S, Krishnan AV, Boland RA, Kiernan MC. Neurophysiological index as a biomarker for ALS progression: validity of mixed effects models. Amyotrophic Lateral Sclerosis. 2011; 12(1):33-38

115 Chinnapongse R, Gullo K, Nemeth P, Zhang Y, Griggs L. Safety and efficacy of botulinum toxin type B for treatment of sialorrhea in Parkinson's disease: a prospective double-blind trial. Movement Disorders. 2012; 27(2):219-226

116 Chio A, Bottacchi E, Buffa C, Mutani R, Mora G, PARALS. Positive effects of tertiary centres for amyotrophic lateral sclerosis on outcome and use of hospital facilities. Journal of Neurology, Neurosurgery and Psychiatry. 2006; 77(8):948-950

117 Chio A, Brignolio F, Leone M. A survival analysis of 155 cases of progressive muscular atrophy. Acta Neurologica Scandinavica. 1985; 72(4):407-413

118 Chio A, Finocchiaro E, Meineri P, Bottacchi E, Schiffer D. Safety and factors related to survival after percutaneous endoscopic gastrostomy in ALS. ALS Percutaneous Endoscopic Gastrostomy Study Group. Neurology. 1999; 53(5):1123-1125

119 Chio A, Gauthier A, Calvo A, Ghiglione P, Mutani R. Caregiver burden and patients' perception of being a burden in ALS. Neurology. 2005; 64(10):1780-1782

120 Chio A, Gauthier A, Montuschi A, Calvo A, Di Vito N, Ghiglione P et al. A cross sectional study on determinants of quality of life in ALS. Journal of Neurology, Neurosurgery and Psychiatry. 2004; 75(11):1597-1601

121 Chio A, Ilardi A, Cammarosano S, Moglia C, Montuschi A, Calvo A. Neurobehavioral dysfunction in ALS has a negative effect on outcome and use of PEG and NIV. Neurology. 2012; 78(14):1085-1089

122 Chio A, Montuschi A, Cammarosano S, De Mercanti S, Cavallo E, Ilardi A et al. ALS patients and caregivers communication preferences and information seeking behaviour. European Journal of Neurology. 2008; 15(1):55-60

123 Chio A, Mora G, Leone M, Mazzini L, Cocito D, Giordana MT et al. Early symptom progression rate is related to ALS outcome: a prospective population-based study. Neurology. 2002; 59(1):99-103

124 Chio A, Silani V, Italian ALS Study Group. Amyotrophic lateral sclerosis care in Italy: a nationwide study in neurological centers. Journal of the Neurological Sciences. 2001; 191(1-2):145-150

125 Chio A, Vignola A, Mastro E, Giudici AD, Iazzolino B, Calvo A et al. Neurobehavioral symptoms in ALS are negatively related to caregivers' burden and quality of life. European Journal of Neurology. 2010; 17(10):1298-1303

126 Chio A, Hammond ER, Mora G, Bonito V, Filippini G. Development and evaluation of a clinical staging system for amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry. 2015; 86(1):38-44

127 Chnag CT, Chen P. A phase II, double-blind, randomized, placebo-controlled 4-way crossover study to evaluate the relative efficacy and safety of OC oral solution (oxybutynin and clonidine) for sialorrhoea in patients with Parkinson's disease. Movement Disorders. 2012; 27(Suppl.1):S111-S112

128 Choi WA, Park JH, Kim DH, Kang SW. Cough assistance device for patients with glottis dysfunction and/or tracheostomy. Journal of Rehabilitation Medicine. 2012; 44(4):351-354

129 Chou KL, Evatt M, Hinson V, Kompoliti K. Sialorrhea in Parkinson's disease: a review. Movement Disorders. 2007; 22(16):2306-2313

130 Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. Journal of Pain and Symptom Management. 2004; 28(2):140-175

131 Chow TW, Fam D, Graff-Guerrero A, Verhoeff NPG, Tang-Wai DF, Masellis M et al. Fluorodeoxyglucose positron emission tomography in semantic dementia after 6months of memantine: an open-label pilot study. International Journal of Geriatric Psychiatry. 2013; 28(3):319-325

132 Christensen PB, Hojer-Pedersen E, Jensen NB. Survival of patients with amyotrophic lateral sclerosis in 2 Danish counties. Neurology. 1990; 40(4):600-604

133 Chung BHY, Wong VCN, Ip P. Spinal muscular atrophy: Survival pattern and functional status. Pediatrics. 2004; 114(5):e548-e553

134 Ciccarelli O, Behrens TE, Johansen-Berg H, Talbot K, Orrell RW, Howard RS et al. Investigation of white matter pathology in ALS and PLS using tract-based spatial statistics. Human Brain Mapping. 2009; 30(2):615-624

135 Cipolletta S, Amicucci L. The family experience of living with a person with amyotrophic lateral sclerosis: A qualitative study. International Journal of Psychology. 2014; 50(4):288-294

136 Clarke S, Hickey A, O'Boyle C, Hardiman O. Assessing individual quality of life in amyotrophic lateral sclerosis. Quality of Life Research. 2001; 10(2):149-158

137 Clavelou P, Blanquet M, Peyrol F, Ouchchane L, Gerbaud L. Rates of progression of weight and forced vital capacity as relevant measurement to adapt amyotrophic lateral sclerosis management for patient Result of a French multicentre cohort survey. Journal of the Neurological Sciences. 2013; 331(1-2):126-131

138 Cleary S, Misiaszek JE, Kalra S, Wheeler S, Johnston W. The effects of lung volume recruitment on coughing and pulmonary function in patients with ALS. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(2):111-115

139 Clemens KE, Klaschik E. Morphine in the management of dyspnoea in ALS. A pilot study. European Journal of Neurology. 2008; 15(5):445-450

140 Cobb AK, Hamera E. Illness experience in a chronic disease-ALS. Social Science and Medicine. 1986; 23(7):641-650. DOI:http://dx.doi.org/10.1016/0277-9536%2886%2990111-5

141 Cocchiarella A, Downey JA, Darling RC. Evaluation of the effect of diazepam on spasticity. Archives of Physical Medicine and Rehabilitation. 1967; 48(8):393-396

142 Connolly S, Galvin M, Hardiman O. End-of-life management in patients with amyotrophic lateral sclerosis. The Lancet Neurology.: Elsevier Science. 2015; 14(4):435-442

143 Connolly S, Heslin C, Mays I, Corr B, Normand C, Hardiman O. Health and social care costs of managing amyotrophic lateral sclerosis (ALS): An Irish perspective. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2015; 16(1-2):58-62

144 Coon EA, Sorenson EJ, Whitwell JL, Knopman DS, Josephs KA. Predicting survival in frontotemporal dementia with motor neuron disease. Neurology. 2011; 76(22):1886-1893

145 Cordesse V, Sidorok F, Schimmel P, Holstein J, Meininger V. Coordinated care affects hospitalization and prognosis in amyotrophic lateral sclerosis: a cohort study. BMC Health Services Research. 2015; 15:134

146 Cox DL. Perspectives of motor neurone disease. Clinical Rehabilitation. 1992; 6(4):333-339. DOI:http://dx.doi.org/10.1177/026921559200600409

147 Cranston JM, Crockett A, Currow D, Ekström M. Oxygen therapy for dyspnoea in adults. Cochrane Database of Systematic Reviews. 2013; Issue 11:CD004769. DOI:10.1002/14651858.CD004769.pub3

148 Creemers H, Veldink JH, Grupstra HF, Nollet F, Beelen A, Van Den Berg LH. A randomised controlled trial on the effect of case management on quality of care, quality of life and caregiver burden in ALS. Amyotrophic Lateral Sclerosis. 2011; 12(S1):73-74

149 Creemers H, Beelen A, Grupstra H, Nollet F, van den Berg LH. The provision of assistive devices and home adaptations to patients with ALS in the Netherlands: Patients' perspectives. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(5-6):420-425

150 Creemers H, Veldink JH, Grupstra H, Nollet F, Beelen A, van den Berg LH. Cluster RCT of case management on patients' quality of life and caregiver strain in ALS. Neurology. 2014; 82(1):23-31

151 Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, Munneke M, van Engelen BG, Hendricks HT et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Archives of Physical Medicine and Rehabilitation. 2007; 88(11):1452-1464

152 Currow DC, McDonald C, Oaten S, Kenny B, Allcroft P, Frith P et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. Journal of Pain and Symptom Management. 2011; 42(3):388-399

153 Currow DC, Plummer J, Frith P, Abernethy AP. Can we predict which patients with refractory dyspnea will respond to opioids? Journal of Palliative Medicine. 2007; 10(5):1031-1036

154 Curtis L. Unit costs of health and social care 2012. Canterbury: Personal Social Services Research Unit, University of Kent; 2012. Available from: http://www.pssru.ac.uk/archive/pdf/uc/uc2012/full-with-covers.pdf

155 Curtis L. Unit costs of health and social care 2013. Canterbury: Personal Social Services Research Unit, University of Kent; 2013. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2013/index.php

156 Czaplinski A, Appel SH. Amyotrophic lateral sclerosis: Can we predict the course of disease? Schweizer Archiv Fur Neurologie Und Psychiatrie. 2006; 157(7):317-322

157 Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. Journal of Neurology, Neurosurgery and Psychiatry. 2006; 77(3):390-392

158 Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. Journal of Neurology. 2006; 253(11):1428-1436

159 Czaplinski A, Yen AA, Simpson EP, Appel SH. Predictability of disease progression in amyotrophic lateral sclerosis. Muscle and Nerve. 2006; 34(6):702-708

160 Czaplinski A, Yen AA, Simpson EP, Appel SH. Slower disease progression and prolonged survival in contemporary patients with amyotrophic lateral sclerosis: is the natural history of amyotrophic lateral sclerosis changing? Archives of Neurology. 2006; 63(8):1139-1143

161 Czell D, Bauer M, Binek J, Schoch OD, Weber M. Outcomes of percutaneous endoscopic gastrostomy tube insertion in respiratory impaired amyotrophic lateral sclerosis patients under noninvasive ventilation. Respiratory Care. 2013; 58(5):838-844

162 Dal Bello-Haas V, Florence JM, Kloos AD, Scheirbecker J, Lopate G, Hayes SM et al. A randomized controlled trial of resistance exercise in individuals with ALS. Neurology. 2007; 68(23):2003-2007

163 Davis S and NICE Decision Support Unit. Assessing technologies that are not cost-effective at zero price. Sheffield. Decision Support Unit, School of Health and Related Research, University of Sheffield, 2014. Available from: http://www.nicedsu.org.uk/Not_CE_at_zero_price_FINAL_14.07.14.pdf

164 Dawson S, Kristjanson LJ. Mapping the journey: family carers' perceptions of issues related to end-stage care of individuals with muscular dystrophy or motor neurone disease. Journal of Palliative Care. 2003; 19(1):36-42

165 de Carvalho M, Miranda PC, Luis ML, Ducla-Soares E. Cortical muscle representation in amyotrophic lateral sclerosis patients: changes with disease evolution. Muscle and Nerve. 1999; 22(12):1684-1692

166 de Carvalho M, Chio A, Dengler R, Hecht M, Weber M, Swash M. Neurophysiological measures in amyotrophic lateral sclerosis: markers of progression in clinical trials. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2005; 6(1):17-28

167 de Carvalho M, Evangelista T, Sales-Luis ML. The corticomotor threshold is not dependent on disease duration in amyotrophic lateral sclerosis (ALS). Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002; 3(1):39-42

168 de Carvalho M, Pinto S, Costa J, Evangelista T, Ohana B, Pinto A. A randomized, placebo-controlled trial of memantine for functional disability in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2010; 11(5):456-460

169 de Carvalho M, Scotto M, Lopes A, Swash M. Quantitating progression in ALS. Neurology. 2005; 64(10):1783-1785

170 de Carvalho M, Swash M. Can selection of rapidly progressing patients shorten clinical trials in amyotrophic lateral sclerosis? Archives of Neurology. 2006; 63(4):557-560

171 de Carvalho M, Swash M. Sensitivity of electrophysiological tests for upper and lower motor neuron dysfunction in ALS: a six-month longitudinal study. Muscle and Nerve. 2010; 41(2):208-211

172 De Groot IJM, Post MWM, van HT, Van Den Berg LH, Lindeman E. Cross-sectional and longitudinal correlations between disease progression and different health-related quality of life domains in persons with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2007; 8(6):356-361

173 De Groot IJM, Post MWM, van Heuveln T, van den Berg LH, Lindeman E. Measurement of decline of functioning in persons with amyotrophic lateral sclerosis: responsiveness and possible applications of the Functional Independence Measure, Barthel Index, Rehabilitation Activities Profile and Frenchay Activities Index. Amyotrophic Lateral Sclerosis. 2006; 7(3):167-172

