National Clinical Guideline Centre

Motor neurone disease

Motor neurone disease: assessment and management

Clinical guideline <...>

Methods, evidence and recommendations

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1 Guideline summary

1.1 Full list of recommendations

Recognition and referral

1. Ensure that robust protocols and pathways are in place to:
    - inform healthcare professionals about motor neurone disease (MND) and how it may present
    - inform healthcare professionals in all settings about local referral arrangements
    - ensure continued and integrated care for people with MND across all care settings. [new 2016]
2. Be aware that MND causes progressive muscular weakness that may first present as isolated and unexplained symptoms. These symptoms may include:
    - functional effects of muscle weakness, such as loss of dexterity, falls or trips
    - speech or swallowing problems, or tongue fasciculations (this is known as bulbar presentation)
    - muscle problems, such as weakness, wasting, twitching, cramps and stiffness
    - breathing problems, such as shortness of breath on exertion or respiratory symptoms that are hard to explain
    - effects of reduced respiratory function, such as excessive daytime sleepiness, fatigue, early morning headache or shortness of breath when lying down. [new 2016]
3. Be aware that MND may first present with cognitive features, which may include:
    - behavioural changes
    - emotional lability (not related to dementia)
    - frontotemporal dementia. [new 2016]
4. If you suspect MND, refer the person without delay and specify the possible diagnosis in the referral letter. Contact the consultant neurologist directly if you think the person needs to be seen urgently. [new 2016]
5. Provide information and support for people and their family members and/or carers (as appropriate) throughout the diagnostic process, particularly during periods of diagnostic uncertainty or delay. [new 2016]

Information and support at diagnosis

6. Information about the diagnosis, prognosis and management of MND should be given by a consultant neurologist with up-to-date knowledge and experience of treating people with MND unless it is clinically necessary to give the diagnosis in an urgent situation. The neurologist should have knowledge and expertise in the following:
    - Symptoms of MND.

- Types and possible causes of MND.
- Treatment options.
- How MND may progress (including cognitive and behavioural changes) and how progression may affect the treatments offered.
- Crisis prevention (for example, if there is an acute hospital admission or a breakdown in care arrangements).
- Opportunities for people with MND to be involved in research.
- Likely needs and concerns of people with MND and their family members and/or carers (as appropriate).
- Advance care planning. [new 2016]

7. Ask people about how much information they wish to receive about MND, and about their preferences for involving their family members and/or carers (as appropriate). [new 2016]
8. Ensure people are provided with information about MND and support at diagnosis or when they ask for it. If the person agrees, share the information with their family members and/or carers (as appropriate). Information should be oral and written, and may include the following:
    - What MND is.
    - Types and possible causes.
    - Likely symptoms and how they can be managed.
    - How MND may progress.
    - Treatment options.
    - Where the person's appointments will take place.
    - Which healthcare professionals and social care practitioners will undertake the person's care.
    - Expected waiting times for consultations, investigations and treatments.
    - Local services (including social care and specialist palliative care services) and how to get in touch with them.
    - Local support groups, online forums and national charities, and how to get in touch with them.
    - Legal rights, including social care support, employment rights and benefits.
    - Requirements for disclosure, such as notifying the Driver and Vehicle Licensing Agency (DVLA).
    - Opportunities for advance care planning. [new 2016]
9. When MND is diagnosed, provide people with a single point of contact for the specialist MND multidisciplinary team (see Chapter 9). Provide information about what to do if there are any concerns between assessments or appointments, during 'out-of-hours' or in an emergency, or if there is a problem with equipment. [new 2016]
10. Offer the person with MND a face-to-face, follow-up appointment with a healthcare professional from the multidisciplinary team, to take place within 4 weeks of diagnosis. [new 2016]

11. When MND is suspected or confirmed, inform the person's GP without delay and provide information about the likely prognosis. [new 2016]
12. Set aside enough time to discuss the person's concerns and questions, which may include the following:
    - What will happen to me?
    - Are there any treatments available?
    - Is there a cure?
    - How long will I live?
    - What will the impact on my day-to-day life be?
    - What will happen next with my healthcare?
    - Will my children get MND?
    - How do I tell my family and friends?
    - How will I die? [new 2016]
13. If the person has any social care needs, refer them to social services for an assessment. Be aware that some people with MND may not have informal care available, and may live alone or care for someone else. [new 2016]
14. Advise carers that they have a legal right to have a Carer's Assessment of their needs; support them with requesting this from their local authority. [new 2016]

Cognitive assessments

15. Be aware that people with MND and frontotemporal dementia may lack mental capacity. Care should be provided in line with the Mental Capacity Act 2005. [new 2016]
16. At diagnosis, and if there is concern about cognition and behaviour, explore any cognitive or behavioural changes with the person and their family members and/or carers as appropriate. If needed, refer the person for a formal assessment in line with the NICE guideline on dementia. [new 2016]
17. Tailor all discussions to the person's needs, taking into account their communication ability, cognitive status and mental capacity. [new 2016]

Prognositc factors

18. When planning care take into account the following prognostic factors, which are associated with shorter survival if they are present at diagnosis:
    - Speech and swallowing problems (bulbar presentation).
    - Weight loss.
    - Poor respiratory function.
    - Older age.
    - Lower Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS or ALSFRS-R) score.
    - Shorter time from first developing symptoms to time of diagnosis. [new 2016]

Organisation of care

19. Provide coordinated care for people with MND, using a clinic-based, specialist MND multidisciplinary team approach. The clinic may be community or hospital based. [new 2016]

20. 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 and coordination 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
    - provide coordinated care for people who cannot attend the clinic, according to the person's needs. [new 2016]

21. The multidisciplinary team should assess, manage and review the following areas, including the person's response to treatment:

    - Weight, diet, nutritional intake and fluid intake, feeding and swallowing (see Chapter 16 and Chapter 17).
    - Muscle problems, such as weakness, stiffness, cramps (see Chapter 13).
    - Physical function, including mobility and activities of daily living (see Chapter 15).
    - Saliva problems, such as drooling of saliva (sialorrhoea) and thick, tenacious saliva (see Chapter 14).
    - Speech and communication (see Chapter 18).
    - Cough effectiveness (see Chapter 20).
    - Respiratory function and respiratory symptoms (see Chapter 19) and Non-invasive ventilation (see Chapter 21).
    - Pain and other symptoms, such as constipation.
    - Cognition and behaviour (see Chapter 7).
    - Psychological support needs (see Chapter 10).
    - Social care needs (see Chapter 11).
    - End of life care needs (see Chapter 12).
    - Information and support needs for the person and their family members and/or carers (as appropriate) (see Chapter 6). [new 2016]

22. 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.
- A healthcare professional with expertise in palliative care (MND palliative care expertise may be provided by the neurologist or nurse in the multidisciplinary team, or by a specialist palliative care professional). [new 2016]

23. The multidisciplinary team should have established relationships with, and prompt access to, the following:
    - Clinical psychology and neuropsychology.
    - Social care.
    - Counselling.
    - Respiratory ventilation services.
    - Specialist palliative care.
    - Gastroenterology.
    - Orthotics.
    - Wheelchair services.
    - Assistive technology services.
    - Alternative and augmentative communication (AAC) services.
    - Community neurological care teams. [new 2016]
24. Tailor the frequency of the multidisciplinary team assessments to the person's symptoms and needs, with more or less frequent assessments as needed. [new 2016]
25. Ensure arrangements are in place to trigger an earlier multidisciplinary team assessment if there is a significant change in symptoms identified by the person, family members and/or carers (as appropriate), or healthcare professionals. [new 2016]
26. 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]
27. 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]
28. 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, ongoing assessments. Priority should be given to ensuring continuity of care and avoiding untimely case closure. [new 2016]
29. Consider referral to a specialist palliative care team for people with current or anticipated significant or complex needs, for example, psychological or social distress, troublesome or rapidly progressing symptoms and complex future care planning needs. [new 2016]

30. For guidance on the use of riluzole for people with MND, see the NICE technology appraisal guidance on the use of riluzole (Rilutek) for the treatment of motor neurone disease. [new 2016]

Psychological support

31. During multidisciplinary team assessments and other appointments, discuss the psychological and emotional impact of MND with the person and ask whether they have any psychological or support care needs. Topics to discuss may include the following:
    - Their understanding of MND and how it affects daily living.
    - Accepting and coping with the diagnosis and prognosis, including concerns and fears about dying.
    - Their ability to continue with current work and usual activities.
    - Adjusting to changes in their life and their perception of self.
    - Changes in relationships, familial roles and family dynamics.
    - Sexuality and intimacy.
    - Concerns about their family members and/or carers.
    - Decision-making. [new 2016]
32. Offer the person information about sources of emotional and psychological support, including support groups and online forums. If needed, refer the person to counselling or psychology services for a specialist assessment and support. [new 2016]
33. During multidisciplinary team assessments and other appointments, discuss the psychological and emotional impact of MND with family members and/or carers (as appropriate), and ask whether they have any psychological or social care support needs. Topics to discuss may include the following:
    - Their understanding of MND and how it affects daily living.
    - Accepting and coping with the diagnosis and prognosis, including concerns and fears about the person with MND dying.
    - Adjusting to changes in their life.
    - Changes in relationships, familial roles and family dynamics, including their change to a carer role (if appropriate).
    - Sexuality and intimacy.
    - Involvement in decision-making.
    - Impact on other family members and/or carers.
    - Their ability and willingness to provide personal care and operate equipment. [new 2016]
34. Offer family members and/or carers (as appropriate) information about respite care and sources of emotional and psychological support, including support groups, online forums and counselling or psychology services. [new 2016]
35. A social care practitioner with knowledge of MND or rapidly progressive complex disabilities should discuss the person's needs and preferences for social care, and provide information and support for them to access the following:

- Personal care, ensuring there is continuity of care with familiar workers, so that wherever possible, personal care and support is carried out by workers known to the person and their family members and/or carers (as appropriate).
- Equipment and practical support (see Chapter 15).
- Financial support and advice (for example, money management, how to access carers' and disability benefits and grants, continuing healthcare funding and funeral expenses).
- Support to engage in work, social activities and hobbies, such as access to social media and physical access to activities outside their home.
- Respite care. [new 2016]

36. Be aware that as MND progresses, people may develop communication problems and have difficulty accessing support or services. For example, they may be unable to access a call centre. Ensure people are given different ways of getting in touch with support or services, and a designated contact if possible. [new 2016]

Planning for end of life

37. 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]

38. Be prepared to discuss end of life issues whenever people wish to do so. [new 2016]

39. Provide support and advice on advance care planning for end of life. Topics to discuss may include:

    - What could happen at the 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.
    - How to ensure advance care plans will be available when needed, for example, including the information on the person's Summary Care Record.
    - When to involve specialist palliative care.
    - Areas that people might wish to plan for, such as:

        i. what they want to happen (for example, their preferred place of death)

        ii. what they do not want to happen (for example, being admitted to hospital)

        iii. who will represent their decisions, if necessary

        iv. what should happen if they develop an intercurrent illness. [new 2016]

40. 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]

41. Offer people the opportunity to talk about, and review any existing, ADRT, DNACPR orders and Lasting Power of Attorney when interventions such as gastrostomy and non-invasive ventilation are planned. [new 2016]

42. 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 carer responsibilities and spend time with the person with MND. [new 2016]

43. Towards the end of life, ensure there is prompt access to the following, if not already provided:

    - A method of communication that meets the person's needs, such as an AAC system.
    - Specialist palliative care.
    - Equipment, if needed, such as syringe drivers, suction machines, riser–recliner chair, hospital bed, commode and hoist.
    - Anticipatory medicines, including opioids and benzodiazepines to treat breathlessness, and antimuscarinic medicines to treat problematic saliva and respiratory secretions. [new 2016]

44. Offer bereavement support to family members and/or carers (as appropriate). [new 2016]

Pharmacological treatments for muscle problems

45. Discuss the available treatment options for muscle problems. Take into account the person's needs and preferences, and whether they have any difficulties taking medicine (for example, if they have problems swallowing). [new 2016]

46. Consider quinine[a] as first-line treatment for muscle cramps in people with MND. If quinine is not effective, not tolerated or contraindicated, consider baclofen[a] instead as second-line treatment. If baclofen is not effective, not tolerated or contraindicated, consider tizanidine[a], dantrolene[a] or gabapentin[a]. [new 2016]

47. Consider baclofen, tizanidine, dantrolene[a] or gabapentin[a] to treat muscle stiffness, spasticity or increased tone in people with MND. If these treatments are not effective, not tolerated or contraindicated, consider referral to a specialist service for the treatment of severe spasticity. [new 2016]

48. Review the treatments for muscle problems during multidisciplinary team assessments, ask about how the person is finding the treatment, whether it is working and whether they have any adverse side effects. [new 2016]

Exercise programmes

49. Consider an exercise programme for people with MND to:

    - maintain joint range of movement
    - prevent contractures
    - reduce stiffness and discomfort

- optimise function and quality of life. [new 2016]

50. Choose a programme that is appropriate to the person's level of function and tailored to their needs, abilities and preferences. Take into account factors such as postural needs and fatigue. The programme might be a resistance programme, an active-assisted programme or a passive programme. [new 2016]

51. Check that family members and/or carers (as appropriate) are willing and able to help with exercise programmes. [new 2016]

52. Give advice to the person and their family members and/or carers (as appropriate) about safe manual handling. [new 2016]

53. If a person needs orthoses to help with muscle problems, they should be referred to orthotics services without delay, and the orthoses should be provided without delay. [new 2016]

Saliva problems

54. If a person with MND has problems with saliva, assess the volume and viscosity of the saliva and the person's respiratory function, swallowing, diet, posture and oral care. [new 2016]

55. If a person with MND has problems with drooling of saliva (sialorrhoea), provide advice on swallowing, diet, posture, positioning, oral care and suctioning. [new 2016]