174 del Aguila MA, Longstreth WTJ, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology. 2003; 60(5):813-819

175 Deltombe T, Jamart J, Hanson P, Gustin T. Soleus H reflex and motor unit number estimation after tibial nerve block and neurotomy in patients with spastic equinus foot. Neurophysiologie Clinique. 2008; 38(4):227-233

176 Department of Health. NHS reference costs 2013-14. 2014. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014 [Last accessed: 20 August 2015]

177 Desport JC, Preux PM, Magy L, Boirie Y, Vallat JM, Beaufrere B et al. Factors correlated with hypermetabolism in patients with amyotrophic lateral sclerosis. American Journal of Clinical Nutrition. 2001; 74(3):328-334

178 Desport JC, Preux PM, Truong CT, Courat L, Vallat JM, Couratier P. Nutritional assessment and survival in ALS patients. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2000; 1(2):91-96

179 Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. Neurology. 1999; 53(5):1059-1063

180 Desport JC, Preux PM, Bouteloup-Demange C, Clavelou P, Beaufrere B, Bonnet C et al. Validation of bioelectrical impedance analysis in patients with amyotrophic lateral sclerosis. American Journal of Clinical Nutrition. 2003; 77(5):1179-1185

181 Desport JC, Mabrouk T, Bouillet P, Perna A, Preux PM, Couratier P. Complications and survival following radiologically and endoscopically-guided gastrostomy in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2005; 6(2):88-93

182 Desport JC, Marin B, Funalot B, Preux PM, Couratier P. Phase angle is a prognostic factor for survival in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2008; 9(5):273-278

183 Di Lazzaro V, Dileone MF, Pilato FF, Profice PF, Ranieri FF, Musumeci GF et al. Repetitive transcranial magnetic stimulation for ALS. A preliminary controlled study. Neuroscience Letters. 2006; 408(2):135-140

184 Di Lazzaro V, Pilato F, Profice P, Ranieri F, Musumeci G, Florio L et al. Motor cortex stimulation for ALS: a double blind placebo-controlled study. Neuroscience Letters. 2009; 464(1):18-21

185 Diana A, Sogos V, Bongioanni P, Miller RG, Moore DH. Gamma aminobutyric acid (GABA) modulators for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2006; Issue 2:CD006049. DOI:10.1002/14651858.CD006049

186 Dogu O, Apaydin D, Sevim S, Talas DU, Aral M. Ultrasound-guided versus 'blind' intraparotid injections of botulinum toxin-A for the treatment of sialorrhoea in patients with Parkinson's disease. Clinical Neurology and Neurosurgery. 2004; 106(2):93-96

187 Donaghy C, Dick A, Hardiman O, Patterson V. Timeliness of diagnosis in motor neurone disease: a population-based study. Ulster Medical Journal. 2008; 77(1):18-21

188 Dooley DM. Demyelinating, degenerative, and vascular disease. Neurosurgery. 1977; 1(2):220-224

189 Dorst J, Cypionka J, Ludolph AC. High-caloric food supplements in the treatment of amyotrophic lateral sclerosis: A prospective interventional study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(7-8):533-536

190 Dreyer PS, Felding M, Klitnaes CS, Lorenzen CK. Withdrawal of invasive home mechanical ventilation in patients with advanced amyotrophic lateral sclerosis: ten years of Danish experience. Journal of Palliative Medicine. 2012; 15(2):205-209

191 Drory VE, Goltsman E, Reznik JG, Mosek A, Korczyn AD. The value of muscle exercise in patients with amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 2001; 191(1-2):133-137

192 Duffy J. Apraxia of speech in degenerative neurologic disease. Aphasiology. 2006; 20(6):511-527

193 Duning T, Schiffbauer H, Warnecke T, Mohammadi S, Floel A, Kolpatzik K et al. G-CSF prevents the progression of structural disintegration of white matter tracts in amyotrophic lateral sclerosis: a pilot trial. PloS One. 2011; 6(3):e17770

194 Eidenberger M, Nowotny S. Inspiratory muscle training in patients with Amyotrophic Lateral Sclerosis: A systematic review. NeuroRehabilitation. 2014; 35(3):349-361

195 Eiland LS. Glycopyrrolate for chronic drooling in children. Clinical Therapeutics. 2012; 34(4):735-742

196 Eisen A, Entezari-Taher M, Stewart H. Cortical projections to spinal motoneurons: Changes with aging and amyotrophic lateral sclerosis. Neurology. 1996; 46(5):1396-1404

197 Elamin M, Bede P, Montuschi A, Pender N, Chio A, Hardiman O. Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. Journal of Neurology. 2015; 262(6):1447-1454

198 Elamin M, Phukan J, Bede P, Jordan N, Byrne S, Pender N et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. Neurology. 2011; 76(14):1263-1269

199 Elamin M, Bede P, Byrne S, Jordan N, Gallagher L, Wynne B et al. Cognitive changes predict functional decline in ALS: a population-based longitudinal study. Neurology. 2013; 80(17):1590-1597

200 Ellenbogen AL, Bardram KM, Chang CT, Chen P. A phase II, double blind, randomized placebo-controlled 4-way crossover study to evaluate the relative efficacy and safety of OC oral solution (oxybutynin and clonidine) for sialorrhea in patients with Parkinson's disease. Movement Disorders. 2013; 28(Suppl.1):S175

201 Elsworth C, Dawes H, Sackley C, Soundy A, Howells K, Wade D et al. A study of perceived facilitators to physical activity in neurological conditions... including commentary by Cup E, Pieterse A, Block P. International Journal of Therapy and Rehabilitation. 2009; 16(1):17-24

202 Engel WK, Siddique T, Nicoloff JT. Effect on weakness and spasticity in amyotrophic lateral sclerosis of thyrotropin-releasing hormone. Lancet. 1983; 2(8341):73-75

203 Esquenazi A, Albanese A, Chancellor MB, Elovic E, Segal KR, Simpson DM et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of adult spasticity in the upper motor neuron syndrome. Toxicon. 2013; 67:115-128

204 Evangelos A, Michael R, Theodoros A, Vasiliki Z, Thomas Z, Ioannis E. Volume matters: the influence of different botulinum toxin-A dilutions for sialorrhea in amyotrophic lateral sclerosis. Muscle and Nerve. 2013; 47(2):276-278

205 Fanos JH, Gelinas DF, Foster RS, Postone N, Miller RG. Hope in palliative care: from narcissism to self-transcendence in amyotrophic lateral sclerosis. Journal of Palliative Medicine. 2008; 11(3):470-475

206 Faull C, Rowe Haynes C, Oliver D. Issues for palliative medicine doctors surrounding the withdrawal of non-invasive ventilation at the request of a patient with motor neurone disease: a scoping study. BMJ Supportive and Palliative Care. 2014; 4(1):43-49

207 Fegg MJ, Wasner M, Neudert C, Borasio GD. Personal values and individual quality of life in palliative care patients. Journal of Pain and Symptom Management. 2005; 30(2):154-159

208 Fimland MS, Helgerud J, Gruber M, Leivseth G, Hoff J. Enhanced neural drive after maximal strength training in multiple sclerosis patients. European Journal of Applied Physiology. 2010; 110(2):435-443

209 Fini N, Georgoulopoulou E, Vinceti M, Monelli M, Pinelli G, Vacondio P et al. Noninvasive and invasive ventilation and enteral nutrition for ALS in Italy. Muscle and Nerve. 2014; 50(4):508-516

210 Flaherty-Craig CV, Brothers A, Yang C, Svoboda R, Simmons Z. Declines in problem solving and anosognosia in amyotrophic lateral sclerosis: application of Guilford's structure of intellect theory. Cognitive and Behavioral Neurology. 2011; 24(1):26-34

211 Foley G, O'Mahony P, Hardiman O. Perceptions of quality of life for persons with motor neurone disease/amyotrophic lateral sclerosis: a qualitative study. Physical Therapy Reviews. 2006; 11(3):209

212 Foley G, Timonen V, Hardiman O. A systematic review of als service users ' Perceptions of services and decision making in care. Amyotrophic Lateral Sclerosis. 2011; 12(S1):13

213 Foley G, Timonen V, Hardiman O. Life stage and perceptions of ageing in motor neurone disease. Irish Journal of Medical Science. 2013; 182(6S):S291

214 Foley G, Timonen V, Hardiman O. How and why people with amyotrophic lateral sclerosis engage with health care sServices: a qualitative study of service users' experiences in Ireland. Palliative Medicine. 2014; 28(6):619

215 Foley G, O'Mahony P, Hardiman O. Perceptions of quality of life in people with ALS: effects of coping and health care. Amyotrophic Lateral Sclerosis. 2007; 8(3):164-169

216 Foley G, Timonen V, Hardiman O. Experience of services as a key outcome in amyotrophic lateral sclerosis (ALS) care: the case for a better understanding of patient experiences. American Journal of Hospice and Palliative Care. 2012; 29(5):362-367

217 Foley G, Timonen V, Hardiman O. Patients' perceptions of services and preferences for care in amyotrophic lateral sclerosis: a review. Amyotrophic Lateral Sclerosis. 2012; 13(1):11-24

218 Foley G, Timonen V, Hardiman O. Acceptance and decision making in amyotrophic lateral sclerosis from a life-course perspective. Qualitative Health Research. 2014; 24(1):67-77

219 Foley G, Timonen V, Hardiman O. Exerting control and adapting to loss in amyotrophic lateral sclerosis. Social Science and Medicine. 2014; 101:113-119

220 Foley G, Timonen V, Hardiman O. Understanding psycho-social processes underpinning engagement with services in motor neurone disease: A qualitative study. Palliative Medicine. 2014; 28(4):318-325

221 Fondell E, O'Reilly EJ, Fitzgerald KC, Falcone GJ, Kolonel LN, Park Y et al. Dietary fiber and amyotrophic lateral sclerosis: results from 5 large cohort studies. American Journal of Epidemiology. 2014; 179(12):1442-1449

222 Forbes RB, Colville S, Cran GW, Swingler RJ, Scottish Motor Neurone Disease Register. Unexpected decline in survival from amyotrophic lateral sclerosis/motor neurone disease. Journal of Neurology, Neurosurgery and Psychiatry. 2004; 75(12):1753-1755

223 Francisco GE. The role of intrathecal baclofen therapy in the upper motor neuron syndrome. Europa Medicophysica. 2004; 40(2):131-143

224 Fraraccio M, Panisset M. Comparison of OnabotulinumtoxinA injections targeting submandibular versus parotid glands in the treatment of sialorrhea for patients with Parkinson's disease. Journal of Parkinson's Disease. 2013; 3(Suppl.1):90

225 Freedman DM, Kuncl RW, Weinstein SJ, Malila N, Virtamo J, Albanes D. Vitamin E serum levels and controlled supplementation and risk of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(4):246-251

226 Freer S. Motor neurone disease: the experience of family carers. Palliative Medicine. 2010; 24(4 Suppl.1):S164

227 Fryda-Kaurimsky Z, Muller-Fassbender H. Tizanidine (DS 103-282) in the treatment of acute paravertebral muscle spasm: a controlled trial comparing tizanidine and diazepam. Journal of International Medical Research. 1981; 9(6):501-505

228 Fuster Torres MA, Berini Aytes L, Gay Escoda C. Salivary gland application of botulinum toxin for the treatment of sialorrhea. Medicina Oral, Patologia Oral y Cirugia Bucal. 2007; 12(7):E511-E517

229 Galinsky-Malaguti D, Malaguti R, Andres P, Munsat T. Amyotrophic lateral sclerosis: a comprehensive review. Physician Assistant. 1996; 20(8):65-6, 68, 72

230 Gallo V, Wark PA, Jenab M, Pearce N, Brayne C, Vermeulen R et al. Prediagnostic body fat and risk of death from amyotrophic lateral sclerosis: the EPIC cohort. Neurology. 2013; 80(9):829-838

231 Ganzini L, Goy ER, Dobscha SK. Prevalence of depression and anxiety in patients requesting physicians' aid in dying: cross sectional survey. BMJ. 2008; 337:a1682

232 Ganzini L, Johnston WS, Silveira MJ. The final month of life in patients with ALS. Neurology. 2002; 59(3):428-431

233 Garnock-Jones KP. Glycopyrrolate oral solution: for chronic, severe drooling in pediatric patients with neurologic conditions. Paediatric Drugs. 2012; 14(4):263-269

234 Gauthier A, Vignola A, Calvo A, Cavallo E, Moglia C, Sellitti L et al. A longitudinal study on quality of life and depression in ALS patient-caregiver couples. Neurology. 2007; 68(12):923-926