56. Consider a trial of antimuscarinic medicine[b] as the first-line treatment for sialorrhoea in people with MND. [new 2016]

57. Consider glycopyrrolate[b] as the first-line treatment for sialorrhoea in people with MND who have cognitive impairment, because it has fewer central nervous system side effects. [new 2016]

58. If first-line treatment for sialorrhoea is not effective, not tolerated or contraindicated, consider referral to a specialist service for Botulinum toxin A[c]. [new 2016]

59. If a person with MND has thick, tenacious saliva:

    - review all current medicines, especially any treatments for sialorrhoea
    - provide advice on swallowing, diet, posture, positioning, oral care, suctioning and hydration
    - consider treatment with humidification, nebulisers and carbocisteine. [new 2016]

Equipment and adaptations to aid activities of daily living and mobility

60. Healthcare professionals and social care practitioners, which will include physiotherapists and occupational therapists, should assess and anticipate changes in the person's daily living needs, taking into account the following:

    - Activities of daily living, including personal care, dressing and bathing, housework, shopping, food preparation, eating and drinking, and ability to continue with current work and usual activities.
    - Mobility and avoiding falls and problems from loss of dexterity.
    - The home environment and the need for adaptations.
    - The need for assistive technology, such as environmental control systems. [new 2016]

61. Provide equipment and adaptations that meet the person's needs without delay, so that people can participate in activities of daily living and maintain their quality of life as much as possible. [new 2016]

62. Refer people to specialist services without delay if assistive technology such as environmental control systems is needed. People should be assessed and assistive technology provided without delay. [new 2016]

63. Refer people to wheelchair services without delay if needed. Wheelchair needs should be assessed and a manual and/or powered wheelchair that meets the person's needs should be provided without delay. [new 2016]

64. Ensure that equipment, adaptations, daily living aids, assistive technology and wheelchairs meet the changing needs of the person and their family and/or carers (as appropriate) to maximise mobility and participation in activities of daily living. [new 2016]

65. Ensure regular, ongoing monitoring of the person with MND's mobility and daily life needs and abilities as their disease progresses. Regularly review their ability to use equipment and to adapt equipment as necessary. [new 2016]

66. Healthcare professionals, social care practitioners and other services providing equipment should liaise to ensure that all equipment provided can be integrated, for example, integrating AAC aids and devices and environmental control systems with wheelchairs. [new 2016]

67. Enable prompt access and assessment for funding for home adaptation. If the person is not eligible for funding, continue to offer information and support in arranging home environment adaptations. [new 2016]

Nutrition and gastrostomy

Please also refer to the recommendations in NICE's guideline on nutrition support in adults.

68. At diagnosis and at multidisciplinary team assessments, or if there are any concerns about weight, nutrition or swallowing, assess the person's weight, diet, nutritional intake, fluid intake, hydration, oral health, feeding, drinking and swallowing, and offer support, advice and interventions as needed. [new 2016]

69. Assess the person's diet, hydration, nutritional intake and fluid intake by taking into account:

- fluids and food intake versus nutritional and hydration needs
- nutritional supplements, if needed
- appetite and thirst
- gastrointestinal symptoms, such as nausea or constipation
- causes of reduced oral intake (for example, swallowing difficulties, limb weakness or the possibility of low mood or depression causing loss of appetite). [new 2016]

70. Assess the person's ability to eat and drink by taking into account:

- the need for eating and drinking aids and altered utensils to help them take food from the plate to their mouth
- the need for help with food and drink preparation

- advice and aids for positioning, seating and posture while eating and drinking
- dealing with social situations (for example, eating out). [new 2016]

71. Arrange for a clinical swallowing assessment if swallowing problems are suspected. [new 2016]

72. Assess and manage factors that may contribute to problems with swallowing, such as:

- positioning
- seating
- the need to modify food and drink consistency and palatability
- respiratory symptoms and risk of aspiration and/or choking
- fear of choking and psychological considerations (for example, wanting to eat and drink without assistance in social situations). [new 2016]

73. Discuss gastrostomy at an early stage, and at regular intervals as MND progresses, taking into account the person's preferences and issues, such as ability to swallow, weight loss, respiratory function, effort of feeding and drinking and risk of choking. Be aware that some people will not want to have a gastrostomy. [new 2016]

74. Explain the benefits of early placement of a gastrostomy, and the possible risks of a late gastrostomy (for example, low critical body mass, respiratory complications, risk of dehydration, different methods of insertion, and a higher risk of mortality and procedural complications). [new 2016]

75. If a person is referred for a gastrostomy, it should take place without unnecessary delay. [new 2016]

76. Pay particular attention to the nutritional and hydration needs of people with MND who have frontotemporal dementia and who lack mental capacity. The multidisciplinary team assessment should include the support they need from carers, and their ability to understand the risks of swallowing difficulties. [new 2016]

77. Before a decision is made on the use of gastrostomy for a person with MND who has frontotemporal dementia, the neurologist from the multidisciplinary team should assess the following:

- The person's ability to make decisions and to give consent.[d]
- The severity of frontotemporal dementia and cognitive problems.
- Whether the person is likely to accept and cope with treatment.

Discuss with the person's family members and/or carers (as appropriate; with the person's consent if they have the ability to give it). [new 2016]

Communication

78. When assessing speech and communication needs during multidisciplinary team assessments and other appointments, discuss face-to-face and remote communication, for example, using the telephone, email, the Internet and social media. Ensure that the assessment and review is carried out by a speech and language therapist without delay. [new 2016]

79. Provide AAC equipment that meets the needs of the person without delay to maximise participation in activities of daily living and maintain quality of life.

The use of both low-level technologies, for example, alphabet, word or picture boards and high-level technologies, for example, PC or tablet-based voice output communication aids may be helpful. Review the person's communication needs during multidisciplinary team assessments. [new 2016]

80. Liaise with, or refer the person with MND to, a specialised NHS AAC hub if complex high technology AAC equipment (for example, eye gaze access) is needed or is likely to be needed. [new 2016]

81. Involve other healthcare professionals, such as occupational therapists, to ensure that AAC equipment is integrated with other assistive technologies, such as environmental control systems and personal computers or tablets. [new 2016]

82. Ensure regular, ongoing monitoring of the person's communication needs and abilities as MND progresses, and review their ability to use AAC equipment. Reassess and liaise with a specialised NHS AAC hub if needed. [new 2016]

83. Provide ongoing support and training for the person with MND, and their family members and/or carers (as appropriate), in using AAC equipment and other communication strategies. [new 2016]

Respiratory function and respiratory symptoms

84. Assess and monitor the person's respiratory function and symptoms. Treat people with MND and worsening respiratory impairment for reversible causes (for example, respiratory tract infections or secretion problems) before considering other treatments. [new 2016]

85. Offer non-invasive ventilation as treatment for people with respiratory impairment (see Chapter 21). Decisions to offer non-invasive ventilation should be made by the multidisciplinary team in conjunction with the respiratory ventilation service, and the person (see recommendations 19–23). [new 2016]

86. Consider urgent introduction of non-invasive ventilation for people with MND who develop worsening respiratory impairment and are not already using non-invasive ventilation. [new 2016]

87. Consider opioids[e] as an option to relieve symptoms of breathlessness. Take into account the route of administration and acquisition cost of medicines. [new 2016]

88. Consider benzodiazepines[e] to manage breathlessness that is exacerbated by anxiety. Take into account the route of administration and acquisition cost of medicines. [new 2016]

Cough effectiveness

89. Offer cough augmentation techniques such as manual assisted cough to people with MND who cannot cough effectively. [new 2016]

90. Consider unassisted breath stacking and/or manual assisted cough as the first-line treatment for people with MND who have an ineffective cough. [new 2016]

91. For patients with bulbar dysfunction, or whose cough is ineffective with unassisted breath stacking, consider assisted breath stacking (for example, using a lung volume recruitment bag). [new 2016]

92. Consider a mechanical cough assist device if assisted breath stacking is not effective, and/or during a respiratory tract infection. [new 2016]

Information and support about non-invasive ventilation

93. Offer to discuss the possible use of non-invasive ventilation with the person and (if the person 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
    - if the person asks for information. [2010]

94. 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 box 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]

95. When discussing non-invasive ventilation, explain 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 medication for breathing problems
    - psychological techniques and support. [new 2016]

96. Check that the person thinking about non-invasive ventilation:
    - understands what non-invasive ventilation is and 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.
    - understands possible problems with compatibility with other equipment, for example, eye gaze access systems.[new 2016]

97. 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. Inform people that medicines can be used to alleviate symptoms (see recommendation 121). [new 2016]

98. Ensure that families and carers:

- have an initial assessment if the person they care for decides to use non-invasive ventilation, which should include:

i. their ability and willingness to assist in providing non-invasive ventilation

ii. their training needs

- have the opportunity to discuss any concerns they may have with members of the multidisciplinary team, the respiratory ventilation service and/or other healthcare professionals. [2010]

Identification and assessment of respiratory impairment

Symptoms and signs

99. Monitor the symptoms and signs listed in box 1 to detect potential respiratory impairment. [2010, amended 2016]

Box 1 Symptoms and signs of potential respiratory impairment

Symptoms	**Signs**
Breathlessness	**Increased respiratory rate**
Orthopnoea	**Shallow breathing**
Recurrent chest infections	**Weak cough**[1]
Disturbed sleep	**Weak sniff**
Non-refreshing sleep	**Abdominal paradox (inward movement of the abdomen during inspiration)**
Nightmares	**Use of accessory muscles of respiration**
Daytime sleepiness	**Reduced chest expansion on maximal inspiration**
Poor concentration and/or memory	
Confusion	
Hallucinations	
Morning headaches	
Fatigue	

Poor appetite	

[1] Weak cough could be assessed by measuring peak cough flow.

Respiratory function tests

100. 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 person's baseline respiratory function:

- oxygen saturation measured by pulse oximetry (SpO_2):

i. this should be a single measurement of SpO_2 with the person at rest and breathing room air

ii. if it is not possible to perform pulse oximetry locally, refer the person to a respiratory ventilation service.

Then one or both of the following:

- forced vital capacity (FVC) or vital capacity (VC)[f]
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP). [2010]

101. If the person has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment:

- ensure that SpO_2 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 person. [2010]

102. 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 box 1)
- the rate of progression of MND
- the person's preference and circumstances. [2010, amended 2016]

103. Perform arterial or capillary blood gas analysis if the person's SpO_2 (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 person to a respiratory ventilation service. [2010]

104. If the person's SpO_2 (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 respiratory ventilation service for continuous 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 person agrees) their family and carers. [2010]

105. If the person's arterial partial pressure of carbon dioxide ($PaCO_2$) is greater than 6 kPa:

- refer them urgently to a respiratory ventilation service (to be seen within 1 week) and
- explain the reasons for and implications of the urgent referral to the person and (if the person agrees) their family and carers. [2010]

106. If the person's $PaCO_2$ is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnoea (see recommendation 107):

- refer them to a respiratory ventilation service for nocturnal (overnight) oximetry and/or a limited sleep study and
- discuss both the impact of respiratory impairment and treatment options with the person and (if the person agrees) their family and/or carers (as appropriate). [2010]

107. If any of the results listed in box 2 is obtained, discuss with the person and (if appropriate) their family and carers:

- their respiratory impairment
- their treatment options
- possible referral to a respiratory ventilation service for further assessment based on discussion with the person, and their wishes. [2010, amended 2016]

Box 2 Results of respiratory function tests

Forced vital capacity (FVC) or vital capacity (VC)	**Sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)** **(if both tests are performed, base the assessment on the better respiratory function reading)**
FVC or VC less than 50% of predicted value **FVC or VC less than 80% of predicted value plus any symptoms or signs of respiratory impairment (see recommendation 99), particularly orthopnoea**	**SNIP or MIP less than 40 cmH_2O** **SNIP or MIP less than 65 cmH_2O for men or 55 cmH_2O for women plus any symptoms or signs of respiratory impairment (see recommendation 99), particularly orthopnoea**

	Repeated regular tests show a rate of decrease of SNIP or MIP of more than 10 cm H_2O per 3 months

People with a diagnosis of frontotemporal dementia

108. 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[g]
    - 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. [2010, amended 2016]

Non-invasive ventilation for treatment of respiratory impairment in people with MND

109. 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]

110. 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]

111. Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should carry out and coordinate a patient-centred risk assessment, after discussion with the person and their family and carers. This should consider:
    - the most appropriate type of non-invasive ventilator and interfaces, based on the person's needs and lifestyle factors and safety
    - the person's tolerance of the treatment
    - the risk, and possible consequences, of ventilator failure
    - the power supply required, including battery back-up
    - how easily the person 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. [2010]

112. Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should prepare a comprehensive care plan, after discussion with the person and their family and carers (who should be offered a 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 augmentation (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]

113. When starting non-invasive ventilation:

- perform initial acclimatisation during the day when the person is awake
- usually start regular treatment at night, before and during sleep
- gradually build up the person's hours of use as necessary. [2010]

114. Continue non-invasive ventilation if the clinical reviews show:

- symptomatic and/or physiological improvements for a person without severe bulbar impairment and without severe cognitive problems
- an improvement in sleep-related symptoms for a person with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment. [2010]

115. 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:

i. emergency procedures

ii. night-time assistance if the person is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)

iii. how to use the equipment with a wheelchair or other mobility aids if required

iv. 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 the person and their family and carers. [2010, amended 2016]

116. Discuss all decisions to continue or withdraw non-invasive ventilation with the person and (if the person agrees) their family and carers. [2010]

117. Before a decision is made on the use of non-invasive ventilation for a person with a diagnosis of frontotemporal dementia, the multidisciplinary team together with the respiratory ventilation service should carry out an assessment that includes:

- the person's capacity to make decisions and to give consent[h]
- 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]

118. Consider prescribing medicines to help ease breathlessness that people using non-invasive ventilation can take on an 'as-needed' basis at home, for example, opioids[i] or benzodiazepines. [new 2016]

119. Inform services that may see the person in crisis situations, such as their GP and services that provide emergency or urgent care, that the person is using non-invasive ventilation. [new 2016]

Stopping non-invasive ventilation

120. The healthcare professionals responsible for starting non-invasive ventilation treatment in people with MND should ensure that support is available for other healthcare professionals who may be involved if there is a plan to stop non-invasive ventilation, including the legal and ethical implications. [new 2016]

121. If a person on continuous non-invasive ventilation wishes to stop treatment, ensure that they have support from healthcare professionals with knowledge and expertise of:

- stopping non-invasive ventilation
- the ventilator machine
- palliative medicines (see the NICE guideline on care of the dying adult)
- supporting the person, family members and/or carers (as appropriate)
- supporting other healthcare professionals involved with the person's care
- legal and ethical frameworks and responsibilities. [new 2016]

122. If a person on continuous non-invasive ventilation wishes to stop treatment, seek advice from healthcare professionals who have knowledge and experience of stopping non-invasive ventilation. [new 2016]

123. Healthcare professionals involved in stopping non-invasive ventilation should have up-to-date knowledge of the law regarding the Mental Capacity Act, DNACPR, ADRT orders and Lasting Power of Attorney. [new 2016]

1.2 Key research recommendations

- 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?
- Is the ALS Prognostic Index an accurate predictor of survival in people with MND under NHS care in England and/or Wales?
- How is excessive drooling of saliva (sialorrhoea) managed in people with MND?
- Does a high calorific diet prolong survival of people with MND if initiated following diagnosis or following initiation of feeding using a gastrostomy?
- What is the current pattern of provision and use of augmentative and alternative communication (AAC) by people with MND in England?

1.3 How this guideline amalgamates with NICE guideline CG105

Please see Appendix O for details of how this guideline amalgamates new guidance on the assessment and management of motor neurone disease with NICE guideline CG105 (published July 2010), and will replace NICE guideline CG105.

2 Introduction

Motor neurone disease (MND) is a neurodegenerative condition that affects the brain and spinal cord. MND is characterised by the degeneration of primarily motor neurones, leading to muscle weakness.

The presentation of the disease varies and can be as muscle weakness, wasting, cramps and stiffness of arms and/or legs, problems with speech and/or swallowing or, more rarely, with breathing problems. Whichever area the disease starts, as the disease progresses the pattern of signs and symptoms becomes similar, with increasing muscle weakness in the person's arms and legs, problems swallowing and communicating and weakness of the muscles used for breathing, which ultimately leads to death. Most people die within 2–3 years of developing symptoms, but 25% are alive at 5 years and 5–10% at 10 years. The most common type of MND is amyotrophic lateral sclerosis (ALS). There are rarer forms of MND such as progressive muscular atrophy and primary lateral sclerosis, which may have a slower rate of progression.

Every person with MND has an individual progression of the disease. About 10–15% of people with MND will show signs of frontotemporal dementia, which causes cognitive dysfunction and issues with decision-making. A further 35% of people with MND show signs of mild cognitive change, which may affect their ability to make decisions and plan ahead.

MND is a disorder which can affect adults of any age. However, incidence is highest in people aged 55–79; onset below the age of 40 years is uncommon. There are approximately 4,000 people living with MND in England and Wales at any one time. The cause of MND is unknown. About 5–10% of people with MND have a family history of the disease and several abnormal genes have been identified.

As there is no cure for MND, care focuses on maintaining functional ability and enabling people with MND and their family members to live life as fully as possible. Early diagnosis, without delay after investigation, may be helpful as it allows for the provision of medication and aids, as well as for communication about the disease and advance care planning to be undertaken appropriately.

Care of people with MND varies across England and Wales, with MND multidisciplinary team clinics and networks providing coordinated multidisciplinary care. However, some people with MND are left isolated and their care is less than ideal. This guideline aims to consider the clinical- and cost-effectiveness evidence for the care of people with MND from the time of diagnosis, including communication of the diagnosis. It covers monitoring of disease progression, management of symptoms (in particular muscle weakness, excess secretions, breathing and nutrition problems), ongoing support and services, mobility, emotional and psychological changes, and preparation for end of life. Particular emphasis is placed on determining the best way to organise the care and management of people with MND.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

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

NICE clinical guidelines can:

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

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

We produce our guidelines using the following steps:

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

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

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

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

3.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

The assessment and management of motor neurone disease.

3.3 Who developed this guideline?

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

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr David Oliver in accordance with guidance from NICE.

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

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

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

3.3.1 What this guideline covers

This guideline covers the assessment and management of adults with motor neurone disease. Specific consideration was given to people with frontotemporal dementia. The key areas covered include timeliness of diagnosis, communicating with patients and their families about the diagnosis, the prognosis and ongoing care, symptom management, psychosocial support and identification of social care needs for patients and their carers, managing the stopping of non-invasive ventilation and preparing for the end of life. NICE clinical guideline 105 (CG105) on Motor neurone disease: The use of non-invasive ventilation in the management of motor neurone disease has been amalgamated with this guideline. The guideline did not update evidence reviews conducted for CG105. For further details please refer to the scope in Appendix A and the review questions in Chapters 5 to 21.

3.3.2 What this guideline does not cover

This guideline does not cover children and young people under 18 years, adults with other neurodegenerative disorders who do not have motor neurone disease or people diagnosed with Kennedy's disease.

The diagnosis of motor neurone disease, complementary therapies, riluzole, tracheostomy, dietary supplements for modification of disease progression and enteral feeding are not covered.

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE technology appraisals:

- Riluzole (rilutek) for the treatment of motor neurone disease. NICE technology appraisal guidance 20 (2001).

Related NICE interventional procedures guidance:

- Functional electrical stimulation for drop foot of central neurological origin. NICE interventional procedure guidance 278 (2009).

Related NICE clinical guidelines:

- Multiple sclerosis. NICE clinical guideline 186 (2014).
- Pressure ulcers. NICE clinical guideline 179 (2014).
- 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).
- Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. NICE clinical guideline 113 (2011)
- Medicines adherence. NICE clinical guideline 76 (2009).
- Depression in adults with a chronic physical health problem. NICE clinical guideline 91 (2009).
- Nutrition support in adults. NICE clinical guideline 32 (2006).
- Dementia. NICE clinical guideline 42 (2006).

Related NICE guidelines:

- Care of dying adults in the last days of life. NICE guideline 31 (2015)
- Transition between inpatient hospital settings and community or care home settings for adults with social care needs. NICE guideline 27 (2015)
- Home care. NICE guideline 21 (2015).
- Medicines optimisation. NICE guideline 5 (2015).

Related NICE quality standards:

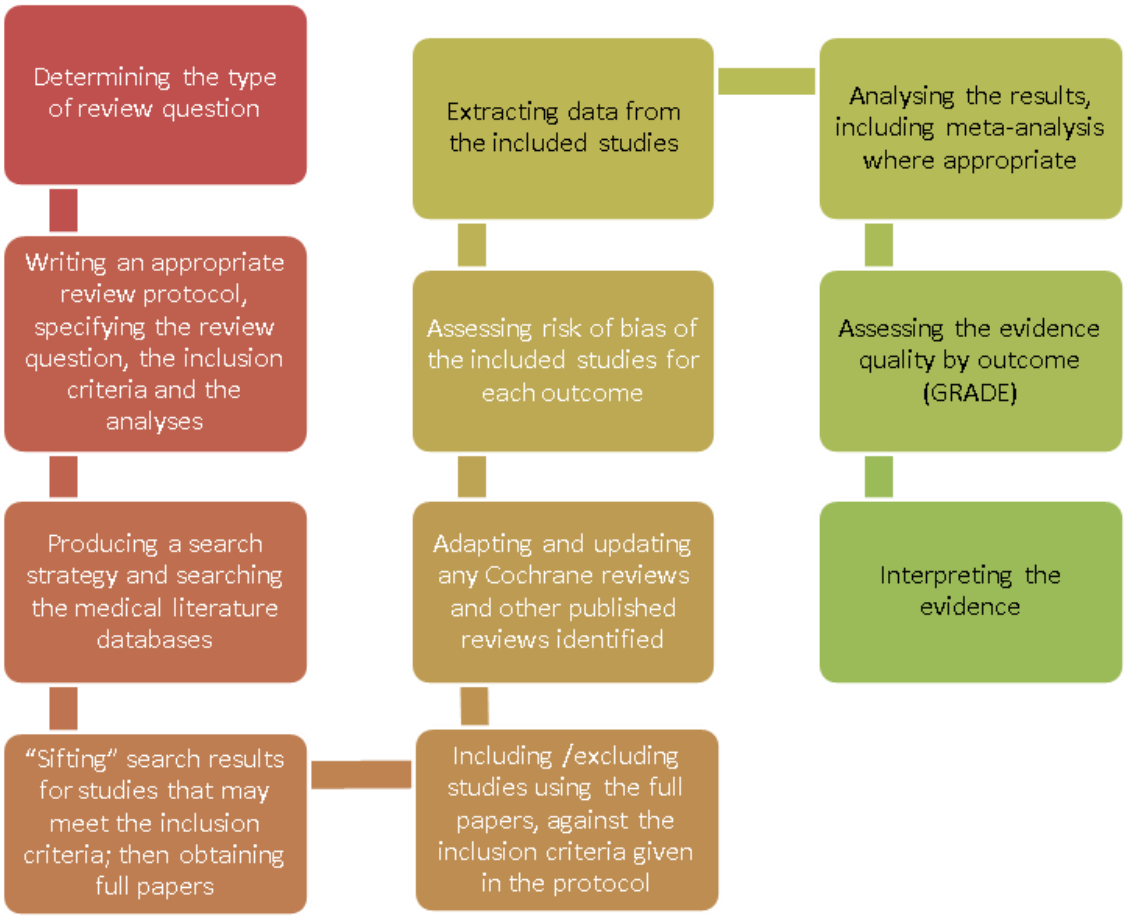
- End of life care for adults. NICE quality standard 13 (2011).

4 Methods

This chapter sets out the methods used to review the evidence and to develop the recommendations that are presented in the guideline chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2012 and 2014 versions.[84,87]

Section 4.3 describes the process of reviewing clinical evidence (summarised in Figure 1) and Section 4.4 the process of reviewing the cost-effectiveness evidence.

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



4.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 21 review questions were identified.

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

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5	Qualitative	What factors impact upon timeliness of diagnosis in people with MND in the UK?	Examples of themes include timeliness in: • Identification of MND • Referral to a neurologist • Carrying out relevant investigations • Obtaining results of investigations • People seeking help
6	Qualitative	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?	Examples of themes 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
7	Intervention	What is the optimum frequency of assessing cognitive function in people with MND?	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)
8	Prognostic	What are the most accurate prognostic tools for estimating survival in people with MND?	Survival
		What risk factors predict survival in people with MND?	Mortality

Chapter	Type of review	Review questions	Outcomes
9	Intervention	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?	Critical: • Survival • Health-related quality of life – patient and carer • Number of unplanned hospital admissions Important: • Reduction in 'crisis management interventions' • Hospital length of stay • ALSFRS scale
		What is the optimum frequency of assessment required to assess disease progression of MND?	Critical: • Health-related quality of life • Patient/carer/healthcare professional satisfaction with the process
10	Qualitative	What psychological support is needed for people with MND and their families and carers?	Examples of themes searched for include: • Coping with the diagnosis • Managing family relationships • Change in identity/roles • Sexuality • Psychological factors associated with employment (employment support is included in the 'Social care support' review) • Management of anxiety and depression • Respite care
11	Qualitative	What are the social care support needs of people with MND and their families and carers?	Examples of themes include: • Financial support • Employment support • Transport • Support with eating • Support with dressing/washing • Support to engage with social activities • Adaptations at home • Appropriate housing
12	Qualitative	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?	Examples of themes include: • Access to MND specialists (for example doctor, nurse, respiratory consultant, palliative care specialist) • Advance care planning • Advance refusal of treatment (including DNACPR) • Timing of discussion about end

Chapter	Type of review	Review questions	Outcomes
			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
13	Intervention	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?	Critical: • Quality of life • Reduction of muscle weakness • Reduction of increased tone • Reduction of muscle cramps Important: • Mobility • Patient/carer reported outcomes • Adverse effects of treatment
		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?	Critical: • Reduction of increased tone, muscle cramps and muscle weakness • Health-related quality of life Important: • Patient/carer reported outcomes • Mobility

Chapter	Type of review	Review questions	Outcomes
			• Adverse effects of treatment
14	Intervention	What is the clinical- and cost-effectiveness of interventions for saliva management in people with MND?	Critical: • Health-related quality of life • Patient/carer reported outcomes • Aspiration pneumonia Important: • Function measured by disability scores • Hospital admissions • Adverse effects of treatment
15	Qualitative	What are the equipment needs of people with MND for improving mobility and fulfilling activities of daily living due to muscle weakness?	• These would emerge from the qualitative review • Patient-reported requirements
16	Intervention	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?	Critical: • Health-related quality of life • Patient/carer reported outcomes • Survival • Change in nutritional status Important: • Hospital admissions
17	Prognostic	What is the clinically appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND?	Critical: • Health-related quality of life • Patient/carer reported outcomes • Hospital readmissions and unplanned admissions • Time to death • Mortality related to procedure Important: • Nutritional status • Hospital length of stay
18	Intervention	What is the clinical- and cost-effectiveness of augmentative and alternative communication (AAC) systems for supporting communication in people with MND?	Critical: • Health-related quality of life • Patient/carer reported outcomes Important: • Function measured by disability scores • Speech and language scales
19	Intervention	What is the clinical- and cost-effectiveness of pharmacological treatments for managing breathing difficulties in people with MND?	Critical: • Health-related quality of life • Patient-reported outcomes Important: • Hospital admissions • Adverse events of treatment

Chapter	Type of review	Review questions	Outcomes
			• Mortality
20	Intervention	What is the clinical- and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?	Critical: • Survival • Health-related quality of life • Patient/carer reported outcomes Important: • Change in peak cough flow • Reduction of chest infection Hospital admissions
21	Qualitative	What factors influenced the experience of discontinuation, at a patient's request, of NIV for relatives/carers/healthcare/social care professionals?	Examples of themes include: • 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 • Carer/family support • Where it is done • Time to death
	Intervention	What is the most appropriate management of discontinuation, at a patient's request, of NIV?	Critical: • Pain • Distress of the person with MND • Respiratory symptoms including rapid breathing • Time to death

4.2 Searching for evidence

4.2.1 Clinical literature search

The aim of the literature search was to systematically identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual.[84,87] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Foreign language studies were not reviewed and, where possible, searches were restricted to articles published in the English language. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject specific databases (CINAHL and PsycINFO) were used for some questions. All searches were updated on 18 May 2015. No papers published after this date were considered except RAFIQ2015. We were aware that this paper was due for publication soon after the cut-off date and wished to include it in the cough augmentation question (see Chapter 20).