235 Gay PC, Westbrook PR, Daube JR, Litchy WJ, Windebank AJ, Iverson R. Effects of alterations in pulmonary function and sleep variables on survival in patients with amyotrophic lateral sclerosis. Mayo Clinic Proceedings. 1991; 66(7):686-694

236 Gelinas DF, O'Connor P, Miller RG. Quality of life for ventilator-dependent ALS patients and their caregivers. Journal of the Neurological Sciences. 1998; 160(Suppl.1):S134-S136

237 Gelinas DF. Patient and caregiver communications and decisions. Neurology. 1997; 48(4 Suppl.4):S9-S14

238 Gent C, McGarry J, Pinnington L. Motor neurone disease: carers' experiences, behaviour and coping methods. British Journal of Neuroscience Nursing. 2009; 5(12):567-573

239 Gibbons CJ, Thornton EW, Young CA. The patient experience of fatigue in motor neurone disease. Frontiers in Psychology. 2013; 4:788

240 Gil J, Preux PM, Alioum A, Ketzoian C, Desport JC, Druet-Cabanac M et al. Disease progression and survival in ALS: first multi-state model approach. Amyotrophic Lateral Sclerosis. 2007; 8(4):224-229

241 Gledhill T, Ormerod C, Lekharaju V, Smith A, Bliss P. Survival of patients with motor neurone disease (MND) following referral for nutritional assessment. Proceedings of the Nutrition Society. 2011; 70:E315

242 Goldblatt D, Greenlaw J. Starting and stopping the ventilator for patients with amyotrophic lateral sclerosis. Neurologic Clinics. 1989; 7(4):789-806

243 Goldstein LH, Adamson M, Jeffrey L, Down K, Barby T, Wilson C et al. The psychological impact of MND on patients and carers. Journal of the Neurological Sciences. 1998; 160 Suppl 1:S114-S121

244 Goldstein LH, Atkins L, Landau S, Brown R, Leigh PN. Predictors of psychological distress in carers of people with amyotrophic lateral sclerosis: a longitudinal study. Psychological Medicine. 2006; 36(6):865-875

245 Goldstein LH, Atkins L, Landau S, Brown RG, Leigh PN. Longitudinal predictors of psychological distress and self-esteem in people with ALS. Neurology. 2006; 67(9):1652-1658

246 Goldstein LH, Atkins L, Leigh PN. Correlates of Quality of Life in people with motor neuron disease (MND). Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002; 3(3):123-129

247 Goldstein LH, Leigh PN. Motor neurone disease: A review of its emotional and cognitive consequences for patients and its impact on carers. British Journal of Health Psychology. 1999; 4(Part 3):193-208. DOI:http://dx.doi.org/10.1348/135910799168579

248 Gooch CL, Doherty TJ, Chan KM, Bromberg MB, Lewis RA, Stashuk DW et al. Motor unit number estimation: A technology and literature review. Muscle and Nerve. 2014; 50(6):884-893

249 Gooch CL, Pullman SL, Shungu DC, Ulug AM, Chane S, Gordon PH et al. Motor unit number estimation (MUNE) in diseases of the motor neuron: utility and comparative analysis in a multimodal biomarker study. Supplements to Clinical Neurophysiology. 2009; 60:153-162

250 Good P, Richard R, Syrmis W, Jenkins-Marsh S, Stephens J. Medically assisted nutrition for adult palliative care patients. Cochrane Database of Systematic Reviews. 2014; Issue 4:CD006274. DOI:10.1002/14651858.CD006274.pub3

251 Gordon PH, Cheng B, Salachas F, Pradat PF, Bruneteau G, Corcia P et al. Progression in ALS is not linear but is curvilinear. Journal of Neurology. 2010; 257(10):1713-1717

252 Gordon PH, Salachas F, Lacomblez L, Le Forestier N, Pradat PF, Bruneteau G et al. Predicting survival of patients with amyotrophic lateral sclerosis at presentation: a 15-year experience. Neuro-Degenerative Diseases. 2013; 12(2):81-90

253 Gracies JM. Physiological effects of botulinum toxin in spasticity. Movement Disorders. 2004; 19(Suppl.8):S120-S128

254 Gredal O, Jakobsen S, Hovmand B. Preliminary evaluation of ENDOF-life care for patients suffering from motor neuron disease in Denmark. Amyotrophic Lateral Sclerosis. 2012; 13:140

255 Green C, Kiebert G, Murphy C, Mitchell JD, O'Brien M, Burrell A et al. Patients' health-related quality-of-life and health state values for motor neurone disease/amyotrophic lateral sclerosis. Quality of Life Research. 2003; 12(5):565-574

256 Gregory S, Siderowf A, Golaszewski AL, McCluskey L. Gastrostomy insertion in ALS patients with low vital capacity: respiratory support and survival. Neurology. 2002; 58(3):485-487

257 Grehl T, Rupp M, Budde P, Tegenthoff M, Fangerau H. Depression and QOL in patients with ALS: how do self-ratings and ratings by relatives differ? Quality of Life Research. 2011; 20(4):569-574

258 Grosskreutz J, Kaufmann J, Fradrich J, Dengler R, Heinze HJ, Peschel T. Widespread sensorimotor and frontal cortical atrophy in Amyotrophic Lateral Sclerosis. BMC Neurology. 2006; 6:17

259 Gruis K, Wren P, Huggins J. Amyotrophic lateral sclerosis patients' self-reported satisfaction with assistive technology. Amyotrophic Lateral Sclerosis. 2010; 11(S1):42

260 Guidubaldi A, Fasano A, Ialongo T, Piano C, Pompili M, Mascianà R et al. Botulinum toxin A versus B in sialorrhea: a prospective, randomized, double-blind, crossover pilot study in patients with amyotrophic lateral sclerosis or Parkinson's disease. Movement Disorders. 2011; 26(2):313-319

261 Guo J, Zhou M, Yang M, Zhu C, He L. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease. Cochrane Database of Systematic Reviews. 2011;(9):CD008554. DOI:10.1002/14651858.CD008554.pub2.

262 Hadjikoutis S, Wiles CM, Eccles R. Cough in motor neuron disease: a review of mechanisms. QJM. 1999; 92(9):487-494

263 Hagena A, Stananought N, Greene M, Asiam E, Pybus L, Carroll F et al. Motor neurone disease: what are the support needs of patients and carers? European Journal of Palliative Care. 2014; 21(5):232-235

264 Handa I, Matsushita N, Ihashi K, Yagi R, Mochizuki R, Mochizuki H et al. A clinical trial of therapeutic electrical stimulation for amyotrophic lateral sclerosis. Tohoku Journal of Experimental Medicine. 1995; 175(2):123-134

265 Hannan LM, Dominelli GS, Chen Y-W, Darlene RW, Road J. Systematic review of non-invasive positive pressure ventilation for chronic respiratory failure. Respiratory Medicine. 2014; 108(2):229-243

266 Hashizume A, Katsuno M, Banno H, Suzuki K, Suga N, Tanaka F et al. Difference in chronological changes of outcome measures between untreated and placebo-treated patients of spinal and bulbar muscular atrophy. Journal of Neurology. 2012; 259(4):712-719

267 Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain. 1995; 118(Pt.3):707-719

268 Hecht M, Hillemacher T, Grasel E, Tigges S, Winterholler M, Heuss D et al. Subjective experience and coping in ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002; 3(4):225-231

269 Hecht MJ, Graesel E, Tigges S, Hillemacher T, Winterholler M, Hilz MJ et al. Burden of care in amyotrophic lateral sclerosis. Palliative Medicine. 2003; 17(4):327-333

270 Hennies OL. A new skeletal muscle relaxant (DS 103-282) compared to diazepam in the treatment of muscle spasm of local origin. Journal of International Medical Research. 1981; 9(1):62-68

271 Herz H, McKinnon PM, Butow PN. Proof of love and other themes: A qualitative exploration of the experience of caring for people with motor neurone disease. Progress in Palliative Care. 2006; 14(5):209-214

272 Higo R, Tayama N, Nito T. Longitudinal analysis of progression of dysphagia in amyotrophic lateral sclerosis. Auris, Nasus, Larynx. 2004; 31(3):247-254

273 Hobson-Webb LD. Neuromuscular ultrasound in polyneuropathies and motor neuron disease. Muscle and Nerve. 2013; 47(6):790-804

274 Hocking C, Brott T, Paddy A. Caring for people with motor neurone disease. Journal of the Australasian Rehabilitation Nurses' Association (JARNA). 2006; 9(3):24-28

275 Hocking C, Brott T, Paddy A. Caring for people with motor neurone disease... including commentary by Love AW and Hughes R. International Journal of Therapy and Rehabilitation. 2006; 13(8):351-356

276 Hogden A, Greenfield D, Nugus P, Kiernan MC. Engaging in patient decision-making in multidisciplinary care for amyotrophic lateral sclerosis: the views of health professionals. Patient Preference and Adherence. 2012; 6:691-701

277 Hogden A, Greenfield D, Nugus P, Kiernan MC. What influences patient decision-making in amyotrophic lateral sclerosis multidisciplinary care? A study of patient perspectives. Patient Preference and Adherence. 2012; 6:829-838

278 Hogden A, Greenfield D, Nugus P, Kiernan MC. What are the roles of carers in decision-making for amyotrophic lateral sclerosis multidisciplinary care? Patient Preference and Adherence. 2013; 7:171-181

279 Hosaka M, Hoshiyama Y. Effects of diazepam on quality of life in patients receiving home oxygen therapy: A double-blind, crossover, placebo-controlled clinical trial. Journal of the Showa Medical Association. 1996; 56(5):522-529

280 Househam E, Swash M. Diagnostic delay in amyotrophic lateral sclerosis: what scope for improvement? Journal of the Neurological Sciences. 2000; 180(1-2):76-81

281 Hubbard RW, Will AD, Peterson GW, Sanchez A, Gillan WW, Tan SA. Elevated plasma glucagon in amyotrophic lateral sclerosis. Neurology. 1992; 42(8):1532-1534

282 Hugel H, Pih N, Dougan CP, Rigby S, Young CA. Identifying poor adaptation to a new diagnosis of motor neuron disease: A pilot study into the value of an early patient-led interview. Amyotrophic Lateral Sclerosis. 2010; 11(1-2):104-109

283 Hughes RA, Down K, Sinha A, Higginson IJ, Leigh PN. Building user involvement in motor neurone disease: key lessons. Journal of Interprofessional Care. 2004; 18(1):80-81

284 Hughes RA, Sinha A, Higginson I, Down K, Leigh PN. Living with motor neurone disease: lives, experiences of services and suggestions for change. Health and Social Care in the Community. 2005; 13(1):64-74

285 Hunter MD, Robinson IC, Neilson S. The functional and psychological status of patients with amyotrophic lateral sclerosis: some implications for rehabilitation. Disability and Rehabilitation. 1993; 15(3):119-126

286 Ingram DA, Swash M. Central motor conduction is abnormal in motor neuron disease. Journal of Neurology, Neurosurgery and Psychiatry. 1987; 50(2):159-166

287 Iwasaki Y, Ikeda K, Kinoshita M. The diagnostic pathway in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2001; 2(3):123-126

288 Jablecki CK, Berry C, Leach J. Survival prediction in amyotrophic lateral sclerosis. Muscle and Nerve. 1989; 12(10):833-841

289 JacKson CE, Gronseth G, Rosenfeld J, Barohn RJ, Dubinsky R, Simpson CB et al. Randomized double-blind study of botulinum toxin type B for sialorrhea in ALS patients. Muscle and Nerve. 2009; 39(2):137-143

290 Janes SEJ, Price CSG, Khan S. Percutaneous endoscopic gastrostomy: 30-day mortality trends and risk factors. Journal of Postgraduate Medicine. 2005; 51(1):23-29

291 Javad Mousavi SA, Zamani B, Shahabi Shahmiri S, Rohani M, Shahidi GA, Mostafapour E et al. Pulmonary function tests in patients with amyotrophic lateral sclerosis and the association between these tests and survival. Iranian Journal of Neurology. 2014; 13(3):131-137

292 Jawaid A, Murthy SB, Wilson AM, Qureshi SU, Amro MJ, Wheaton M et al. A decrease in body mass index is associated with faster progression of motor symptoms and shorter survival in ALS. Amyotrophic Lateral Sclerosis. 2010; 11(6):542-548

293 Jefferies KA, Bromberg MB. The role of a clinical pharmacist in a multidisciplinary amyotrophic lateral sclerosis clinic. Amyotrophic Lateral Sclerosis. 2012; 13(2):233-236

294 Jelsone-Swain L, Persad C, Votruba KL, Weisenbach SL, Johnson T, Gruis KL et al. The Relationship between Depressive Symptoms, Disease State, and Cognition in Amyotrophic Lateral Sclerosis. Frontiers in Psychology. 2012; 3:542

295 Jenkinson C, Levvy G, Fitzpatrick R, Garratt A. The amyotrophic lateral sclerosis assessment questionnaire (ALSAQ-40): tests of data quality, score reliability and response rate in a survey of patients. Journal of the Neurological Sciences. 2000; 180(1-2):94-100

296 Jennings A-L, Davies AN, Higgins JPT, Gibbs JSR, Broadley KE. A systematic review of the use of opioids in the management of dyspnoea. Thorax. 2002; 57(11):939-944

297 Jennings AL, Davies AN, Higgins Julian PT, Anzures-Cabrera J, Broadley KE. Opioids for the palliation of breathlessness in advanced disease and terminal illness. Cochrane Database of Systematic Reviews. 2012; Issue 7:CD002066. DOI:10.1002/14651858.CD002066.pub2

298 Jennum P, Ibsen R, Pedersen SW, Kjellberg J. Mortality, health, social and economic consequences of amyotrophic lateral sclerosis: a controlled national study. Journal of Neurology. 2013; 260(3):785-793

299 Jesus P, Massoulard A, Marin B, Nicol M, Laplagne O, Baptiste A et al. First assessment at home of amyotrophic lateral sclerosis (ALS) patients by a nutrition network in the French region of Limousin. Amyotrophic Lateral Sclerosis. 2012; 13(6):538-543

300 Ji Y, Wei L, Chui D, Wang K, Fan D. Prospective memory tasks: a more sensitive method for screening cognitive impairment in ALS? BMC Neurology. 2012; 12:142

301 Johnson JO, Sulmasy DP, Nolan MT. Patients' experiences of being a burden on family in terminal illness. Journal of Hospice and Palliative Nursing. 2007; 9(5):264-269

302 Johnston M, Earll L, Giles M, McClenahan R, Stevens D, Morrison V. Mood as a predictor of disability and survival in patients newly diagnosed with ALS/MND. British Journal of Health Psychology. 1999; 4(2):127-136

303 Johnston M, Earll L, Mitchell E, Morrison V, Wright S. Communicating the diagnosis of motor neurone disease. Palliative Medicine. 1996; 10(1):23-34

304 Jones AR, Jivraj N, Balendra R, Murphy C, Kelly J, Thornhill M et al. Health utility decreases with increasing clinical stage in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(3-4):285-291

305 Jongerius PH, Rotteveel JJ, van Limbeek J, Gabreels FJM, van Hulst K, van den Hoogen FJA. Botulinum toxin effect on salivary flow rate in children with cerebral palsy. Neurology. 2004; 63(8):1371-1375

306 Jongerius PH, van den Hoogen FJA, van Limbeek J, Gabreels FJ, van Hulst K, Rotteveel JJ. Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. Pediatrics. 2004; 114(3):620-627

307 Kageyama Y, Hirata M, Yanagisawa T, Shimokawa T, Sawada J, Morris S et al. Severely affected ALS patients have broad and high expectations for brain-machine interfaces. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(7-8):513-519

308 Kalf JG, Smit AM, Bloem BR, Zwarts MJ, Mulleners WM, Munneke M. Botulinum toxin A for drooling in Parkinson's disease: a pilot study to compare submandibular to parotid gland injections. Parkinsonism and Related Disorders. 2007; 13(8):532-534

309 Kang SW, Bach JR. Maximum insufflation capacity. Chest. 2000; 118(1):61-65

310 Kang SW, Bach JR. Maximum insufflation capacity: vital capacity and cough flows in neuromuscular disease. American Journal of Physical Medicine and Rehabilitation. 2000; 79(3):222-227

311 Kang S-C, Hwang S-J, Wu P-Y, Tsai C-P. The utilization of hospice care among patients with motor neuron diseases: The experience in Taiwan from 2005 to 2010. Journal of the Chinese Medical Association. 2013; 76(7):390-394

312 Kano O, Iwamoto K, Ito H, Kawase Y, Cridebring D, Ikeda K et al. Limb-onset amyotrophic lateral sclerosis patients visiting orthopedist show a longer time-to-diagnosis since symptom onset. BMC Neurology. 2013; 13:19

313 Karam C, Barrett MJ, Imperato T, Macgowan DJL, Scelsa S. Vitamin D deficiency and its supplementation in patients with amyotrophic lateral sclerosis. Journal of Clinical Neuroscience. 2013; 20(11):1550-1553

314 Karam C, Scelsa SN, Macgowan DJL. The clinical course of progressive bulbar palsy. Amyotrophic Lateral Sclerosis. 2010; 11(4):364-368

315 Kasarskis E. Disease-modifying interventions. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(Suppl.1):76-78

316 Kasarskis EJ, Scarlata D, Hill R, Fuller C, Stambler N, Cedarbaum JM. A retrospective study of percutaneous endoscopic gastrostomy in ALS patients during the BDNF and CNTF trials. Journal of the Neurological Sciences. 1999; 169(1-2):118-125

317 Kaufmann P, Levy G, Thompson JLP, Delbene ML, Battista V, Gordon PH et al. The ALSFRSr predicts survival time in an ALS clinic population. Neurology. 2005; 64(1):38-43

318 Kaufmann P, Pullman SL, Shungu DC, Chan S, Hays AP, Del Bene ML et al. Objective tests for upper motor neuron involvement in amyotrophic lateral sclerosis (ALS). Neurology. 2004; 62(10):1753-1757

319 Keenan MA, Lee GA, Tuckman AS, Esquenazi A. Improving calf muscle strength in patients with spastic equinovarus deformity by transfer of the long toe flexors to the Os calcis. Journal of Head Trauma Rehabilitation. 1999; 14(2):163-175

320 Khedr EM, Ahmed MA, Hamdy A, Shawky OA. Cortical excitability of amyotrophic lateral sclerosis: Transcranial magnetic stimulation study. Neurophysiologie Clinique. 2011; 41(2):73-79

321 Kihira T, Yoshida S, Okamoto K, Kazimoto Y, Ookawa M, Hama K et al. Survival rate of patients with amyotrophic lateral sclerosis in Wakayama Prefecture, Japan, 1966 to 2005. Journal of the Neurological Sciences. 2008; 268(1-2):95-101

322 Kim DH, Kang SW, Park YG, Choi WA, Lee HR. Artificial external glottic device for passive lung insufflation. Yonsei Medical Journal. 2011; 52(6):972-976

323 Kimura F, Fujimura C, Ishida S, Nakajima H, Furutama D, Uehara H et al. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology. 2006; 66(2):265-267

324 King SJ, Duke MM, O'Connor BA. Living with amyotrophic lateral sclerosis/motor neurone disease (ALS/MND): decision-making about 'ongoing change and adaptation'. Journal of Clinical Nursing. 2009; 18(5):745-754

325 Kissel JT, Elsheikh B, King WM, Freimer M, Scott CB, Kolb SJ et al. SMA valiant trial: a prospective, double-blind, placebo-controlled trial of valproic acid in ambulatory adults with spinal muscular atrophy. Muscle and Nerve. 2014; 49(2):187-192

326 Kleopa KA, Sherman M, Neal B, Romano GJ, Heiman-Patterson T. Bipap improves survival and rate of pulmonary function decline in patients with ALS. Journal of the Neurological Sciences. 1999; 164(1):82-88

327 Kloos AD, Dal Bello-Haas V, Thome R, Cassidy J, Lewis L, Cusma T et al. Interrater and intrarater reliability of the Tinetti Balance Test for individuals with amyotrophic lateral sclerosis. Journal of Neurologic Physical Therapy. 2004; 28(1):12-19

328 Kollewe K, Mauss U, Krampfl K, Petri S, Dengler R, Mohammadi B. ALSFRS-R score and its ratio: a useful predictor for ALS-progression. Journal of the Neurological Sciences. 2008; 275(1-2):69-73

329 Korner S, Siniawski M, Kollewe K, Rath KJ, Krampfl K, Zapf A et al. Speech therapy and communication device: Impact on quality of life and mood in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(1):20-25

330 Korner S, Hendricks M, Kollewe K, Zapf A, Dengler R, Silani V et al. Weight loss, dysphagia and supplement intake in patients with amyotrophic lateral sclerosis (ALS): impact on quality of life and therapeutic options. BMC Neurology. 2013; 13:84

331 Kostic Dedic SI, Stevic Z, Dedic V, Stojanovic VR, Milicev M, Lavrnic D. Is hyperlipidemia correlated with longer survival in patients with amyotrophic lateral sclerosis? Neurological Research. 2012; 34(6):576-580

332 Krampe H, Bartels C, Victorson D, Enders CK, Beaumont J, Cella D et al. The influence of personality factors on disease progression and health-related quality of life in people with ALS. Amyotrophic Lateral Sclerosis. 2008; 9(2):99-107

333 Krampfl K, Mohammadi B, Komissarow L, Dengler R, Bufler J. Mirror movements and ipsilateral motor evoked potentials in ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(3):154-163

334 Kristjanson LJ, Aoun SM, Yates P. Are supportive services meeting the needs of Australians with neurodegenerative conditions and their families? Journal of Palliative Care. 2006; 22(3):151-157

335 Krivickas LS, Shockley L, Mitsumoto H. Home care of patients with amyotrophic lateral sclerosis (ALS). Journal of the Neurological Sciences. 1997; 152 Suppl 1:S82-S89

336 Kubler A, Winter S, Ludolph AC, Hautzinger M, Birbaumer N. Severity of depressive symptoms and quality of life in patients with amyotrophic lateral sclerosis. Neurorehabilitation and Neural Repair. 2005; 19(3):182-193

337 Kuhnlein P, Kubler A, Raubold S, Worrell M, Kurt A, Gdynia HJ et al. Palliative care and circumstances of dying in German ALS patients using non-invasive ventilation. Amyotrophic Lateral Sclerosis. 2008; 9(2):91-98

338 Kurt A, Nijboer F, Matuz T, Kubler A. Depression and anxiety in individuals with amyotrophic lateral sclerosis: Epidemiology and management. CNS Drugs. 2007; 21(4):279-291

339 Kurtzke JF. Risk factors in amyotrophic lateral sclerosis. Advances in Neurology. 1991; 56:245-270

340 Labra J, Allen C, Morrison S. The impact of percutaneous endoscopic gastrostomy on survival in patients with motor neurone disease: Results from an Australian mnd service. Amyotrophic Lateral Sclerosis. 2011; 12(S1):67

341 Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Movement Disorders. 2006; 21(5):704-707

342 Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG. Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling. Journal of Neurology. 2009; 256(4):563-567

343 Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins. 2013; 5(5):1010-1031

344 Lange DJ, Lechtzin N, Davey C, David W, Heiman-Patterson T, Gelinas D et al. High-frequency chest wall oscillation in ALS: an exploratory randomized, controlled trial. Neurology. 2006; 67(6):991-997

345 Lataste X, Emre M, Davis C, Groves L. Comparative profile of tizanidine in the management of spasticity. Neurology. 1994; 44(11 Suppl.9):S53-S59

346 Lee C, Chun J, Im JP, Kim JW, Kim S-E, Ryu DY et al. Risk factors for complications and mortality of percutaneous endoscopic gastrostomy: A multicenter, retrospective study. Gastrointestinal Endoscopy. 2013; 77(5 Suppl.1):AB247

347 Lee CT-C, Chiu YW, Wang KC, Hwang CS, Lin KH, Lee IT et al. Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan. Journal of Epidemiology / Japan Epidemiological Association. 2013; 23(1):35-40

348 Lee JRJ, Annegers JF, Appel SH. Prognosis of amyotrophic lateral sclerosis and the effect of referral selection. Journal of the Neurological Sciences. 1995; 132(2):207-215

349 Lemoignan J, Ells C. Amyotrophic lateral sclerosis and assisted ventilation: how patients decide. Palliative and Supportive Care. 2010; 8(2):207-213

350 Leonardis L, Dolenc Groselj L, Vidmar G. Factors related to respiration influencing survival and respiratory function in patients with amyotrophic lateral sclerosis: a retrospective study. European Journal of Neurology. 2012; 19(12):1518-1524

351 Lerum SV, Solbraekke KN, Holmoy T, Frich JC. Unstable terminality: negotiating the meaning of chronicity and terminality in motor neurone disease. Sociology of Health and Illness. 2015; 37(1):81-96

352 Levine TD, Bowser R, Hank N, Saperstein D. A pilot trial of memantine and riluzole in ALS: correlation to CSF biomarkers. Amyotrophic Lateral Sclerosis. 2010; 11(6):514-519