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any

additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F: Literature search strategies.

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

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

Guidelines International Network database (www.g-i-n.net)

- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov)
- NHS Evidence Search (www.evidence.nhs.uk).

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to motor neurone disease in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2012, to ensure recent publications that had not yet been indexed by the economic databases were identified. Foreign language studies were not reviewed and, where possible, searches were restricted to articles published in the English language.

The health economic search strategies are included in Appendix F: Literature search strategies. All searches were updated on 18 May 2015. No papers published after this date were considered.

4.3 Evidence gathering and analysis

The tasks of the research fellow are listed below and described in further detail in Sections 4.3.1 to 4.3.6. The research fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts, and deciding which should be ordered as full papers. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (see Appendix C: Review protocols).
- Critically appraised relevant studies using the appropriate study design checklists as specified in The Guidelines Manual [National Institute for Health and Clinical Excellence (2012)]. Available from: https://www.nice.org.uk/article/PMG6/chapter/1Introduction
- Critically appraised relevant studies with a prognostic or qualitative study design using the NCGC checklist.
- Extracted key information about interventional study methods and results using Evibase, NCGC purpose-built software. Evibase produces summary evidence tables, with critical appraisal ratings. Key information about non-interventional study methods and results were manually extracted onto standard evidence tables and critically appraised separately (see Appendix G: Clinical evidence tables).

- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  i. Randomised data were meta analysed where appropriate and reported in GRADE profiles
  ii. Observational data were presented separately in GRADE profiles
  iii. Prognostic data were meta-analysed where appropriate and reported in GRADE profiles.
  iv. Qualitative data were summarised across studies where appropriate and reported in themes.
- A sample of a minimum of 10% of the abstract lists of each review was conducted. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  i. papers were included or excluded appropriately
  ii. a sample of the data extractions
  iii. correct methods were used to synthesise data
  iv. a sample of the risk of bias assessments.

4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols (see Appendix C). Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults (aged 18 and over) with motor neurone disease.

The key population exclusion criteria were:

- Children and young people (under 18 years).
- Adults with other neurodegenerative disorders who do not have MND.
- People diagnosed with Kennedy's disease.

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

4.3.2 Type of studies

Randomised trials, non-randomised trials, and observational studies (including diagnostic and prognostic studies) were included in the evidence reviews as appropriate. Qualitative reviews were included where relevant to a particular question, and specified in the protocol.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were appropriate for the questions 'What is the clinical- and cost-effectiveness of interventions for saliva management in people with MND?' and 'What is the clinical and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?' If non-randomised studies were appropriate for inclusion: that is, non-drug trials with no randomised evidence, the GDG identified a-priori in the protocol that the variables must either be equivalent at baseline or that the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion it was excluded. Please refer to Appendix C: Review protocols for full details of the study design of studies selected for each review question.

For prognostic reviews, prospective and retrospective cohort and case-control studies were included.

4.3.3 Methods of combining evidence

4.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the data from the studies for each of the outcomes in the review question using RevMan5[2] software.

Analyses were stratified for by relevant populations such as 'people with cognitive impairment including frontotemporal dementia', which meant that different studies with predominant cognitive impairment strata were not combined and analysed together with studies that did not predominantly include this population. Stratification tended to vary by question, and this is documented in the individual question protocols (see Appendix C). If additional strata were used this led to sub-strata (for example, 2 stratification criteria would lead to 4 sub-strata categories, or 3 stratification criteria would lead to 9 sub-strata categories) which would be analysed separately.

Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk) for binary outcomes, which varied according to question but included:

- Mortality
- Adverse events

The absolute risk difference was also calculated using GRADEpro[50,50] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or lower than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Where there was sufficient information provided, hazard ratios were calculated for outcomes such as survival.

Continuous outcomes

The continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes varied but included:

- Heath-related quality of life
- Patient/carer satisfaction
- Hospital length of stay

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of the two), where each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager

(RevMan5)[2] software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if a p value was reported as "p ≤0.001", the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

Generic inverse variance

If a study reported only the summary statistic and 95% confidence intervals, the generic-inverse variance method was used to enter data into RevMan5[2]. If the control event rate was reported this was used to generate the absolute risk difference in GRADEpro.[50,50] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported, no absolute risk difference was calculated.

Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at p<0.1, or an I-squared inconsistency statistic of >50%, as indicating significant heterogeneity as well as the distribution of effects. Where significant heterogeneity was present, a priori sub-grouping of studies was carried out which was relevant to that particular question, for example types of MND (ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis).

If the sub-group analysis resolved heterogeneity within all of the derived sub-groups, then each of the derived sub-groups would be adopted as separate outcomes. Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such are subject to uncontrolled confounding.

For some questions additional sub-grouping was applied, and this is documented in the individual question protocols (see Appendix C). These additional sub-grouping strategies were applied independently, so sub-units of sub-groups were not created, unlike the situation with strata. Other sub-grouping strategies were only used if the age category sub-group was unable to explain heterogeneity: then, these further sub-grouping strategies were applied in order of priority. Again, once a sub-grouping strategy was found to explain heterogeneity from all derived sub-groups, further sub-grouping strategies were not used.

If all pre-defined strategies of sub-grouping were unable to explain statistical heterogeneity within each derived sub-group, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence intervals around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the GDG considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

Complex analysis /further analysis

Network meta-analysis was considered for the comparison of interventional treatments, but was not pursued because of insufficient data available for the outcomes.

Where studies had used a cross-over design, paired continuous data were extracted where possible, and forest plots were generated in RevMan5[2] with the Generic Inverse Variance function. When a cross-over study had categorical data, the standard error (of the log RR) was calculated using the simplified Mantel Haenszel method for paired outcomes, when the number of subjects with an event in both interventions was known. Forest plots were generated in RevMan5[2] with the Generic Inverse

Variance function. If paired continuous or categorical data were not available from the cross-over studies, the separate group data were analysed in the same way as data from parallel groups, on the basis that this approach would over-estimate the confidence intervals and thus artificially reduce study weighting resulting in a conservative effect. Where a meta-analysis had a mixture of studies using both paired and parallel group approaches, all data were entered into RevMan5[2] using the Generic Inverse Variance function.

4.3.3.2 Data synthesis for prognostic factor reviews

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors were extracted from the studies. Studies were only included if the risk factors pre-specified by the GDG were adjusted for each other using multivariate analysis.

4.3.3.3 Data synthesis for risk prediction rules

Evidence reviews on risk prediction rules/tools results were presented separately for discrimination and calibration. The discrimination data was analysed according to the principles outlined under the section on data synthesis for diagnostic accuracy studies. Calibration data, for example R^2, if reported was presented separately to the discrimination data. The results were presented for each study separately along with the quality rating for the study. Inconsistency and imprecision were not assessed.

4.3.3.4 Data synthesis for qualitative reviews

For each included paper, sub-themes were identified and linked to a generic theme. An example of a sub-theme identified by patients and carers is 'Subsequent feelings after diagnosis – making sense of it' and this is linked to a broader generic theme of 'Coping with the diagnosis.' A summary evidence table of generic themes and underpinning sub-themes was then produced alongside the quality of the evidence. The methodological quality of each study was assessed by one reviewer using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome. This took into account the applicability and theme saturation/sufficiency of the evidence. The evidence was graded 'applicable' if the evidence was directly applicable to the question, and graded partially applicable if it was related but not sufficiently. The theme was 'saturated' if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people, and authors followed up enough people to have sufficient saturation of data. This was detailed in the accompanying footnotes. Grading of the evidence started at high and was downgraded by one increment if assessed as not applicable and downgraded one increment if the theme was not saturated.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Interventional studies

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[50,50]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional and assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an over-estimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

Risk of bias

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each paper first. For each paper, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just one domain, the risk of bias was given a 'serious' rating of -1, but if there was risk of bias in two or more domains the risk of bias was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example, if the most precise studies tended to each have a score of -1 for that outcome, the overall score for that outcome would tend towards -1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias – sequence generation and allocation concealment	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of 1) knowledge of that participant's likely prognostic characteristics and 2) a desire for one group to do better than the other.
Performance and	Patients, caregivers, those adjudicating and/or recording outcomes, and data analysts

Limitation	Explanation
detection bias - Lack of patient and health care professional blinding	should not be aware of the arm to which patients are allocated. Knowledge of group can influence 1) the experience of the placebo effect, 2) performance in outcome measures, 3) the level of care and attention received, and 4) the methods of measurement or analysis, all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from loss of data beyond a certain level (a differential of 10% between groups) which is not accounted for. Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes lack of washout periods to avoid carry-over effects in cross-over trials Recruitment bias in cluster randomised trials

Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for risk of bias, each outcome had its indirectness assessed within each paper first. For each paper, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just one source (for example in terms of population), indirectness was given a 'serious' rating of -1, but if there was indirectness in two or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of -2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account study precision. For example if the most precise studies tended to have an indirectness score of -1 each for that outcome, the overall score for that outcome would probably tend towards -1.

Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (Chi square $p<0.1$ or I^2 inconsistency statistic of >50%), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of -1 if the I^2 was 50–74, and a 'very serious' score of -2 if the I^2 was 75 or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each sub-group had an I^2 <50), the GDG took this into account and considered whether to make separate recommendations on new outcomes based on the sub-groups defined by the assumed explanatory factors. In such a situation, the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

Imprecision

The criteria applied for imprecision were based on the confidence intervals for the pooled estimate of effect, and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either of the 95% confidence intervals of the overall estimate of effect crossed one of the MID lines, imprecision was regarded as serious and a 'serious' score of -1 was given. This was because the overall result, as represented by the span of the confidence intervals, was consistent with two interpretations as defined by the MID (for example, no clinically important effect and either clinical benefit or harm). If both MID lines were crossed by either or both of the confidence intervals then imprecision was regarded as very serious and a 'very serious' score of -2 was given. This was because the overall result was consistent with three interpretations defined by the MID (no clinically important effect and clinical benefit and clinical harm). This is illustrated in Figure 2. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values as reported in the literature. "Anchor-based" methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or "anchoring" them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, the minimum amount of change in an outcome necessary to make a patient decide that they felt their quality of life had "significantly improved" might define the MID for that outcome. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, any MIDs reported in the literature will inevitably be based on expert consensus: as such, MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, as so are not amenable to patient-centred "anchor" methods.

In the absence of literature values, the alternative approach to deciding on MID levels is the "default" method, as follows:

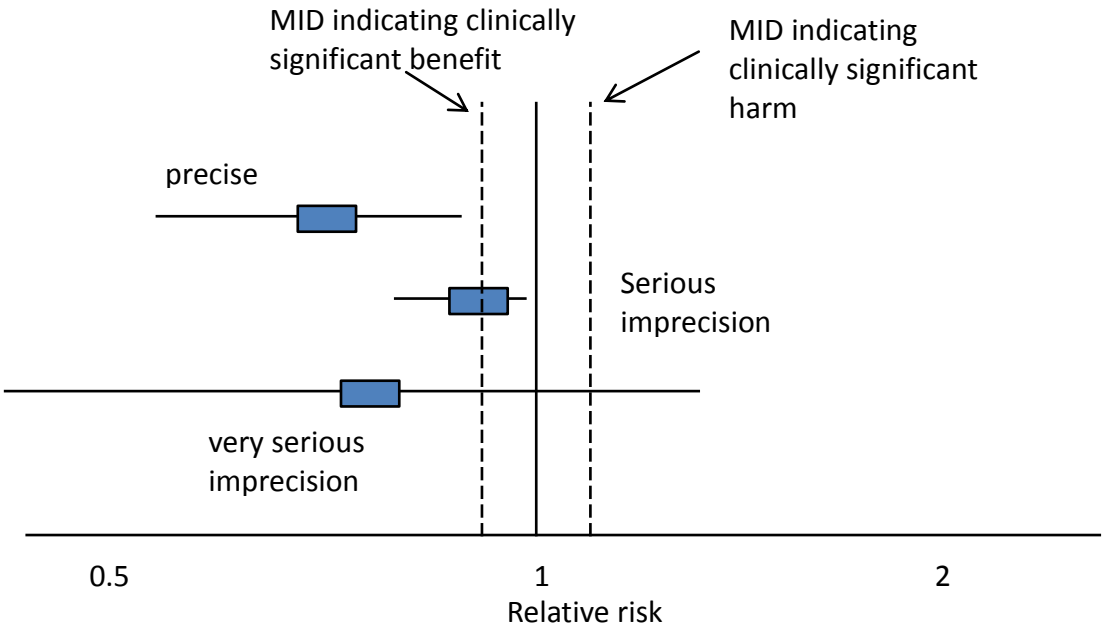
- For categorical outcomes the MIDs are taken as RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For continuous outcome variables the MID is taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit will be positive for a "positive" outcome (for example, a quality of life measure where a higher score denotes better health), and negative for a "negative" outcome (for example, a VAS pain score). Clinically significant harms will be the converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.
- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the two groups, and are thus effectively expressed in units of "numbers of standard deviation". The 0.5 MID value in this context

therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the GDG. If the GDG decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was used.