353 Li TM, Swash M, Alberman E, Day SJ. Diagnosis of motor neuron disease by neurologists: a study in three countries. Journal of Neurology, Neurosurgery and Psychiatry. 1991; 54(11):980-983

354 Lillo P, Mioshi E, Hodges JR. Caregiver burden in amyotrophic lateral sclerosis is more dependent on patients' behavioral changes than physical disability: a comparative study. BMC Neurology. 2012; 12:156

355 Lillo P, Mioshi E, Zoing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? Amyotrophic Lateral Sclerosis. 2011; 12(1):45-51

356 Lima NMFV, Nucci A. Clinical attention and assistance profile of patients with amyotrophic lateral sclerosis. Arquivos De Neuro-Psiquiatria. 2011; 69(2A):170-175

357 Limousin N, Blasco H, Corcia P, Gordon PH, De Toffol B, Andres C et al. Malnutrition at the time of diagnosis is associated with a shorter disease duration in ALS. Journal of the Neurological Sciences. 2010; 297(1-2):36-39

358 Lin CH, Winstein CJ, Fisher BE, Wu AD. Neural correlates of the contextual interference effect in motor learning: a transcranial magnetic stimulation investigation. Journal of Motor Behavior. 2010; 42(4):223-232

359 Lin YC, Shieh JY, Cheng ML, Yang PY. Botulinum toxin type A for control of drooling in Asian patients with cerebral palsy. Neurology. 2008; 70(4):316-318

360 Lipp A, Trottenberg T, Schink T, Kupsch A, Arnold G. A randomized trial of botulinum toxin A for treatment of drooling. Neurology. 2003; 61(9):1279-1281

361 Little SA, Kubba H, Hussain SSM. An evidence-based approach to the child who drools saliva. Clinical Otolaryngology. 2009; 34(3):236-239

362 Liu XX, Zhang J, Zheng JY, Zhang S, Xu YS, Kang DX et al. Stratifying disease stages with different progression rates determined by electrophysiological tests in patients with amyotrophic lateral sclerosis. Muscle and Nerve. 2009; 39(3):304-309

363 Lo Coco G, Lo Coco D, Cicero V, Oliveri A, Lo Verso G, Piccoli F et al. Individual and health-related quality of life assessment in amyotrophic lateral sclerosis patients and their caregivers. Journal of the Neurological Sciences. 2005; 238(1-2):11-17

364 Locock L, Brown JB. 'All in the same boat'? Patient and carer attitudes to peer support and social comparison in Motor Neurone Disease (MND). Social Science and Medicine. 2010; 71(8):1498-1505

365 Locock L, Mazanderani F, Powell J. Metaphoric language and the articulation of emotions by people affected by motor neurone disease. Chronic Illness. 2012; 8(3):201-213

366 Locock L, Ziebland S, Dumelow C. Biographical disruption, abruption and repair in the context of motor neurone disease. Sociology of Health and Illness. 2009; 31(7):1043-1058

367 Lopez BJ, Perestelo PL, Monton AF, Serrano AP, Alfonso SJL. Social economic costs and health-related quality of life in patients with amyotrophic lateral sclerosis in Spain. Amyotrophic Lateral Sclerosis. 2009; 10(4):237-243

368 Louwerse ES, Visser CE, Bossuyt PMM, Weverling GJ. Amyotrophic lateral sclerosis: Mortality risk during the course of the disease and prognostic factors. Journal of the Neurological Sciences. 1997; 152(Suppl.1):S10-S17

369 Louwerse ES, Weverling GJ, Bossuyt PM, Meyjes FE, Jong JM. Randomized, double-blind, controlled trial of acetylcysteine in amyotrophic lateral sclerosis. Archives of Neurology. 1995; 52(6):559-564

370 Love A, Street A, Harris R, Lowe R. Social aspects of caregiving for people living with motor neurone disease: their relationships to carer well-being. Palliative and Supportive Care. 2005; 3(1):33-38

371 Lui AJ, Byl NN. A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis. Journal of Neurologic Physical Therapy. 2009; 33(2):68-87

372 Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain. 2001; 124(Pt.10):2000-2013

373 Mancini F, Zangaglia R, Cristina S, Sommaruga MG, Martignoni E, Nappi G et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Movement Disorders. 2003; 18(6):685-688

374 Mandrioli J, Faglioni P, Nichelli P, Sola P. Amyotrophic lateral sclerosis: prognostic indicators of survival. Amyotrophic Lateral Sclerosis. 2006; 7(4):211-220

375 Mannino M, Cellura E, Grimaldi G, Volanti P, Piccoli F, La Bella V. Telephone follow-up for patients with amyotrophic lateral sclerosis. European Journal of Neurology. 2007; 14(1):79-84

376 Marin B, Desport JC, Kajeu P, Jesus P, Nicolaud B, Nicol M et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. Journal of Neurology, Neurosurgery, and Psychiatry. 2011; 82(6):628-634

377 Martin J, Turnbull J. Lasting impact in families after death from ALS. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2001; 2(4):181-187

378 Mato A, Limeres J, Tomas I, Munoz M, Abuin C, Feijoo JF et al. Management of drooling in disabled patients with scopolamine patches. British Journal of Clinical Pharmacology. 2010; 69(6):684-688

379 Matsumura T, Saito T, Fujimura H, Shinno S, Sakoda S. Lung inflation training using a positive end-expiratory pressure valve in neuromuscular disorders. Internal Medicine. 2012; 51(7):711-716

380 Mayer RF. Living with amyotrophic lateral sclerosis (ALS). Loss, Grief and Care. 1990; 4(3-4):23-30

381 Mazzini L, Mora G, Balzarini C, Brigatti M, Pirali I, Comazzi F et al. The natural history and the effects of gabapentin in amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 1998; 160(Suppl.1):S57-S63

382 McCluskey L, Casarett D, Siderowf A. Breaking the news: a survey of ALS patients and their caregivers. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(3):131-135

383 McConigley R, Kristjanson LJ, Aoun SM, Oldham L, Currow DC, O'Connor M et al. Staying just one step ahead: providing care for patients with motor neurone disease. BMJ Supportive and Palliative Care. 2014; 4(1):38-42

384 McDermott CJ, Maguire C, Cooper CL, Ackroyd R, Baird WO, Baudouin S et al. Protocol for diaphragm pacing in patients with respiratory muscle weakness due to motor neurone disease (DiPALS): a randomised controlled trial. BMC Neurology. 2012; 12:74

385 McDonald P, St Leger S. Provision of environmental control systems in the north west of England. Journal of Public Health Medicine. 1996; 18(4):443-448

386 McElhiney MC, Rabkin JG, Gordon PH, Goetz R, Mitsumoto H. Prevalence of fatigue and depression in ALS patients and change over time. Journal of Neurology, Neurosurgery and Psychiatry. 2009; 80(10):1146-1149

387 McKelvey M, Evans DL, Kawai N, Beukelman D. Communication styles of persons with ALS as recounted by surviving partners. Augmentative and Alternative Communication. 2012; 28(4):232-242

388 McKim DA, King J, Walker K, Leblanc C, Timpson D, Wilson KG et al. Formal ventilation patient education for ALS predicts real-life choices. Amyotrophic Lateral Sclerosis. 2012; 13(1):59-65

389 McLeod JE, Clarke DM. A review of psychosocial aspects of motor neurone disease. Journal of the Neurological Sciences. 2007; 258(1-2):4-10

390 McNaughton D, Light J, Groszyk L. "Don't give up": employment experiences of individuals with amyotrophic lateral sclerosis who use augmentative and alternative communication. AAC: Augmentative and Alternative Communication. 2001; 17(3):179-195

391 Mefferd AS, Green JR, Pattee G. A novel fixed-target task to determine articulatory speed constraints in persons with amyotrophic lateral sclerosis. Journal of Communication Disorders. 2012; 45(1):35-45

392 Menke RAL, Abraham I, Thiel CS, Filippini N, Knight S, Talbot K et al. Fractional anisotropy in the posterior limb of the internal capsule and prognosis in amyotrophic lateral sclerosis. Archives of Neurology. 2012; 69(11):1493-1499

393 Mier RJ, Bachrach SJ FAU, Lakin RC FAU, Barker TF, Childs JF, Moran M. Treatment of sialorrhea with glycopyrrolate: A double-blind, dose-ranging study. Archives of Pediatrics and Adolescent Medicine. 2000; 154(12):1214-1218

394 Miller RG, JacKson CE, Kasarskis EJ. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009; 73(15):1227-1233

395 Miller RG, Moore D, Young LA, Armon C, Barohn RJ, Bromberg MB et al. Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis. WALS Study Group. Western Amyotrophic Lateral Sclerosis Study Group. Neurology. 1996; 47(6):1383-1388

396 Miller RG, Moore DH, Gelinas DF, Dronsky V, Mendoza M, Barohn RJ et al. Phase III randomized trial of gabapentin in patients with amyotrophic lateral sclerosis. Neurology. 2001; 56(7):843-848

397 Mills KR. The natural history of central motor abnormalities in amyotrophic lateral sclerosis. Brain. 2003; 126(Pt 11):2558-2566

398 Mistry K, Simpson J. Exploring the transitional process from receiving a diagnosis to living with motor neurone disease. Psychology and Health. 2013; 28(8):939-953

399 Mitchell SL, Tetroe JM. Survival after percutaneous endoscopic gastrostomy placement in older persons. Journals of Gerontology Series A, Biological Sciences and Medical Sciences. 2000; 55(12):M735-M739

400 Mitsumoto H, Davidson M, Moore D, Gad N, Brandis M, Ringel S et al. Percutaneous endoscopic gastrostomy (PEG) in patients with ALS and bulbar dysfunction. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2003; 4(3):177-185

401 Mitsumoto H, Ulug AM, Pullman SL, Gooch CL, Chan S, Tang MX et al. Quantitative objective markers for upper and lower motor neuron dysfunction in ALS. Neurology. 2007; 68(17):1402-1410

402 Miyashita M, Narita Y, Sakamoto A, Kawada N, Akiyama M, Kayama M et al. Care burden and depression in caregivers caring for patients with intractable neurological diseases at home in Japan. Journal of the Neurological Sciences. 2009; 276(1-2):148-152

403 Mock SE. Coping with ALS: The role of optimism and social coping among patients and caregivers. Dissertation Abstracts International: Section B: Sciences and Engineering. 2005; 66(4-B):2326

404 Mockford C, Jenkinson C, Fitzpatrick R. A Review: carers, MND and service provision. Amyotrophic Lateral Sclerosis. 2006; 7(3):132-141

405 Mockford C, Jenkinson C, Fitzpatrick R. Development of the Motor Neuron Disease Carer Questionnaire. Amyotrophic Lateral Sclerosis. 2009; 10(5-6):463-469

406 Mohammadi B, Kollewe K, Samii A, Dengler R, Munte TF. Functional neuroimaging at different disease stages reveals distinct phases of neuroplastic changes in amyotrophic lateral sclerosis. Human Brain Mapping. 2011; 32(5):750-758

407 Mondrup K, Pedersen E. The effect of the GABA-agonist, progabide, on stretch and flexor reflexes and on voluntary power in spastic patients. Acta Neurologica Scandinavica. 1984; 69(4):191-199

408 Moore MJ, Moore PB, Shaw PJ. Mood disturbances in motor neurone disease. Journal of the Neurological Sciences. 1998; 160 Suppl 1:S53-S56

409 Morassutti I, Giometto M, Baruffi C, Marcon ML, Michieletto S, Giometto B et al. Nutritional intervention for amyotrophic lateral sclerosis. Minerva Gastroenterologica e Dietologica. 2012; 58(3):253-260

410 Morgan RK, McNally S, Alexander M, Conroy R, Hardiman O, Costello RW. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. American Journal of Respiratory and Critical Care Medicine. 2005; 171(3):269-274

411 Morozova N, Weisskopf MG, McCullough ML, Munger KL, Calle EE, Thun MJ et al. Diet and amyotrophic lateral sclerosis. Epidemiology. 2008; 19(2):324-337

412 Morris ME, Perry A, Bilney B, Curran A, Dodd K, Wittwer JE et al. Outcomes of physical therapy, speech pathology, and occupational therapy for people with motor neuron disease: a systematic review. Neurorehabilitation and Neural Repair. 2006; 20(3):424-434

413 Morris MA, Dudgeon BJ, Yorkston K. A qualitative study of adult AAC users' experiences communicating with medical providers. Disability and Rehabilitation: Assistive Technology. 2013; 8(6):472-481

414 Moss AH, Casey P, Stocking CB, Roos RP, Brooks BR, Siegler M. Home ventilation for amyotrophic lateral sclerosis patients: outcomes, costs, and patient, family, and physician attitudes. Neurology. 1993; 43(2):438-443

415 Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. Archives of Physical Medicine and Rehabilitation. 1997; 78(5):521-524

416 Munsat TM, Riviere M, Swash M, Leclerc C. Economic burden of amyotrophic lateral sclerosis in the United Kingdom. British Journal of Medical Economics. 1998; 1:235-245:235-245

417 Mustfa N, Aiello M, Lyall RA, Nikoletou D, Olivieri D, Leigh PN et al. Cough augmentation in amyotrophic lateral sclerosis. Neurology. 2003; 61(9):1285-1287

418 Nakajima M, Eisen A, Stewart H. Diverse abnormalities of corticomotoneuronal projections in individual patients with amyotrophic lateral sclerosis. Electroencephalography and Clinical Neurophysiology. 1997; 105(6):451-457

419 National Institute for Health and Clinical Excellence. Social value judgements: principles for the development of NICE guidance. 2nd edition. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf

420 National Institute for Health and Clinical Excellence. Motor neurone disease: the use of non-invasive ventilation in the management of motor neurone disease. NICE clinical guideline 105. London. National Institute for Health and Clinical Excellence, 2010. Available from: http://guidance.nice.org.uk/CG105

421 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/

422 Nelson ND, Trail M, Van JN, Appel SH, Lai EC. Quality of life in patients with amyotrophic lateral sclerosis: perceptions, coping resources, and illness characteristics. Journal of Palliative Medicine. 2003; 6(3):417-424

423 Neppelberg E, Haugen DF, Thorsen L, Tysnes OB. Radiotherapy reduces sialorrhea in amyotrophic lateral sclerosis. European Journal of Neurology. 2007; 14(12):1373-1377

424 Neudert C, Oliver D, Wasner M, Borasio GD. The course of the terminal phase in patients with amyotrophic lateral sclerosis. Journal of Neurology. 2001; 248(7):612-616

425 Ng L, Kee K, Amatya B, Khan F, ChiÃƒÂ² A. Patient/carer perceptions of disability in motor neurone disease and carer coping... ...including commentary by Chio A. International Journal of Therapy and Rehabilitation. 2011; 18(10):568-578

426 Ng L, Talman P, Khan F. Motor neurone disease: disability profile and service needs in an Australian cohort. International Journal of Rehabilitation Research. 2011; 34(2):151-159

427 NHS Business Services Authority. NHS electronic drug tariff. 2014. Available from: http://www.ppa.org.uk/edt/August_2014/mindex.htm [Last accessed: 20 August 2015]

428 Nolan MT, Kub J, Hughes MT, Terry PB, Astrow AB, Carbo CA et al. Family health care decision making and self-efficacy with patients with ALS at the end of life. Palliative and Supportive Care. 2008; 6(3):273-280

429 Nordgarden H, Osterhus I, Moystad A, Asten P, Johnsen ULH, Storhaug K et al. Drooling: are botulinum toxin injections into the major salivary glands a good treatment option? Journal of Child Neurology. 2012; 27(4):458-464

430 Norris FH, Ks U, Sachais B, Carey M. Trial of baclofen in amyotrophic lateral sclerosis. Archives of Neurology. 1979; 36:715-716

431 Noseda A, Carpiaux JP, Markstein C, Meyvaert A, de Maertelaer V. Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. European Respiratory Journal. 1997; 10(5):1079-1083

432 O'Brien MR. Information-seeking behaviour among people with motor neurone disease. British Journal of Nursing. 2004; 13(16):964-968

433 O'Brien MR, Whitehead B, Jack BA, Mitchell JD. The need for support services for family carers of people with motor neurone disease (MND): views of current and former family caregivers a qualitative study. Disability and Rehabilitation. 2012; 34(3):247-256

434 O'Brien MR, Whitehead B, Jack BA, Mitchell JD. From symptom onset to a diagnosis of amyotrophic lateral sclerosis/motor neuron disease (ALS/MND): experiences of people with ALS/MND and family carers - a qualitative study. Amyotrophic Lateral Sclerosis. 2011; 12(2):97-104

435 O'Brien MR, Whitehead B, Murphy PN, Mitchell JD, Jack BA. Social services homecare for people with motor neurone disease/amyotrophic lateral sclerosis: why are such services used or refused? Palliative Medicine. 2012; 26(2):123-131

436 O'Connor EJ, McCabe MP. Predictors of quality of life in carers for people with a progressive neurological illness: a longitudinal study. Quality of Life Research. 2011; 20(5):703-711

437 O'Neill CL, Williams TL, Peel ET, McDermott CJ, Shaw PJ, Gibson GJ et al. Non-invasive ventilation in motor neuron disease: an update of current UK practice. Journal of Neurology, Neurosurgery and Psychiatry. 2012; 83(4):371-376

438 O'Reilly EJ, Wang H, Weisskopf MG, Fitzgerald KC, Falcone G, McCullough ML et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(3):205-211

439 Oates BR, Glover EI, West DW, Fry JL, Tarnopolsky MA, Phillips SM. Low-volume resistance exercise attenuates the decline in strength and muscle mass associated with immobilization. Muscle and Nerve. 2010; 42(4):539-546

440 Oh H. Living with Amyotrophic Lateral Sclerosis in South Korea: An Ethnographic study with photo-elicitation University of Washington; 2011.

441 Oh H, Schepp K. Wives becoming caregivers. Journal of Hospice and Palliative Nursing. 2013; 15(4):244-250

442 Oh SI, Park A, Kim HJ, Oh KW, Choi H, Kwon MJ et al. Spectrum of cognitive impairment in Korean ALS patients without known genetic mutations. PloS One. 2014; 9(2):e87163

443 Olm C, Elman L, McCluskey L, McMillan C, Grossman M. Cognitive decline is associated with progressive grey matter disease in amyotrophic lateral sclerosis (ALS). Neurology. 2014; 82(10 Suppl.1):P2. 175

444 Olsson Ozanne AG, Graneheim UH, Persson L, Strang S. Factors that facilitate and hinder the manageability of living with amyotrophic lateral sclerosis in both patients and next of kin. Journal of Clinical Nursing. 2012; 21(9-10):1364-1373

445 Olsson Ozanne AG, Graneheim UH, Strang S. Finding meaning despite anxiety over life and death in amyotrophic lateral sclerosis patients. Journal of Clinical Nursing. 2013; 22(15-16):2141-2149

446 Olsson AG, Markhede I, Strang S, Persson LI. Differences in quality of life modalities give rise to needs of individual support in patients with ALS and their next of kin. Palliative and Supportive Care. 2010; 8(1):75-82

447 Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. 2004; 62(1):37-40

448 Oyebode JR, Smith HJ, Morrison K. The personal experience of partners of individuals with motor neuron disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(1):39-43

449 Paganoni S, Deng J, Jaffa M, Cudkowicz ME, Wills AM. Body mass index, not dyslipidemia, is an independent predictor of survival in amyotrophic lateral sclerosis. Muscle and Nerve. 2011; 44(1):20-24

450 Pagnini F, Lunetta C, Rossi G, Banfi P, Gorni K, Cellotto N et al. Existential well-being and spirituality of individuals with amyotrophic lateral sclerosis is related to psychological well-being of their caregivers. Amyotrophic Lateral Sclerosis. 2011; 12(2):105-108

451 Paillisse C, Lacomblez L, Dib M, Bensimon G, Garcia-Acosta S, Meininger V. Prognostic factors for survival in amyotrophic lateral sclerosis patients treated with riluzole. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2005; 6(1):37-44

452 Pallero M, Puy C, Guell R, Pontes C, Marti S, Torres F et al. Ambulatory adaptation to noninvasive ventilation in restrictive pulmonary disease: A randomized trial with cost assessment. Respiratory Medicine. 2014; 108(7):1014-1022

453 Palmer J, Stephen N, Endacott R. Facilitating end-of-life discussions in users of home mechanical ventilation that have a life-limiting neuromuscular disease. Thorax. 2012; 67(Suppl.2):A165

454 Park JH, Kang SW. Percutaneous radiologic gastrostomy in patients with amyotrophic lateral sclerosis on noninvasive ventilation. Archives of Physical Medicine and Rehabilitation. 2009; 90(6):1026-1029

455 Park JH, Kang SW, Won JY, Uhm CW. Fluoroscopy-guided percutaneous gastrostomy with pull technique for the amyotrophic lateral sclerosis patients with very low vital capacity. Journal of Parenteral and Enteral Nutrition. 2010; 34(4):421-425

456 Pastula DM, Coffman CJ, Allen KD, Oddone EZ, Kasarskis EJ, Lindquist JH et al. Factors associated with survival in the National Registry of Veterans with ALS. Amyotrophic Lateral Sclerosis. 2009; 10(5-6):332-338

457 Payne C, Wiffen PJ, Martin S. Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database of Systematic Reviews. 2012; Issue 1:CD008427. DOI:10.1002/14651858.CD008427.pub2

458 Pena MJ, Ravasco P, Machado M, Pinto A, Pinto S, Rocha L et al. What is the relevance of percutaneous endoscopic gastrostomy on the survival of patients with amyotrophic lateral sclerosis? Amyotrophic Lateral Sclerosis. 2012; 13(6):550-554

459 Penn RD, Kroin JS, York MM, Cedarbaum JM. Intrathecal ciliary neurotrophic factor delivery for treatment of amyotrophic lateral sclerosis (phase I trial). Neurosurgery. 1997; 40(1):94-100

460 Peters M, Fitzpatrick R, Doll H, Playford ED, Jenkinson C. Patients' experiences of health and social care in long-term neurological conditions in England: a cross-sectional survey. Journal of Health Services Research and Policy. 2013; 18(1):28-33

461 Peterson GM, Young RS, Dunne PF, Galloway JG, Parks TE. Pilot study of nebulised morphine for dyspnoea in palliative care patients. Australian Journal of Hospital Pharmacy. 1996; 26(5):545-547

462 Peysson S, Vandenberghe N, Philit F, Vial C, Petitjean T, Bouhour F et al. Factors predicting survival following noninvasive ventilation in amyotrophic lateral sclerosis. European Neurology. 2008; 59(3-4):164-171

463 Pinto A, de CM. Randomised controlled trial in non-invasive ventilation: What trial? Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(4):255-256

464 Pinto AC, Alves M, Nogueira A, Evangelista T, Carvalho J, Coelho A et al. Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? Journal of the Neurological Sciences. 1999; 169(1-2):69-75

465 Pinto S, Pinto A, de Carvalho M. Phrenic nerve studies predict survival in amyotrophic lateral sclerosis. Clinical Neurophysiology. 2012; 123(12):2454-2459

466 Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2012; 13(1):33-43

467 Polkey MI, Lyall RA, Green M, Nigel Leigh P, Moxham J. Expiratory muscle function in amyotrophic lateral sclerosis. American Journal of Respiratory and Critical Care Medicine. 1998; 158(3):734-741

468 Pongratz D. The diagnostic process in ALS. Journal of the Neurological Sciences. 1999; 165(Suppl.1):S10-S13

469 Preston H, Fineberg IC, Callagher P, Mitchell DJ. The preferred priorities for care document in motor neurone disease: views of bereaved relatives and carers. Palliative Medicine. 2012; 26(2):132-138

470 Preux PM, Couratier P, Boutros-Toni F, Salle JY, Tabaraud F, Bernet-Bernady P et al. Survival prediction in sporadic amyotrophic lateral sclerosis. Age and clinical form at onset are independent risk factors. Neuroepidemiology. 1996; 15(3):153-160

471 Raaphorst J, Beeldman E, Jaeger B, Schmand B, Van Den Berg LH, Weikamp JG et al. Is the Frontal Assessment Battery reliable in ALS patients? Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(1):73-74

472 Rabkin JG, Albert SM, Del Bene ML, O'Sullivan I, Tider T, Rowland LP et al. Prevalence of depressive disorders and change over time in late-stage ALS. Neurology. 2005; 65(1):62-67

473 Rabkin JG, Wagner GJ, Del Bene M. Resilience and distress among amyotrophic lateral sclerosis patients and caregivers. Psychosomatic Medicine. 2000; 62(2):271-279

474 Radunovic A, Annane D, Rafiq MK, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database of Systematic Reviews. 2013; Issue 3:CD004427. DOI:10.1002/14651858.CD004427.pub3

475 Rafiq MK. Non-invasive ventilation (NIV) in patients with Amyotrophic Lateral Sclerosis (ALS). Physiotherapy. 2013; 99(1):92

476 Rafiq MK, Bradburn M, Proctor AR, Billings CG, Bianchi S, McDermott CJ et al. A preliminary randomized trial of the mechanical insufflator-exsufflator versus breath-stacking technique in patients with amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2015; E publication