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of dichotomous outcomes in a forest plot. Note that all 3 results would be pooled estimates and would not, in practice, be placed on the same forest plot



Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores from each of the main quality elements (0, -1 or -2) were summed to give a score that could be anything from 0 (the best possible) to -8 (the worst possible). However, scores were capped at -3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if the overall score was -1, -2 or -3 points respectively. The significance of these overall ratings is explained in Table 3. The reasons or criteria used for downgrading were specified in the footnotes of the GRADE tables.

On the other hand, observational interventional studies started at LOW, and so a score of -1 would be enough to take the grade to the lowest level of VERY LOW. Observational studies could, however, be upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect.

Table 4: Overall quality of outcome evidence in GRADE

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

4.3.4.2 Prognostic studies

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

Risk of bias

The quality of evidence for prognostic studies was evaluated according to the criteria given in Table 5.

Table 5: Description of quality elements for prospective studies

Quality element	Description of cases where the quality measure would be downgraded
Selection bias	Was there a lack of reported attempts made to achieve some group comparability between the risk factor and non-risk factor groups? (ignore if 2 or more risk factors considered)
	Was there a lack of consideration of any of the key confounders, or was this unclear?
	Was there a lack of consideration of non-key plausible confounders, or was this unclear?
	If the outcome is categorical: were there <10 events per variable included in the multivariable analysis? If the outcome is continuous: were there <10 people per variable included in the multivariable analysis?
	Was it very clear that one group was more likely to have had more outcomes occurring at baseline than another group?
Detection bias	Was there a lack of assessor blinding and the outcome was not completely objective?
	Were the risk factors measured in a way that would systematically favour either group?
	Were the outcomes measured in a way that would systematically favour either group?
	If there were multiple raters, was there lack of adjustment for systematic inter-rater measurement errors, or was inter-rater reliability unreported?
	Was there an excessively short follow up, such that there was not enough time for outcomes to occur?
Attrition bias	Was there >10% group differential attrition (for reasons related to outcome) and there was no appropriate imputation? (if one risk factor) or Was there >10% overall attrition (for reasons related to outcome) and there was no appropriate imputation? (if >1 risk factor).

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

Indirectness

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

Inconsistency

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

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each sub-group had an I^2 <50), the GDG took this into account and considered whether to make separate recommendations on new outcomes based on the sub-groups defined by the assumed explanatory factors. In such a situation the quality of evidence was not downgraded for those emergent outcomes.

Imprecision

In meta-analysed outcomes, or for non-pooled outcomes, the position of the confidence intervals in relation to the null line determined the existence of imprecision. If the confidence intervals did not cross the null line then no serious imprecision was recorded. If the confidence intervals crossed the null line then serious imprecision was recorded.

Quality rating started at LOW for observational studies, and each major limitation (see Table 6) brought the rating down by one increment to a minimum grade of VERY LOW, as explained for observational interventional studies.

4.3.4.3 Qualitative reviews

Table 6 below summarises the factors which were assessed to inform the quality rating for each sub-theme. The overall quality rating for each theme is reported in a summary table in the evidence report.

Table 6: Summary of factors assessed in qualitative reviews

Quality element	

Quality element	
Limitations of evidence	• Were qualitative studies/ surveys an appropriate approach? • Were the studies approved by an ethics committee? • Were the studies clear in what they seek to do? • Is the context clearly described? • Is the role of the researcher clearly described? • How rigorous was the research design/methods? • Is the data collection rigorous? • Is the data analysis rigorous? • Are the data rich (for qualitative study and open ended survey questions)? • Are the findings relevant to the aims of the study? • Are the findings and conclusions convincing?
Coherence of findings	• Do the sub-themes identified complement, reinforce or contradict each other?
Applicability of evidence	• Are the findings of the study applicable to the evidence review? For example population and setting.
Theme saturation	• Was the evidence for a theme based on a broad range of views, including quotes and experience from a range of people, and did authors follow up enough people to have sufficient saturation of data? This was detailed in the accompanying footnotes.

4.3.5 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[50,50] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews. The GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group then this intervention would be considered beneficial. The same point estimate but in the opposite direction would apply if the outcome was negative. However, the control group rate was always taken into consideration and smaller control group rates could identify a clinical benefit/harm for the intervention group at lower than 100 participants.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.6 Clinical evidence statements

Clinical evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty/uncertainty in the estimate of effect. The evidence statements were presented by outcome and encompassed the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.

- An indication of the direction of clinical importance (if one treatment is beneficial or harmful compared to the other or whether there is no difference between the two tested treatments).
- A description of the overall quality of evidence (GRADE overall quality).

4.4 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical- and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost.[84] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

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

4.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in the NICE guidelines manual.[84,87]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

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

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 1999 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a High quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see Table 7 below and the economic evaluation checklist (Appendix G of the NICE guidelines manual 2012[87]) and the health economics review protocol in Appendix C.

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

4.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[87] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 7 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[100]

Table 7: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost-effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost-effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost-effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data,

Item	Description
	as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of the NICE guidelines manual (2012)[87]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified coordination of care as the highest priority area for original economic modelling. This question was chosen as it will impact every individual with MND regardless of the type of MND they have or severity of symptoms, meaning it could have large resource implications. Secondly, it was expected that good evidence would exist that would allow a robust analysis to be undertaken.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[88]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- Where published data were not available, GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analysis for coordination of care are described in Appendix M.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[85] 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 cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[85]

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis,

results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of economic evidence

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

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

4.5 Developing recommendations

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

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H.
- Summaries of clinical and economic evidence and quality (as presented in Chapters 5 to 21).
- Forest plots (Appendix J).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix M).

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

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 4.5.1 below).

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

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

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in the NICE guidelines manual[87]).

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

4.5.1 Research recommendations

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

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

4.5.2 Validation process

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

4.5.3 Updating the guideline

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

4.5.4 Disclaimer

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

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

4.5.5 Funding

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

5 Recognition and referral

5.1 Introduction

Motor neurone disease is a rare disease. Early symptoms can be vague and attributable to more common causes of muscle weakness or behaviour change. Diagnosis can be delayed if healthcare professionals do not think about the possibility of MND. This is true both for GPs and for specialists other than neurologists. People with MND who present with voice or swallowing problems may for example be referred initially to ear, nose and throat (ENT) specialists. The GDG were interested in the experience of the diagnostic process of people with MND and their families and carers for insights into how the process might be improved.

5.2 Review question: What factors impact upon timeliness of diagnosis in people with MND in the UK?

For full details the see review protocol in Appendix C.

Table 8: PICO characteristics of review question

Population and setting	• Adults (aged 18 and over) with MND and their family/carers
Topic of interest	• To establish what factors impact upon timeliness of diagnosis in people with MND in the UK
Context (specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	Potential themes identified by the GDG that would be relevant for inclusion in this review included timeliness in: • Identification of MND • Referral to a neurologist • Carrying out relevant investigations • Obtaining results of investigations • People seeking help
Review strategy	• Qualitative studies were sought for inclusion in this review. Studies will be analysed using thematic analysis. Results to be presented as a narrative, and diagrammatically where appropriate. 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.

5.3 Clinical evidence

Three studies were included in the review;[58,60,79,93] these are summarised in Table 9 below. The themes identified in this review are summarised in Table 10. Evidence from these studies is summarised in the clinical evidence summary below (Table 11). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, and excluded studies list in Appendix K.

Table 9: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (1:1 interviews, focus groups, partner interviews, semi-structured interviews)				
Hugel 2006[60]	Semi-structured interviews	People with MND	To explore patients' experiences regarding their recent diagnosis of MND.	This study was also included in the 'Information and support at

				diagnosis' review.
Mistry 2013[79]	Semi-structured interviews	People with MND	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.	This study was also included in the 'Psychological support' review.
O'Brien 2011[93]	Narrative interviews	People with MND, current carers and former carers of family members with MND	To explore the personal perspectives of the diagnostic experience of people with MND and their family and carers, identifying issues that could impact positively or negatively on these experiences.	This study was also included in the 'Psychological support' review.

Evidence

5.3.1.1 Themes and sub-themes derived from the evidence

Table 10: Themes and sub-themes

Main theme	Sub-themes
Factors impacting on timeliness of diagnosis	Perception of reduced functioning
	Problems with identification by health professionals
	Problems with referral

Table 11: Summary of evidence: Theme 1 – factors impacting on timeliness of diagnosis

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Perception of reduced functioning					
3 (Hugel 2006; Mistry 2013; O'Brien 2011)	Interviews	Initially patients did not think that the physical/functional changes were significant, often thinking they were due to the ageing process, work hazards or poor fitness. It was variable when people sought help but in some instances it was when symptoms progressed. Clinicians found patients had limited awareness of MND. One patient suspected they had MND but was too afraid to ask, in order not to 'tempt fate'. Often acquaintances were the first to notice.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Problems with identification by health professionals					
3 (O'Brien 2011; Mistry 2013; Hugel	Interviews	Patients expressed that they were a 'puzzle' to clinicians, or occasionally not taken seriously. GPs often did not recognise symptoms or their significance.	Applicability of evidence	Applicable[a]	High
			Theme	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
2006)		Concurrent health problems confused matters.	saturation/sufficiency		
Sub-theme 3: Problems with referral					
2 (Mistry 2013; O'Brien 2011)	Interviews	As people had different symptoms they were referred into many medical specialties according to initial symptoms. Lack of urgency within primary care resulted in delayed referral for specialist investigations. More delays occurred when directed to specialities other than neurology. Some patients with bulbar difficulties were initially referred to ENT departments. Many patients were referred to local general hospitals for initial investigations when GPs failed to recognise neurological problems warranting a specialist opinion. Some patients sought a neurologist consultation privately as they were not being referred.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

5.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

5.5 Evidence statements

5.5.1 Clinical

Perception of reduced functioning:

- Patients at first did not think the physical/ functional changes were significant. It was variable when people sought help but in some instances it was when symptoms progressed. Clinicians found patients had limited awareness of MND.

Problems with identification by health professionals:

- Patients felt they were a 'puzzle' to clinicians, or sometimes not taken seriously. GPs often did not recognise the significance of their symptoms, with concurrent health problems confusing matters.

Problems with referral:

- Different initial symptoms meant patients were referred to a variety of medical specialties. Delays in referral occurred because of a lack of realisation of the significance of symptoms and because patients were directed to specialities other than neurology, such as bulbar patients referred to ENT departments. Some patients sought a neurologist consultation privately as they were not being referred.

5.5.2 Economic

- No relevant economic evaluations were identified.

5.6 Recommendations and link to evidence

Recommendations	**Recognition and referral** **1. Ensure that robust protocols and pathways are in place to:** • **inform healthcare professionals about motor neurone disease (MND) and how it may present** • **inform healthcare professionals in all settings about local referral arrangements** • **ensure continued and integrated care for people with MND across all care settings. [new 2016]** **2. Be aware that MND causes progressive muscular weakness that may first present as isolated and unexplained symptoms. These symptoms may include:** • **functional effects of muscle weakness, such as loss of dexterity, falls or trips** • **speech or swallowing problems, or tongue fasciculations (this is**

	known as bulbar presentation) • **muscle problems, such as weakness, wasting, twitching, cramps and stiffness** • **breathing problems, such as shortness of breath on exertion or respiratory symptoms that are hard to explain** • **effects of reduced respiratory function, such as excessive daytime sleepiness, fatigue, early morning headache or shortness of breath when lying down. [new 2016]** **3. Be aware that MND may first present with cognitive features, which may include:** • **behavioural changes** • **emotional lability (not related to dementia)** • **frontotemporal dementia. [new 2016]** **4. If you suspect MND, refer the person without delay and specify the possible diagnosis in the referral letter. Contact the consultant neurologist directly if you think the person needs to be seen urgently. [new 2016]** **5. Provide information and support for people and their family members and/or carers (as appropriate) throughout the diagnostic process, particularly during periods of diagnostic uncertainty or delay. [new 2016]**
Relative values of different outcomes	The aim of the review was to understand factors that impacted on timeliness of diagnosis by understanding individual patient experience and perception of the process.
Trade-off between clinical benefits and harms	Diagnosis allows people with MND and their families and carers to access medicines and services to treat MND and manage MND symptoms. It also allows them to make plans for future care as well as personal and financial arrangements. It is recognised that MND diagnosis can be traumatic and informing the person of the diagnosis must be done sensitively and according to the individual's wishes. Ensuring that a person who has presented to medical care is seen by the right specialist is not considered to be of harm.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. A discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations.
Quality of evidence	Qualitative studies were sought for inclusion in this review. Studies were analysed using thematic analysis. Results were presented as a narrative. The methodological quality of each study was assessed using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome. This took into account the applicability and theme saturation/sufficiency of the evidence. The studies were graded as moderate quality.
Other considerations	The recommendations were informed by the evidence review and by the expertise of the GDG. The GDG noted that in some instances, a delay to diagnosis is inevitable as time may be required for symptoms to manifest clinically. In the early stages of the disease, it is sometimes not possible to make a definitive diagnosis of MND. While healthcare professionals may want to be sure before giving someone such a devastating diagnosis, it can be difficult for people to access the services and equipment that they require without a definitive diagnosis. Currently people can miss out on

support without a diagnosis being made. The neurologist and multidisciplinary team (MDT) are however best placed to manage this balance and the difficulties of diagnosis are not a reason for delayed referral to a specialist.

People with MND need first to decide that their symptoms are significant in order to seek medical advice. This may happen because of the symptom and/or because of concern about the likely cause. The evidence review indicated that patients and their families had a lack of knowledge about MND. The GDG discussed that there has been a significant increase in awareness of MND over the past year in the media, but that the effect of this might be short-term.

The GDG noted that the delay in referral by healthcare professions can be a significant factor in delay to diagnosis. This can be because MND is not considered as a possible diagnosis, as it is rare, and for this reason the GDG chose to highlight the need for education and information for both primary and secondary healthcare professionals in their recommendations. People with bulbar symptoms for example are commonly referred to ear, nose and throat (ENT) specialists. As well as the provision of education, clear pathways should be designed so that healthcare professionals know how to refer to a neurologist in their area. The GDG were concerned about the difficulty of referring between specialists and that diagnosis can be delayed because the person is referred back to the GP for referral to neurology. While there may be good reasons to reduce inter-specialty referral in general, the GDG considered that this was less appropriate in the case of diagnosis of conditions such as MND.

The GDG wished to highlight common presentations of MND and the detail of their recommendation was informed by the Red Flag diagnosis tool, developed by the MND Association and the Royal College of General Practitioners.[1,81] The tool includes symptoms related to muscle weakness and to cognitive or behavioural changes.

The GDG agreed that GPs should consider speaking to specialists directly if MND is suspected to receive advice and reduce unnecessary delay in being seen by a specialist.

Referral, investigations and diagnosis can be a time of uncertainty and frustration for the person with MND and their family members or carers, and the GDG agreed that support and information was necessary throughout the process. Explanation of the reason for delay and difficulties in diagnosis should be explained to the person. The GDG made a specific recommendation to highlight the importance of providing support and information, particularly during periods of diagnostic uncertainty or delay. This support should be in place for the person even if their diagnosis is suspected but has not been confirmed, and support should include help to manage the issues that may arise, such provision of appropriate equipment.

6 Information and support at diagnosis

6.1 Introduction

MND is a rare condition seldom seen by GPs or other healthcare professionals. The diagnosis is likely to be accompanied by a variety of questions and concerns for the person with MND and for their family and carers. It is essential that the diagnosis is delivered with compassion and understanding by a healthcare profession who possesses skill in communicating this devastating diagnosis and who can provide accurate and up-to-date information to the patient. An evidence review of people's experience of information and support informed the recommendations made by the GDG.

6.2 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?

For full details see the review protocol in Appendix C.

Table 12: PICO characteristics of review question

Population and setting	• Adults (aged 18 and over) with MND • Family and carers of adults with MND • Health professionals who support patients with MND
Topic of interest	• 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
Context(specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	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
Review strategy	Qualitative studies were sought for inclusion in this review. Studies will be analysed using thematic analysis. Results to be presented as a narrative, and diagrammatically where appropriate. 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.

6.3 Clinical evidence

Nine papers (from 6 studies) were included in the review;[14,55-57,60,61,74,90,93] these are summarised in Table 13 below. The themes and sub-themes identified in this review are summarised in Table 14. Evidence from these studies is summarised in the clinical evidence summary below (Table 15, Table 16, Table 17 and Table 18). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 13: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (including 1:1 interviews, focus groups, partner interviews, semi-structured interviews)				
Hocking 2006A[56]; Hocking 2006[55]; Brott 2007[14]	Semi-structured interviews	People with MND	To explore the experience of living with MND	This study was also included in the 'Psychological support' review.
Hogden 2012A[57]	Semi-structured interviews	Health professionals and advisors from MND New South Wales	To explore clinicians' perspectives on patient decision-making in multidisciplinary care for ALS; to identify factors influencing decision-making	This study was also included in the 'Psychological support' review.
Hugel 2006[60]	Semi-structured interviews	People with MND	To explore patients' experiences regarding their recent diagnosis of MND	This study was also included in the 'Recognition and referral' review.
Hughes 2005[61]	Semi-structured interviews	People with MND and their carers and health professionals	To look at the lives, experiences of services and suggestions for change of people living with MND	This study was also included in the 'Psychological support' review.
McConigley 2014[74]	Interviews and focus groups	Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) with experience of providing palliative care for people with MND; Australian study	To determine the experiences of, and need for, education of health professionals who may be required to provide care for people with MND	
O'Brien 2011[93]; O'Brien 2011A[90]	Narrative interviews	People with MND, current carers and former carers of family members with MND	To explore the personal perspectives of the diagnostic experience of people with MND and their family	This study was also included in the 'Psychological support' review.

			and carers; identifying issues that could impact positively or negatively on these experiences	

Themes and sub-themes derived from the evidence

Table 14: Themes

Main theme	Sub-themes
Knowledge	Specialist knowledge of MND
	Knowledge of all forms of MND
	Up-to-date knowledge
	Knowledge of disease progression
Knowledge of potential for cognitive change	Knowledge of cognitive change
Knowledge of care and management options	Palliative care
Knowledge of follow-up support post-diagnosis	Support after the diagnosis

Table 15: Summary of evidence: Theme 1: Knowledge

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Specialist knowledge of MND					
2 McConigley 2014; O'Brien 2011	Interviews and focus group	Health professionals (nurses, occupational therapists, case coordinator/care advisor, 3 medical specialists, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) in Australia thought that the care of people with MND required knowledgeable and credible health professionals, however most providers of care are generalists. They thought that poorly prepared staff could undermine the efforts of the care team. Having professionals with specialist knowledge in an MDT clinic was thought to be a major advantage. Carers in the UK felt that MND specialist centre staff were able to provide advice based on sound knowledge and experience of the illness. The effect of limited	Applicability of evidence	Partially applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
		knowledge of the disease among local health staff was minimised if there was a specialist MND centre nearby.			
Sub-theme 2: Knowledge of all forms of MND					
2 McConigley 2014; Hughes 2005	Interviews and focus group	Health professionals (nurses, occupational therapists, case coordinator/care advisor, 3 medical specialists, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) in Australia thought it 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 patient and carer needs. There was a need to provide education about disease aetiology, progression and management. Understanding that the requirements of people with MND were distinct from other life-limiting conditions, and recognising their unique care needs, was paramount. There was a need for health professional training and non-professional staff education on the disease and its progression. Some UK patients 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.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 3: Up-to-date knowledge					
2 McConigley 2014; Hugel 2006	Interviews and focus group	Health professionals (nurses, occupational therapists, case coordinator/care advisor, 3 medical specialists, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) in Australia felt those caring for patients needed to be up-to-date with current MND knowledge and services, but this was difficult for those providing infrequent care.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
		Patients in the UK felt it was important for health professionals to be aware of prominent cases of MND in the media as these may influence patients' reactions to their diagnosis.			
Sub-theme 4: Knowledge of disease progression					
1 McConigley 2014	Interviews and focus group	Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) in Australia felt those involved in patients care needed to stay one step ahead (but not too far ahead for the patient's needs), by being aware of disease progression, anticipating needs and issues and being ready with timely solutions. They felt it better to predict changes in needs than wait until a crisis. Changes which could not be predicted or were very sudden required a quick response. Thought it necessary to know all possible manifestations and disease trajectories. Staging of information and timing of support were important so that patients could digest that information before getting more. Too much information may be detrimental. This required careful negotiations with patients and families.	Applicability of evidence	Partially applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 16: Summary of evidence: Theme 2: Knowledge of potential for cognitive change

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Knowledge of cognitive change					

Study design and sample		Descriptors of themes	Quality assessment		
1 (Hogden 2012A)	Interviews	Health professionals (medical, nursing and allied health professionals from specialised multidisciplinary ALS clinics and regional advisors from the MND New South Wales) felt that 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. They felt that more specific and detailed knowledge of these changes could improve their approach with the patient and carer.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 17: Summary of evidence: Theme 3: Knowledge of care and management options

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Palliative care					
1 McConigley 2014	Interviews and focus group	Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) in Australia felt that it was beneficial to connect the person to a palliative care centre, providing a framework for planning proactive care, tailored to the individual's care needs.	Applicability of evidence	Partially applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 18: Summary of evidence: Theme 4: Knowledge of follow-up support post-diagnosis

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Support after the diagnosis					
3 O'Brien 2011; Hocking 2006; Hugel 2006	Interviews	Patients and carers felt that people with MND should know the follow-up arrangements and have a point of contact post-diagnosis. Information needs varied but insufficient explanation was given. They felt that immediate post-diagnosis support was important for coping. They noted however that some patients felt overwhelmed by the sudden surge in support, which may worsen rather than improve feelings of losing control. Patients felt that coordination of services was not always optimal.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

6.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

6.5 Evidence statements

6.5.1 Clinical

Knowledge

Specialist knowledge of MND

- Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) stated that health professionals should be knowledgeable and credible, but acknowledged that most health professionals involved with people with MND were mainly generalist providers of care. They thought that poorly prepared staff could undermine the efforts of the care team and that specialist knowledge in an MDT was a major advantage. Advice should be based on sound knowledge and experience.
- Carers felt that MND specialist centre staff were able to provide advice based on sound knowledge and experience of the illness.

Knowledge of all forms of MND

- Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) felt that health professionals required more knowledge of the disease and that it was important to be aware of the patient's understanding of MND. They identified the need for education on disease aetiology, progression and management, and an understanding that MND is distinct from other life-limiting conditions and people with MND have unique care needs. They felt that both professional and non-professional staff required training on MND and its progression.

Up-to-date knowledge

- Patients worried about professionals' lack of knowledge and understanding of MND and its impact. They thought that health professionals needed to keep up-to date with MND knowledge and services. Patients acknowledged this is difficult for those providing infrequent care.

Knowledge of disease progression

- Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) believed they needed to stay one step ahead, but not plan too far ahead of the patient's needs, by being aware of all possible manifestations and disease trajectories to anticipate needs and issues and be ready with timely solutions rather than wait for a crisis. It was thought that staging of the provision of information and timing of support was important and should be carefully negotiated.

Knowledge of potential for cognitive change

Knowledge of cognitive change

- Health professionals (medical, nursing and allied health professionals from specialised multidisciplinary ALS clinics and regional advisors from the MND New South Wales) stated that more specific and detailed knowledge of cognitive changes could improve their care of the patient and their understanding of carer challenges.

Knowledge of care and management options

Palliative care

- Health professionals (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain) thought it was important to connect the person with MND to a palliative care centre, providing a framework for planning proactive care, tailored to the individual's care needs.

Knowledge of follow-up support post-diagnosis

Support after the diagnosis

- People with MND and their carers felt that health professionals should be aware of follow-up arrangements and provide them with a point of contact. They identified that the coordination of services is not always optimal.
- The studies showed that every person with MND has distinct information requirements, including different preferences about the type and timing of information that they receive about their disease. Patients included in the studies highlighted the importance of receiving accurate information for accepting the diagnosis and coping with the disease.

6.5.2 Economic

- No relevant economic evaluations were identified.

6.6 Recommendations and link to evidence

Recommendations	**Information and support at diagnosis** **Please also refer to the recommendations in NICE's guideline on patient experience in adult NHS services which includes recommendations on communication, information and coordination of care.** **6. Information about the diagnosis, prognosis and management of MND should be given by a consultant neurologist with up-to-date knowledge and experience of treating people with MND unless it is clinically necessary to give the diagnosis in an urgent situation. The neurologist should have knowledge and expertise in the following:** • **Symptoms of MND.** • **Types and possible causes of MND.** • **Treatment options.** • **How MND may progress (including cognitive and behavioural changes) and how progression may affect the treatments offered.** • **Crisis prevention (for example, if there is an acute hospital admission**

	or a breakdown in care arrangements). • **Opportunities for people with MND to be involved in research.** • **Likely needs and concerns of people with MND and their family members and/or carers (as appropriate).** • **Advance care planning. [new 2016]** **7. Ask people about how much information they wish to receive about MND, and about their preferences for involving their family members and/or carers (as appropriate). [new 2016]** **8. Ensure people are provided with information about MND and support at diagnosis or when they ask for it. If the person agrees, share the information with their family members and/or carers (as appropriate). Information should be oral and written, and may include the following:** • **What MND is.** • **Types and possible causes.** • **Likely symptoms and how they can be managed.** • **How MND may progress.** • **Treatment options.** • **Where the person's appointments will take place.** • **Which healthcare professionals and social care practitioners will undertake the person's care.** • **Expected waiting times for consultations, investigations and treatments.** • **Local services (including social care and specialist palliative care services) and how to get in touch with them.** • **Local support groups, online forums and national charities, and how to get in touch with them.** • **Legal rights, including social care support, employment rights and benefits.** • **Requirements for disclosure, such as notifying the Driver and Vehicle Licensing Agency (DVLA).** • **Opportunities for advance care planning. [new 2016]** **9. When MND is diagnosed, provide people with a single point of contact for the specialist MND multidisciplinary team (see Chapter 9). Provide information about what to do if there are any concerns between assessments or appointments, during 'out-of-hours' or in an emergency, or if there is a problem with equipment. [new 2016]** **10. Offer the person with MND a face-to-face, follow-up appointment with a healthcare professional from the multidisciplinary team, to take place within 4 weeks of diagnosis. [new 2016]** **11. When MND is suspected or confirmed, inform the person's GP without delay and provide information about the likely prognosis. [new 2016]** **12. Set aside enough time to discuss the person's concerns and questions,**