477 Rampoldi A, Lunetta C, De GA, Solcia M, Vercelli R, Migliorisi C et al. Radiologically inserted gastrostomy: Complications and survival in patients with motor neuron disease. Cardiovascular and Interventional Radiology. 2012; 35(1 Suppl.):S231

478 Ray RA, Brown J, Street AF. Dying with motor neurone disease, what can we learn from family caregivers? Health Expectations. 2014; 17(4):466-476

479 Ray RA, Street AF. Caregiver bodywork: family members' experiences of caring for a person with motor neurone disease. Journal of Advanced Nursing. 2006; 56(1):35-43

480 Reid SM, Johnstone BR, Westbury C, Rawicki B, Reddihough DS. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling in children with neurological disorders. Developmental Medicine and Child Neurology. 2008; 50(2):123-128

481 Restivo DA, Casabona A, Nicotra A, Zappia M, Elia M, Romano MC et al. ALS dysphagia pathophysiology: differential botulinum toxin response. Neurology. 2013; 80(7):616-620

482 Riccio A, Mattia D, Simione L, Olivetti M, Cincotti F. Eye-gaze independent EEG-based brain-computer interfaces for communication. Journal of Neural Engineering. 2012; 9(4):045001

483 Rio A, Ellis C, Shaw C, Willey E, Ampong MA, Wijesekera L et al. Nutritional factors associated with survival following enteral tube feeding in patients with motor neurone disease. Journal of Human Nutrition and Dietetics. 2010; 23(4):408-415

484 Rio A, Ampong MA, Turner MR, Shaw AS, Al-Chalabi A, Shaw CE et al. Comparison of two percutaneous radiological gastrostomy tubes in the nutritional management of ALS patients. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2005; 6(3):177-181

485 Rippon GA, Scarmeas N, Gordon PH, Murphy PL, Albert SM, Mitsumoto H et al. An observational study of cognitive impairment in amyotrophic lateral sclerosis. Archives of Neurology. 2006; 63(3):345-352

486 Ritsma BR, Berger MJ, Charland DA, Khoury MA, Phillips JT, Quon MJ et al. NIPPV: prevalence, approach and barriers to use at Canadian ALS centres. Canadian Journal of Neurological Sciences. 2010; 37(1):54-60

487 Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Archives of Neurology. 1998; 55(4):526-528

488 Roach AR, Averill AJ, Segerstrom SC, Kasarskis EJ. The dynamics of quality of life in ALS patients and caregivers. Annals of Behavioral Medicine. 2009; 37(2):197-206

489 Roccatagliata L, Bonzano L, Mancardi G, Canepa C, Caponnetto C. Detection of motor cortex thinning and corticospinal tract involvement by quantitative MRI in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2009; 10(1):47-52

490 Rocchetti I, Taruscio D, Pierannunzio D. Modeling delay to diagnosis for Amyotrophic lateral sclerosis: Under reporting and incidence estimates. BMC Neurology. 2012; 12

491 Rochester L, Vujnovich A, Newstead D, Williams M. The influence of eccentric contractions and stretch on alpha motoneuron excitability in normal subjects and subjects with spasticity. Electromyography and Clinical Neurophysiology. 2001; 41(3):171-177

492 Rodriguez de Rivera FJ, Oreja Guevara C, Sanz Gallego I, San Jose Valiente B, Santiago Recuerda A, Gomez Mendieta MA et al. Outcome of patients with amyotrophic lateral sclerosis attending in a multidisciplinary care unit. Neurologia. 2011; 26(8):455-460

493 Rodwell K, Edwards P, Ware RS, Boyd R. Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review. Developmental Medicine and Child Neurology. 2012; 54(11):977-987

494 Rooney J, Byrne S, Heverin M, Corr B, Elamin M, Staines A et al. Survival analysis of Irish amyotrophic lateral sclerosis patients diagnosed from 1995-2010. PloS One. 2013; 8(9):e47433

495 Rooney J, Byrne S, Heverin M, Tobin K, Dick A, Donaghy C et al. A multidisciplinary clinic approach improves survival in ALS: a comparative study of ALS in Ireland and Northern Ireland. Journal of Neurology, Neurosurgery, and Psychiatry. 2015; 86(5):496-501

496 Rosengren K, Gustafsson I, Jarnevi E. Every Second Counts: Womenâ€™s Experience of Living With ALS in the End-of-Life Situations. Home Health Care Management & Practice. 2015; 27(2):76-82

497 Rowland LP. Diagnosis of amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 1998; 160(Suppl.1):S6-24

498 Rusina R, Ridzon P, Kulist'ak P, Keller O, Bartos A, Buncova M et al. Relationship between ALS and the degree of cognitive impairment, markers of neurodegeneration and predictors for poor outcome. A prospective study. European Journal of Neurology. 2010; 17(1):23-30

499 Rutkove SB, Caress JB, Cartwright MS, Burns TM, Warder J, David WS et al. Electrical impedance myography as a biomarker to assess ALS progression. Amyotrophic Lateral Sclerosis. 2012; 13(5):439-445

500 Rutkove SB, Caress JB, Cartwright MS, Burns TM, Warder J, David WS et al. Electrical impedance myography correlates with standard measures of Als severity. Muscle and Nerve. 2014; 49(3):441-443

501 Sakellariou D, Boniface G, Brown P. Experiences of living with motor neurone disease: a review of qualitative research. Disability and Rehabilitation. 2013; 35(21):1765-1773

502 Sancho J, Servera E, Vergara P, Marin J. Mechanical insufflation-exsufflation vs. tracheal suctioning via tracheostomy tubes for patients with amyotrophic lateral sclerosis: a pilot study. American Journal of Physical Medicine and Rehabilitation. 2003; 82(10):750-753

503 Sancho J, Servera E, Chiner E, Banuls P, Gomez-Merino E, Sancho-Chust JN et al. Noninvasive respiratory muscle aids during PEG placement in ALS patients with severe ventilatory impairment. Journal of the Neurological Sciences. 2010; 297(1-2):55-59

504 Sancho J, Servera E, Diaz J, Marin J. Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. Chest. 2004; 125(4):1400-1405

505 Sarfaty M, Nefussy B, Gross D, Shapira Y, Vaisman N, Drory VE. Outcome of percutaneous endoscopic gastrostomy insertion in patients with amyotrophic lateral sclerosis in relation to respiratory dysfunction. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(7-8):528-532

506 Sarro L, Agosta F, Canu E, Riva N, Prelle A, Copetti M et al. Cognitive functions and white matter tract damage in amyotrophic lateral sclerosis: a diffusion tensor tractography study. American Journal of Neuroradiology. 2011; 32(10):1866-1872

507 Sathasivam S, Doran M, Larner AJ. Frontotemporal lobar degeneration with motor neurone disease (FTLD/MND): Presentations in psychiatric practice. International Journal of Psychiatry in Clinical Practice. 2008; 12(2):138-141

508 Scheffer AR, Erasmus C, Hulst K, Limbeek J, Rotteveel JJ, Jongerius PH et al. Botulinum toxin versus submandibular duct relocation for severe drooling. Developmental Medicine and Child Neurology. 2010; 52(11):1038-1042

509 Schellenberg KL, Schofield SJ, Fang S, Johnston WSW. Breaking bad news in amyotrophic lateral sclerosis: the need for medical education. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(1-2):47-54

510 Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, Lechtzin N. Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. Muscle and Nerve. 2006; 33(1):127-132

511 Scotton WJ, Scott KM, Moore DH, Almedom L, Wijesekera LC, Janssen A et al. Prognostic categories for amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2012; 13(6):502-508

512 Sebring DL, Moglia P. Amyotrophic lateral sclerosis: Psychosocial interventions for patients and their families. Health and Social Work. 1987; 12(2):113-120

513 Senent C, Golmard JL, Salachas F, Chiner E, Morelot-Panzini C, Meninger V et al. A comparison of assisted cough techniques in stable patients with severe respiratory insufficiency due to amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis. 2011; 12(1):26-32

514 Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. Cochrane Database of Systematic Reviews. 2003; Issue 4:CD001332. DOI:10.1002/14651858.CD001332

515 Shaw AS, Ampong MA, Rio A, Al-Chalabi A, Sellars MEK, Ellis C et al. Survival of patients with ALS following institution of enteral feeding is related to pre-procedure oximetry: a retrospective review of 98 patients in a single centre. Amyotrophic Lateral Sclerosis. 2006; 7(1):16-21

516 Sheean G. Botulinum toxin treatment of adult spasticity : a benefit-risk assessment. Drug Safety. 2006; 29(1):31-48

517 Shimizu T, Fujimaki Y, Nakatani-Enomoto S, Matsubara S, Watabe K, Rossini PM et al. Complex fasciculation potentials and survival in amyotrophic lateral sclerosis. Clinical Neurophysiology. 2014; 125(5):1059-1064

518 Shimizu T, Nagaoka U, Nakayama Y, Kawata A, Kugimoto C, Kuroiwa Y et al. Reduction rate of body mass index predicts prognosis for survival in amyotrophic lateral sclerosis: a multicenter study in Japan. Amyotrophic Lateral Sclerosis. 2012; 13(4):363-366

519 Sigan SN, Uzunhan TA, Aydinli N, Eraslan E, Ekici B, Caliskan M. Effects of oral motor therapy in children with cerebral palsy. Annals of Indian Academy of Neurology. 2013; 16(3):342-346

520 Silva LB, Mourão LF, Silva AA, Lima NM, Almeida SR, Franca Jr MC et al. Effect of nutritional supplementation with milk whey proteins in amyotrophic lateral sclerosis patients. Arquivos De Neuro-Psiquiatria. 2010; 68(2):263-268

521 Silva LBdC, Mourao LF, Silva AA, Lima NMFV, Almeida SR, Franca MCJ et al. Amyotrophic lateral sclerosis: combined nutritional, respiratory and functional assessment. Arquivos De Neuro-Psiquiatria. 2008; 66(2B):354-359

522 Silverstein MD, Stocking CB, Antel JP, Beckwith J, Roos RP, Siegler M. Amyotrophic lateral sclerosis and life-sustaining therapy: patients' desires for information, participation in decision making, and life-sustaining therapy. Mayo Clinic Proceedings. 1991; 66(9):906-913

523 Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. Cochrane Database of Systematic Reviews. 2010; Issue 1:CD007354. DOI:10.1002/14651858.CD007354.pub2

524 Smith PE, Wiles CM. Cough responsiveness in neurogenic dysphagia. Journal of Neurology, Neurosurgery and Psychiatry. 1998; 64(3):385-388

525 Solomon N, Clark H. Quantifying orofacial muscle stiffness using damped oscillation. Journal of Medical Speech-Language Pathology. 2010; 18(4):-4p

526 Spataro R, Ficano L, Piccoli F, La Bella V. Percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis: effect on survival. Journal of the Neurological Sciences. 2011; 304(1-2):44-48

527 Squires N, Humberstone M, Wills A, Arthur A. The use of botulinum toxin injections to manage drooling in amyotrophic lateral sclerosis/motor neurone disease: a systematic review. Dysphagia. 2014; 29(4):500-508

528 Srinivasan J, Scala S, Jones HR, Saleh F, Russell JA. Inappropriate surgeries resulting from misdiagnosis of early amyotrophic lateral sclerosis. Muscle and Nerve. 2006; 34(3):359-360

529 Stagg CJ, Knight S, Talbot K, Jenkinson M, Maudsley AA, Turner MR. Whole-brain magnetic resonance spectroscopic imaging measures are related to disability in ALS. Neurology. 2013; 80(7):610-615

530 Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. Neurology. 1998; 50(1):66-72

531 Stanich P, Castro I, Leico OA, Nakao F, Dos Santos SC, Silva T et al. Relevance of nutrition on survival of patients with motor neurone disease. Amyotrophic Lateral Sclerosis. 2011; 12(S1):67

532 Stavroulakis T, Walsh T, Shaw PJ, McDermott CJ, Progas S. Gastrostomy use in motor neurone disease (MND): a review, meta-analysis and survey of current practice. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(2):96-104

533 Steinlechner S, Klein C, Moser A, Lencer R, Hagenah J. Botulinum toxin B as an effective and safe treatment for neuroleptic-induced sialorrhea. Psychopharmacology. 2010; 207(4):593-597

534 Stokholm MG, Bisgard C, Vilholm OJ. Safety and administration of treatment with botulinum neurotoxin for sialorrhoea in ALS patients: Review of the literature and a proposal for tailored

treatment. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013; 14(7-8):516-520