	which may include the following: • **What will happen to me?** • **Are there any treatments available?** • **Is there a cure?** • **How long will I live?** • **What will the impact on my day-to-day life be?** • **What will happen next with my healthcare?** • **Will my children get MND?** • **How do I tell my family and friends?** • **How will I die? [new 2016]** **13. If the person has any social care needs, refer them to social services for an assessment. Be aware that some people with MND may not have informal care available, and may live alone or care for someone else. [new 2016]** **14. Advise carers that they have a legal right to have a Carer's Assessment of their needs; support them with requesting this from their local authority. [new 2016]**
Relative values of different outcomes	This qualitative review aimed to analyse the needs and experiences of people with MND, their families, carers and health professionals to determine the knowledge required by health professionals in order to communicate diagnosis of MND, its prognosis, and choices of ongoing care appropriately. Information from interviews and focus groups was synthesised into themes and sub-themes through thematic analysis.
Trade-off between clinical benefits and harms	Six qualitative studies were included in the review, from which 4 main themes were identified: knowledge, knowledge of potential for cognitive change, knowledge of care and management options, and knowledge of follow-up support post-diagnosis. The following sub-themes were then identified: specialist knowledge of MND, knowledge of all forms of MND, up-to-date knowledge, knowledge of disease progression, knowledge of cognitive change, palliative care and support after the diagnosis. Specialist knowledge, experience and credibility were thought to be very important factors for delivering diagnosis and providing information. Linking to other services and providing planned, proactive, tailored care was important. Harms included the possibility that poorly prepared staff could undermine the efforts of the care team; the potential for professionals to lack knowledge and understanding was possible, given that they may not have cared for many people with MND, which worried patients.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. The GDG noted that additional costs may be incurred by ensuring a consultant neurologist gave the diagnosis and by ensuring a follow-up visit was offered, although relative to current practice these cost increases would be small. Follow-up appointment within 4 weeks after diagnosis is unlikely to have a significant resource impact as the GDG noted that a follow up appointment after diagnosis is current practice and if this follow-up appointment was not conducted the content would need to be discussed at a later point. The recommendation is unlikely therefore to require additional professional time. However, there are implications for service provision, including the allocation of

	appropriate staff to deliver the diagnosis, prognosis and ongoing care options. The GDG considered that these changes to the planning of services would be of clinical benefit in terms of improving the ability of patients to cope with living with MND.
Quality of evidence	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. Six studies were included for the theme of knowledge, which were graded as moderate quality for inclusion. One study was included for knowledge of potential for cognitive change, 1 study was included for knowledge of care and management options and 3 studies were included for knowledge of follow-up support post-diagnosis. The study (McConigley, 2014)[74,74] which informed most of the themes included a variety of practitioners (nurses, occupational therapists, case coordinator/care advisor, medical specialist, physiotherapist, speech pathologist, complementary therapist, counsellor, dietitian, prosthetist, and chaplain), who were less likely to give the diagnosis of MND, but were involved in their palliative care.
Other considerations	The GDG developed recommendations informed by the evidence and their experience of MND. These recommendations were also informed by evidence reviews for psychological support and social support (Chapters 10 and 11 respectively), and the review on planning for end of life in Chapter 12. The GDG noted distinctions between those who have the ability to diagnose MND and those with experience of caring for people with MND. It is acknowledged that MND is distinct from other life-limiting conditions, and knowledge of the condition is required by those delivering the diagnosis, prognosis and ongoing care options. The GDG thought that consultant neurologists who had appropriate knowledge and experience of treating people with MND were best placed to deliver the diagnosis. The provision of information from an expert can give people confidence in their care and reduce uncertainty. The specific expertise considered important is knowledge of: symptoms; types and possible causes of MND; treatment options; how MND may progress; research that people can be involved in; advance care planning. The GDG recognised that there can be situations where the patient needs urgent treatment, such as when a patient is rapidly deteriorating or if they present with breathing problems, where it would not be possible for a consultant neurologist to give the diagnosis. In these circumstances the diagnosis may have to be given by a different professional. The GDG considered that sensitivity is required as not all patients may be able to cope with receiving a lot of information at the time of diagnosis. It was acknowledged that the delivery of information should be responsive to the patient in terms of its content and staging. Information and explanations should be readily available when the patient asks, and shared with family and/or carers with the patient's consent in order that they and others can understand MND better. Common questions concern: what MND is and the different types; what the possible causes and symptoms are and how it may progress; treatment options; who and what will be involved in their care and expected waiting times; their legal rights, required disclosures and advance care planning. Time needs to be set aside to discuss any concerns following diagnosis. The GDG agreed that a follow-up appointment should be offered with a member of the MDT within 4 weeks of diagnosis. This appointment will allow t the person diagnosed with MND to ask further questions, or to obtain general support. The GDG were aware that many centres aim to offer an appointment within 2 weeks but the GDG agreed using consensus to specify a time period of 4 weeks to allow for differences in service organisation. The GDG considered that not all patients would want to accept this appointment, but that it should be offered. People newly diagnosed with MND may have concerns about whether this is

something that they will pass on to their children. A minority of cases do seem to be have a stronger familial pattern but genetic influences are only part of the explanation for MND and the full range of mutations involved has not yet been identified. There may be some diagnostic benefit in genetic testing for patients with a family history and referral to an appropriate genetics service should be considered.

Access to benefits and financial support can require clinicians to provide information about the person and their condition to social services. This information should be provided as soon as possible. Specific mechanisms such as DS1500 forms exist which allow applications to be fast tracked for people with very reduced life expectancy, and there is no prospect of professional sanction if a person with MND lives longer than a clinician had judged that they might.

In order to optimise coordination of care, the person's GP should be informed when MND is diagnosed and information about their prognosis should be provided. A diagnosis of MND is life-changing and has an effect on patients and their families. Their GP is likely to have an important role in supporting the family and liaising with local services. Depending on prognosis the GP should consider adding the patient to the Palliative Care Register so that the patient's needs may be addressed by the wider primary care team. Sharing of information with out of hours services may also be appropriate depending on the prognosis and needs of the patient.

The GDG were also aware that the diagnosis consultation can be very overwhelming for the person with MND, and that they may need to talk to someone after diagnosis who has relevant knowledge of MND. They considered that a single point of contact for the MDT is important for people between appointments, and people should know who to contact in a variety of different circumstances, such as out of hours.

The GDG identified the importance of awareness of cognitive impairment and behavioural change in their recommendations. Knowledge of cognitive impairment and behavioural change was found in the studies to be important to the clinician's approach to the patient, yet it was recognised that cognitive assessment in current practice is neither systematic nor standardised. See Chapter 7 for recommendations on assessing cognitive change at diagnosis.

Information about support groups and national charities can be useful for many people with MND and their families and can also act as a source of information and support following diagnosis. The GDG considered that in order for the consultant neurologist to communicate MND-specific knowledge to the patient, they must consider the context in which the diagnosis, prognosis and ongoing care options are delivered. Factors such as adequate time to deliver information, the setting of the consultation and appropriate ways to communicate with the person are detailed in recommendations 24, 40–49, 50–58 and 59–66 in NICE clinical guideline CG138, Patient experience in adult NHS services. The majority of people with MND will need support from social services as their disease progresses. Local authorities have a duty to assess a person who needs care or support. People with social care needs should therefore be referred to social services for an assessment.

The GDG were aware that a significant number of people with MND live alone or are older people. This means that they may not have access to informal care or may themselves be carers for partners who have health needs. The GDG considered it important that this is recognised as these people may be in particular need of social services support, either for themselves or for the family members they can no longer provide care for. Carers are also entitled to an assessment of their own needs and should be supported and encouraged to access this.

7 Cognitive assessments

7.1 Introduction

Up to 50% of those affected by MND have changes in cognitive function. There is a broad spectrum of change ranging from minimal cognitive impairment to frontotemporal dementia. A small number of people with MND exhibit frontotemporal dementia with severe cognitive and behaviour change, which interferes with their ability to function on a day-to-day basis. Specialist services including neuropsychology and/or neuropsychiatry may well be needed as part of the ongoing care of those with frontotemporal dementia. NICE has developed guidance on Dementia: Supporting people with dementia and their carers in health and social care (CG42). That guideline includes recommendations for people with frontotemporal dementia.

People can present with symptoms related to cognitive changes. The presence of significant cognitive change has implications for communication, decision-making and the type and amount of care people may need.

7.2 Review question: What is the optimum frequency of assessing cognitive function in people with MND?

For full details see the review protocol in Appendix C.

Table 19: PICO characteristics of review question

Population	Adults (aged 18 years and over) with MND
Intervention	Time points as specified by studies
Comparison	The above as compared to 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)
Study design	RCTs or systematic reviews of RCTs, cohorts if no RCTs retrieved

The purpose of this review was to evaluate the most appropriate frequency of assessing cognitive function in people with MND. It is unclear whether cognitive function needs to be repeatedly assessed and if so what the optimum frequency of assessment is. The GDG decided if there was heterogeneity in findings to subgroup the population between those who had and those who had not been diagnosed with cognitive change, including frontotemporal dementia. The GDG noted that there is a lack of clarity over which is the most accurate method of identifying cognitive change in MND, and which method of delivery (for example, interview or questionnaire) was preferable to patients. For the purposes of this review, all methods were included, and the GDG chose to subgroup by the method of assessment if there was heterogeneity in the data.

7.3 Clinical evidence

No clinical evidence was identified.

7.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

7.5 Evidence statements

7.5.1 Clinical

- No relevant clinical evidence was identified.

7.5.2 Economic

- No relevant economic evaluations were identified.

7.6 Recommendations and link to evidence

Recommendations	**Cognitive assessments** **Please also refer to the recommendations in NICE's guideline on patient experience in adult NHS services.** **15. Be aware that people with MND and frontotemporal dementia may lack mental capacity. Care should be provided in line with the Mental Capacity Act 2005. [new 2016]** **16. At diagnosis, and if there is concern about cognition and behaviour, explore any cognitive or behavioural changes with the person and their family members and/or carers as appropriate. If needed, refer the person for a formal assessment in line with the NICE guideline on dementia. [new 2016]** **17. Tailor all discussions to the person's needs, taking into account their communication ability, cognitive status and mental capacity. [new 2016]**
Research recommendation	**1. 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?**
Relative values of different outcomes	The following outcomes were identified as critical: health-related quality of life; timeliness of identifying cognitive change; patient/carer/healthcare professional satisfaction with the diagnostic process; patient/carer knowledge/understanding of cognitive change (that is, allowing clearer discussion of care/options and advice for carers, and thus more appropriate care/decision making).
Trade-off between clinical benefits and harms	The GDG considered that the identification of cognitive change would be of clinical benefit to people and is unlikely to be harmful.
Trade-off between net health effects	No relevant economic evaluations were identified.

and costs	Identifying people with MND who also have cognitive impairment and behavioural change at the point of diagnosis can have a particular impact on ensuring that equipment provided is useable to the person with cognitive impairment and thus more appropriate to their needs. Ensuring equipment is tailored to the individual's needs can reduce costs to the NHS and improve health outcomes by avoiding the provision of inappropriate equipment that eventually has to be replaced.
Quality of evidence	No relevant clinical evidence was identified.
Other considerations	No relevant clinical evidence was identified. The GDG had advice from a co-opted expert in this area and used informal consensus to develop recommendations and a research recommendation. The GDG considered that it is not usual practice to systematically assess cognitive function. They considered that an assessment to establish any cognitive or behavioural change should be made at diagnosis. Their experience is that, where cognitive change is present, it often occurs early in disease progression. The identification of cognitive and behavioural change has a substantial impact on the care pathway: in particular, the specific everyday care options available to the person with MND. Therefore, a recommendation to assess this at diagnosis is important for all aspects of the person's care throughout their disease. Assessment at this stage of the disease would allow for appropriate planning during disease progression. The assessment is likely to require inquiry of family and/or carers for an account of changes they may have noticed. Although no specific evidence in relation to frequency of assessment was found, the GDG included cognition and behaviour as an area to be covered at the MDT review. The intention is not that all people require repeated comprehensive assessment but to ensure that brief enquiry is made even for people not considered to have frontotemporal dementia. The GDG emphasised that the diagnosis of cognitive and/or behavioural change does not mean that a person with MND will no longer be able to make decisions but rather that care should be provided in a way that accommodates for the cognitive or behavioural changes, for example allowing more time for decision making and an understanding of behaviour change. This will also enable all carers, family and professionals to be aware of the need to help the person with MND more appropriately, such as providing a person with 2 clear choices rather than having a complex discussions about options. The GDG discussed how cognitive function should be assessed but were aware that at present there is not a validated tool specifically to assess people with MND and that a variety of tools are used by psychologists when conducting formal assessments. **Research recommendation** In response to the lack of evidence, the GDG developed a high-priority research recommendation to assess the impact of cognitive assessment and also whether repeated assessment, in addition to that at diagnosis, might provide benefit. For further details please see Appendix N: Research recommendations.

8 Prognostic factors

8.1 Introduction

Motor neurone disease is a progressive disease. The most common forms of MND have a life expectancy of only a few years but prognosis is variable. Accurate prediction of survival in people with MND would be helpful to clinicians and to the person with MND, their family and carers.

People with MND are often unsure about their prognosis and disease progression and may make decisions which later cause them distress. Accurate predictions would enable people with MND to be clearer about their prognosis and make plans for the remainder of their life, including a well-prepared and dignified transition into the end of life phase. Accurate predictions of survival would facilitate health professionals and carers in creating and delivering more effective management and care plans that take into account the person's disease trajectory and make the best use of resources. This includes accessing services, for example specialist palliative care, when it is most appropriate.

8.2 Review questions:

A) What are the most accurate prognostic tools for estimating survival in people with MND?

B) What risk factors predict survival in people with MND?

This review sought to identify the most accurate tool for estimating survival time in people with MND and initially a prognostic tools protocol was developed for this purpose (Question A). However, as only 1 validated tool was identified, a second review was undertaken to find the risk factors that influence survival time in people with MND (Question B).

For full details see the review protocols in Appendix C.

Table 20: PICO characteristics of prognostic tools review question (Question A)

Population	• Adults (aged 18 and over) with MND
Intervention and comparison	Any externally validated tools for predicting survival in people with MND
Outcomes	Survival
Study design	Prospective/retrospective prognostic risk tool studies
Review strategy	Stratification: • Type of MND and presence of cognitive change/frontotemporal dementia If no validated risk tools are found then a risk factor review will be undertaken.