535 Stone CA, O'Leary N. Systematic review of the effectiveness of botulinum toxin or radiotherapy for sialorrhea in patients with amyotrophic lateral sclerosis. Journal of Pain and Symptom Management. 2009; 37(2):246-258

536 Stoppel CM, Vielhaber S, Eckart C, Machts J, Kaufmann J, Heinze HJ et al. Structural and functional hallmarks of amyotrophic lateral sclerosis progression in motor- and memory-related brain regions. NeuroImage Clinical. 2014; 5:277-290

537 Stutzki R, Weber M, Reiter-Theil S, Simmen U, Borasio GD, Jox RJ. Attitudes towards hastened death in ALS: A prospective study of patients and family caregivers. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(1-2):68-76

538 Suleman M, Abaza KT, Gornall C, Kinnear WJM, Wills JS, Mahajan RP. The effect of a mechanical glottis on peak expiratory flow rate and time to peak flow during a peak expiratory flow manoeuvre: a study in normal subjects and patients with motor neurone disease. Anaesthesia. 2004; 59(9):872-875

539 Suleman M, Whitely A, Kinnear W. Expiratory muscle training in motor neurone disease [Abstract]. Thorax. 2003; 58(Suppl 3):iii77

540 Sundling I-M, Ekman S-L, Weinberg J, Klefbeck B. Patients' with ALS and caregivers' experiences of non-invasive home ventilation. Advances in Physiotherapy. 2009; 11(3):114-120

541 Swash M. Survey of non-invasive ventilation use in ALS in Britain. Journal of Neurology, Neurosurgery and Psychiatry. 2012; 83(4):370

542 Takeuchi Y, Katsuno M, Banno H, Suzuki K, Kawashima M, Atsuta N et al. Walking capacity evaluated by the 6-minute walk test in spinal and bulbar muscular atrophy. Muscle and Nerve. 2008; 38(2):964-971

543 Taylor B. The impact of assistive equipment on intimacy and sexual expression. British Journal of Occupational Therapy. 2011; 74(9):435-442

544 Taylor B. Sexuality, intimacy and motor neurone disease: matters of concern. British Journal of Neuroscience Nursing. 2014; 10(5):242-251

545 Taylor L, Wicks P, Leigh PN, Goldstein LH. Prevalence of depression in amyotrophic lateral sclerosis and other motor disorders. European Journal of Neurology. 2010; 17(8):1047-1053

546 Testa D, Lovati R, Ferrarini M, Salmoiraghi F, Filippini G. Survival of 793 patients with amyotrophic lateral sclerosis diagnosed over a 28-year period. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(4):208-212

547 Thijs V, Peeters E, Theys P, Matthijs G, Robberecht W. Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. Acta Neurologica Belgica. 2000; 100(2):84-90

548 Thomsen TR, Galpern WR, Asante A, Arenovich T, Fox SH. Ipratropium bromide spray as treatment for sialorrhea in Parkinson's disease. Movement Disorders. 2007; 22(15):2268-2273

549 Thornton FJ, Fotheringham T, Alexander M, Hardiman O, McGrath FP, Lee MJ. Amyotrophic lateral sclerosis: enteral nutrition provision--endoscopic or radiologic gastrostomy? Radiology. 2002; 224(3):713-717

550 Trail M, Nelson N, Van JN, Appel SH, Lai EC. Major stressors facing patients with amyotrophic lateral sclerosis (ALS): a survey to identify their concerns and to compare with those of their caregivers. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2004; 5(1):40-45

551 Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. Journal of Neurology, Neurosurgery and Psychiatry. 2003; 74(9):1258-1261

552 Truong DD, Bhidayasiri R. Evidence for the effectiveness of botulinum toxin for sialorrhoea. Journal of Neural Transmission. 2008; 115(4):631-635

553 Tscheng DZ. Sialorrhea - therapeutic drug options. Annals of Pharmacotherapy. 2002; 36(11):1785-1790

554 Tsou A, Long J, McCluskey L, Elman L, Karlawish J. Predictors of 30 day mortality after gastrostomy in amyotrophic lateral sclerosis. Neurology. 2012; 78(1 Meeting Abstracts):P01.102

555 Turhanoglu AD, Karabulut Z, Bayram H, Turhanoglu S, Erdogan F, Apak I et al. Botulinum toxin A in the treatment of spasticity -- an open label study. Journal of Back and Musculoskeletal Rehabilitation. 2002; 16(2/3):51-56

556 Turner MR, Bakker M, Sham P, Shaw CE, Leigh PN, Al-Chalabi A. Prognostic modelling of therapeutic interventions in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002; 3(1):15-21

557 Turner MR, Osei-Lah AD, Hammers A, Al-Chalabi A, Shaw CE, Andersen PM et al. Abnormal cortical excitability in sporadic but not homozygous D90A SOD1 ALS. Journal of Neurology, Neurosurgery and Psychiatry. 2005; 76(9):1279-1285

558 Turner MR, Scaber J, Goodfellow JA, Lord ME, Marsden R, Talbot K. The diagnostic pathway and prognosis in bulbar-onset amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 2010; 294(1-2):81-85

559 Tysnes OB. Treatment of sialorrhea in amyotrophic lateral sclerosis. Acta Neurologica Scandinavica Supplementum. 2008; 188:77-81

560 Tysnes OB, Vollset SE, Larsen JP, Aarli JA. Prognostic factors and survival in amyotrophic lateral sclerosis. Neuroepidemiology. 1994; 13(5):226-235

561 Ushikubo M, Tomita C, Inokuma A, Ikeda M, Okamoto K. Illness course and circumstances of death among individuals with rapidly progressive amyotrophic lateral sclerosis. International Medical Journal. 2013; 20(4):446-449

562 van den Berg J-P, Kalmijn S, Lindeman E, Veldink JH, de VM, Van Der Graaff MM et al. Multidisciplinary ALS care improves quality of life in patients with ALS. Neurology. 2005; 65(8):1264-1267

563 van den Berg J-P, Kalmijn S, Lindeman E, Wokke JHJ, van den Berg LH. Rehabilitation care for patients with ALS in The Netherlands. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2003; 4(3):186-190

564 van der Steen I, van den Berg J-P, Buskens E, Lindeman E, van den Berg LH. The costs of amyotrophic lateral sclerosis, according to type of care. Amyotrophic Lateral Sclerosis. 2009; 10(1):27-34

565 van Groenestijn AC, van de Port IGL, Schroder CD, Post MWM, Grupstra HF, Kruitwagen ET et al. Effects of aerobic exercise therapy and cognitive behavioural therapy on functioning and quality of life in amyotrophic lateral sclerosis: protocol of the FACTS-2-ALS trial. BMC Neurology. 2011; 11:70

566 van Teijlingen ER, Friend E, Kamal AD. Service use and needs of people with motor neurone disease and their carers in Scotland. Health and Social Care in the Community. 2001; 9(6):397-403

567 Vender RL, Mauger D, Walsh S, Alam S, Simmons Z. Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival. Amyotrophic Lateral Sclerosis. 2007; 8(1):36-41

568 Veronese S, Valle A, Oliver D. The last months of life of people with motor neurone disease in mechanical invasive ventilation: A qualitative study. Palliative Medicine. 2012; 26(4):612

569 Veronese S, Valle A, Chio A, Calvo A, Oliver D. The last months of life of people with amyotrophic lateral sclerosis in mechanical invasive ventilation: a qualitative study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2014; 15(7-8):499-504

570 Verschueren A, Monnier A, Attarian S, Lardillier D, Pouget J. Enteral and parenteral nutrition in the later stages of ALS: an observational study. Amyotrophic Lateral Sclerosis. 2009; 10(1):42-46

571 Visser J, Van den Berg-Vos R, Franssen H, van den Berg LH, Wokke JH, de Jong JMV et al. Disease course and prognostic factors of progressive muscular atrophy. Archives of Neurology. 2007; 64(4):522-528

572 Vitacca M, Clini E, Facchetti D, Pagani M, Poloni M, Porta R et al. Breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis. European Respiratory Journal. 1997; 10(7):1614-1621

573 Vitacca M, Bazza A, Bianchi L, Gile S, Assoni G, Porta R et al. Tele-assistance in chronic respiratory failure: patients' characterization and staff workload of 5-year activity. Telemedicine Journal and E-Health. 2010; 16(3):299-305

574 Wang FC, Bouquiaux O, De Pasqua V, Delwaide PJ. Changes in motor unit numbers in patients with ALS: a longitudinal study using the adapted multiple point stimulation method. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 2002; 3(1):31-38

575 Wasner M, Bold U, Vollmer TC, Borasio GD. Sexuality in patients with amyotrophic lateral sclerosis and their partners. Journal of Neurology. 2004; 251(4):445-448

576 Whitehead B, O'Brien MR, Jack BA, Mitchell D. Experiences of dying, death and bereavement in motor neurone disease: a qualitative study. Palliative Medicine. 2012; 26(4):368-378

577 Wicks P, Abrahams S, Masi D, Hejda-Forde S, Leigh PN, Goldstein LH. Prevalence of depression in a 12-month consecutive sample of patients with ALS. European Journal of Neurology. 2007; 14(9):993-1001

578 Wicks P, Frost J. ALS patients request more information about cognitive symptoms. European Journal of Neurology. 2008; 15(5):497-500

579 Wicks P, Massagli M, Frost J, Brownstein C, Okun S, Vaughan T et al. Sharing health data for better outcomes on patients like me. Journal of Medical Internet Research. 2010; 12(2):117-128

580 Williams MT, Donnelly JP, Holmlund T, Battaglia M. ALS: Family caregiver needs and quality of life. Amyotrophic Lateral Sclerosis. 2008; 9(5):279-286

581 Wills AM, Hubbard J, Macklin EA, Glass J, Tandan R, Simpson EP et al. Hypercaloric enteral nutrition in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet. 2014; 383(9934):2065-2072

582 Winck JC, Goncalves MR, Lourenco C, Viana P, Almeida J, Bach JR. Effects of mechanical insufflation-exsufflation on respiratory parameters for patients with chronic airway secretion encumbrance. Chest. 2004; 126(3):774-780

583 Wissel J, Ward AB, Erztgaard P, Bensmail D, Hecht MJ, Lejeune TM et al. European consensus table on the use of botulinum toxin type A in adult spasticity. Journal of Rehabilitation Medicine. 2009; 41(1):13-25

584 Wolf J, Safer A, Wohrle JC, Palm F, Nix WA, Maschke M et al. Factors predicting one-year mortality in amyotrophic lateral sclerosis patients - data from a population-based registry. BMC Neurology. 2014; 14:197

585 Wu KP-H, Ke JY, Chen CY, Chen CL, Chou MY, Pei YC. Botulinum toxin type A on oral health in treating sialorrhea in children with cerebral palsy: a randomized, double-blind, placebo-controlled study. Journal of Child Neurology. 2011; 26(7):838-843

586 Yi Z, Liu F, Zhai S, Belsh J, Zhan S, Schiffman P. Pharmacological interventions for improving respiratory function in amyotrophic lateral sclerosis. Cochrane Database of Systematic Reviews. 2012; Issue 8:CD010030. DOI:10.1002/14651858.CD010030

587 Young JM, McNicoll P. Against all odds: positive life experiences of people with advanced amyotrophic lateral sclerosis. Health and Social Work. 1998; 23(1):35-43

588 Yuen EC, Olney RK. Longitudinal study of fiber density and motor unit number estimate in patients with amyotrophic lateral sclerosis. Neurology. 1997; 49(2):573-578

589 Yunusova Y, Weismer GG, Lindstrom MJ. Classifications of vocalic segments from articulatory kinematics: healthy controls and speakers with dysarthria. Journal of Speech, Language, and Hearing Research. 2011; 54(5):1302-1311

590 Zanette G, Forgione A, Manganotti P, Fiaschi A, Tamburin S. The effect of repetitive transcranial magnetic stimulation on motor performance, fatigue and quality of life in amyotrophic lateral sclerosis. Journal of the Neurological Sciences. 2008; 270(1-2):18-22

591 Zeller RS, Lee HM, Cavanaugh PF, Davidson J. Randomized phase III evaluation of the efficacy and safety of a novel glycopyrrolate oral solution for the management of chronic severe drooling in children with cerebral palsy or other neurologic conditions. Therapeutics and Clinical Risk Management. 2012; 8:15-23

592 Zhang Y, Schuff N, Woolley SC, Chiang GC, Boreta L, Laxamana J et al. Progression of white matter degeneration in amyotrophic lateral sclerosis: A diffusion tensor imaging study. Amyotrophic Lateral Sclerosis. 2011; 12(6):421-429

593 Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Lepore V et al. ALS multidisciplinary clinic and survival. Results from a population-based study in Southern Italy. Journal of Neurology. 2007; 254(8):1107-1112