Table 21: Characteristics of risk factors review question (Question B)

Population	• Adults (aged 18 and over) with MND
Prognostic variables under consideration	• Functional measurement scales ○ Amyotrophic lateral sclerosis functional rating scale (ALSFRS) ○ Amyotrophic lateral sclerosis functional rating scale revised (ALSFRS-R) • Weight loss ○ Pre- or post- 10% weight loss

	○ BMI greater than or less than 18.5 • Respiratory function measurement ○ Forced vital capacity (FVC) ○ Sniff nasal inspiratory pressure (SNIP) ○ Maximal inspiratory pressure (MIP) ○ Maximal expiratory pressure (MEP) ○ Carbon dioxide (CO_2) ○ Oxygen saturation • Cough/ability to clear secretions (peak cough flow) • Age • Diagnostic delay • Site of onset
Outcomes	Mortality
Study design	Prospective/retrospective prognostic studies. These could be: • Prospective and retrospective cohorts • Randomised trials • Case control studies • Systematic reviews of the above
Review strategy	Stratification: • Where studies begin with a non-invasive ventilation (NIV) population • Where studies begin with a gastrostomy population • Stratify by type of MND and presence of cognitive change/frontotemporal dementia

8.3 Clinical evidence

8.3.1 Prognostic tool review

One study was included in this review;[38,39] evidence from this study is summarised in the clinical evidence summary below (Table 23). See also the study selection flow chart in Appendix D, forest plots in Appendix J, Grade tables in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix K.

The prognostic tool was developed using data from a randomly selected group of 117 people with ALS from an Irish cohort of 204 people. It was then internally validated against the remaining group in the Irish cohort and externally validated against an Italian ALS cohort.

The tool was generated through multivariate analysis using a Cox proportional hazards model. It was designed to classify people with ALS into high, medium and low risk groups at the time of their first full assessment. The risk groups were then tested against the validation cohorts to predict good prognosis and poor prognosis. Good prognosis was defined as survival of 50 months or more and poor prognosis was defined as death within 25 months.

The variables included in the final tool were site of disease onset, ALS functional rating scale revised slope and executive dysfunction. The ALS functional rating scale revised slope is a measure of the speed of disease progression and is calculated using this formula:

$$\text{ALSFRSr } \textit{slope} = \frac{48 - \text{ALSFRSr score}}{\text{disease duration (months)}}$$

Table 22: Summary of studies included in the review

Study	Risk tool	Population	Outcome	Number of events (n)
Elamin 2015[38,39]	ALS Prognostic Index	People with possible, probable or definite ALS according to the El Escorial criteria. Two cohorts: Republic of Ireland (n=204) and Italy (n=122).	Mortality Evaluated using positive and negative predictive values	Irish cohort: 177 events Italian cohort: not reported
Factor			**Points**	**Risk group by points scored**
Site of disease onset		Bulbar or respiratory onset	1	0–1: low risk
		Spinal onset	0	2–3: medium risk
ALSFRS-R slope		<0.25 points per month	0	≥4: high risk
		0.25–0.44 points per month	1	
		0.45–0.99 points per month	2	
		≥1.0 points/month	3	
Executive dysfunction		Present	1	
		Absent	0	

Table 23: Clinical evidence summary: risk tool for predicting survival in people with ALS at first assessment

Risk tool	Number of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Positive predictive value (external validation–internal validation)	Negative predictive value (external validation–internal validation)	Quality
ALS Prognostic Index	1	Development: 117 Validation: 209	HIGH	N/A	No indirectness	Not reported[a] (serious imprecision)			
						High risk group prediction of poor prognosis	73.3%–85.7%		LOW[b]
						High risk group prediction of good prognosis		93.3%–100%	LOW[b]
						Low risk group prediction of good prognosis	59.1%–60.1%		LOW[b]
						Low risk group prediction of poor prognosis		100%–100%	LOW[b]

[a] *Study adjudged to have serious imprecision due to not reporting any measure of imprecision*
[b] *Outcome downgraded for high risk of bias and serious imprecision*

8.3.2 Risk factor review

Eleven studies, reported in 16 papers, were included in the review.[17,27-29,34,47-49,64,71,73,102,103,105,106,127] Evidence from these are summarised in the clinical evidence summary tables below (Table 25, Table 26, Table 27, Table 28, Table 29, Table 30). See also the study selection flow chart in Appendix D, forest plots in Appendix J, Grade tables in Appendix I, study evidence tables in Appendix G and exclusion list in Appendix K.

For a study to be included in this systematic review, it must have accounted in some way for all the prognostic variables under consideration except the functional measurement scale. In this review functional measurement scales included weight loss and respiratory function measures. Additionally, if a study accounted for respiratory function, this was seen as a reasonable proxy for cough/ability to clear secretions. One paper[71] only reported p values resulting from a Cox proportional hazards model and was not fully included in the review. It found change in ALS functional rating scale and change in forced vital capacity to be significant predictors of survival in people with probable or definite ALS defined by the El Escorial Criteria.

Table 24: Summary of studies included in the review

Study	Population	Prognostic variables in the final model	Outcomes	Notes
Capozzo 2015[17]	n=100 12 people died and 17 had tracheostomy (median 1.2 years follow-up) People with ALS by El Escorial criteria	Cox proportional hazards model • Age (years) • Forced vital capacity (%) • ALS functional rating scale revised • Site of onset (limb, bulbar) • Disease duration (5 years) • BMI • Sex (male, female) • Charlson Comorbidity Index	Mortality or tracheostomy (time to event)	Retrospective cohort study conducted in Italy Very high risk of bias due to selection bias
Czaplinski 2006 (3 papers)[27-29]	n=1034 477 people died and 99 had tracheostomy People with definite or probable ALS by El Escorial criteria	Cox proportional hazards model • Age at onset (years) • Bulbar site of onset (limb, bulbar) • Diagnostic delay (months) • Baseline forced vital capacity (%) • Baseline Appel ALS Score (AALSS) • AALSS preslope (change between first symptoms and first exam) • Riluzole use (never, ever) • NIV therapy (never, ever) • PEG (percutaneous endoscopic gastrostomy) therapy (never, ever)	Mortality or tracheostomy (time to event)	Retrospective cohort study conducted in the USA High risk of bias due to selection bias
Desport 1999[34]	n=55 18 people died People with	Cox proportional hazards model • BMI (<18.5 versus >18.5) • Age at onset (years)	Mortality (time to event)	Prospective cohort study conducted in France

Study	Population	Prognostic variables in the final model	Outcomes	Notes
	probable or definite ALS according to the El Escorial criteria	• Site of onset (limb, bulbar) • Diagnostic delay (months) • Vital capacity (<60%) • Duration of riluzole treatment (months) • Presence of gastrostomy		Very high risk of bias due to selection bias and detection bias
Gordon 2013[49] Gordon 2010[48]	n=2037 1471 people died People with probable, laboratory-supported probable, or definite ALS according to the revised El Escorial criteria	Cox proportional hazards model • Age • Site of onset (limb, bulbar) • Diagnostic delay (≤7 months, 7.1–10.6, 10.7–17, >17) • ALS functional rating scale revised (≤35, 36–39, 40–42, >42) • Region of residence (Paris, not Paris) • Year of first visit to clinic (2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009) • Sex	Mortality (time to event)	Cohort study conducted in France No serious risk of bias
Kaufmann 2005[64]	n=267 103 people died or had tracheostomy (mean follow-up of 12 months) People with suspected, possible, probable, or definite ALS according to the El Escorial Criteria	Cox proportional hazards model • ALS functional rating scale revised at baseline • Forced vital capacity (%) • Symptom duration at baseline (years) • Age at baseline (years) • Site of symptom onset (upper extremity, lower extremity, bulbar, respiratory) • Sex • Riluzole use (ever, never)	Mortality or tracheostomy (time to event)	Prospective cohort study conducted in the USA High risk of bias due to selection and detection bias
Marin 2011[73] Gil 2007[47]	n=94 74 people died People with suspected, possible, probable, or definite ALS according to the El Escorial criteria	Cox proportional hazards model • 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 (months) • Sex • Manual muscular testing • Airlie House criteria at diagnosis (definite or probable	Mortality (time to event)	Cohort study conducted in France High risk of bias due to selection bias

Study	Population	Prognostic variables in the final model	Outcomes	Notes
		versus possible)		
Paganoni 2011[102]	n=427 82 people died or had tracheostomy/ permanently assisted ventilation (mean follow-up 335 days) People with probable or definite ALS according to the El Escorial criteria	Cox proportional hazards model • ALS functional rating scale revised at baseline • Age (years) • Time from symptom onset (months) • Forced vital capacity (%) • BMI • BMI^2	Mortality or tracheostomy or permanently assisted ventilation (time to event)	Cohort study conducted in USA High risk of bias due to selection bias and detection bias
Paillisse 2005[103]	n=1398 547 died Adults with probable or definite ALS	Cox proportional hazards model • Age (≤65, >65) • Disease duration (>2 years, <2 years) • Plasma creatinine (≤60 µmol/l^{-1}, >60) • Atrophy (regions) • Pyramidal signs • Spasticity (regions) • Fasciculations • Distal muscle strength score (≤56, >56) • Cough (Norris) • Swallowing (Norris) • Slow vital capacity (%)	Mortality	Cohort study conducted in France High risk of bias due to selection bias and detection bias
Peysson 2008[105]	n=33 24 died and 3 had tracheostomy Adults with probable or definite ALS by El Escorial criteria who started on NIV	Cox proportional hazards model • Age at diagnosis (years) • Site of onset (bulbar, limb) • Mechanically assisted cough (requiring, not requiring) • Oxygenotherapy (requiring, not requiring)	Mortality or tracheostomy (time to event)	Retrospective cohort study conducted in France No serious risk of bias
Pinto 2012[106]	n=254 240 people died People with probable or definite ALS as defined by the El Escorial criteria	Cox proportional hazards model • Onset form (bulbar, limb) • Age (years) • Diagnostic delay (months) • Forced vital capacity (<80%, ≥80%) • Mean phrenic nerve stimulation (<0.4 mV, ≥0.4 mV)	Mortality (time to event)	Cohort study conducted in Portugal High risk of bias due to selection bias
Wolf 2014[127]	n=176 60 people died or had tracheostomy	Multiple logistic regression model • Change in BMI at diagnosis	One-year mortality or tracheostomy	Cohort study conducted in Germany

Study	Population	Prognostic variables in the final model	Outcomes	Notes
	Adults newly diagnosed with possible, probable or definite ALS according to the revised El Escorial criteria	and 6 months before (<1, 1–<2, ≥2) • 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) • Duration of disease (0-6 months, 7–12, 13–24, ≥25) • BMI (<25, ≥25)		High risk of bias due to selection and detection bias

Table 25: Clinical evidence summary: ALS functional rating scale/ALS functional rating scale revised

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)[c]				
Higher score versus lower score	2 (367)	HR 0.94 (0.91 to 0.96)	No imprecision	VERY LOW
36–39 versus ≤35	1 (2037[a])	HR 0.69 (0.6 to 0.8)	No imprecision	LOW
40–42 versus ≤35	1 (2037[a])	HR 0.46 (0.4 to 0.53)	No imprecision	LOW
>42 versus ≤35	1 (2037[a])	HR 0.33 (0.28 to 0.39)	No imprecision	LOW
1-year mortality[d]				
34–36 versus 37–40	1 (70)	OR 1.8 (0.38 to 8.53)	Serious imprecision[b]	VERY LOW
31–33 versus 37–40	1 (70)	OR 2.6 (0.55 to 12.29)	Serious imprecision[b]	VERY LOW
27–30 versus 37–40	1 (70)	OR 12.9 (2.8 to 59.43)	No imprecision	VERY LOW
00–26 versus 37–40	1 (70)	OR 33.8 (6.7 to 170.52)	No imprecision	VERY LOW

HR: hazard ratio, OR: odds ratio
[a] This is the total number of participants in the study rather than the numbers in the groups being compared
[b] Studies were judged to be seriously imprecise if their effect estimate crossed the null line
[c] All studies used ALS functional rating scale revised
[d] Study used ALS functional rating scale

Table 26: Clinical evidence summary: Forced vital capacity

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)				
Higher versus lower (% predicted)	4 (1811)	HR 0.98 (0.97 to 1)	No imprecision	VERY LOW
<80 versus ≥80 (% predicted)	1 (254)	HR 1.49 (1.12 to 1.99)	No imprecision	VERY LOW

HR: hazard ratio

Table 27: Clinical evidence summary: Weight loss

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)				
<18.5 BMI versus ≥18.5	1 (55)	HR 7.39 (1.7 to 32.1)	No imprecision	VERY LOW
Weight change (per 5% decrease)	1 (92)	HR 1.31 (1.08 to 1.6)	No imprecision	VERY LOW
1-year mortality				
BMI change[b] 1 to <2 versus <1	1 (118)	OR 1.26 (0.39 to 4.07)	Serious imprecision[a]	VERY LOW
BMI change[b] ≥2 versus <1	1 (142)	OR 2.8 (1.04 to 7.54)	No imprecision	VERY LOW

HR: hazard ratio, OR: odds ratio
[a] Studies were judged to be seriously imprecise if their effect estimate crossed the null line
[b] Change from 6 months before diagnosis to diagnosis

Table 28: Clinical evidence summary: Age

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)				
Higher versus lower (years)	5 (2065)	HR 1.03 (1.03 to 1.04)	No imprecision	VERY LOW
One-year mortality				
66–75 versus ≤65 (years)	1 (153)	OR 1.13 (0.45 to 2.85)	Serious imprecision[a]	VERY LOW
>75 versus ≤65 (years)	1 (92)	OR 6.12 (1.5 to 25)	No imprecision	VERY LOW
Mortality				
≤65 versus >65 (years)	1 (1398)	RR 0.62 (0.52 to 0.74)	No imprecision	VERY LOW
Mortality or tracheostomy (all participants had non-invasive ventilation from the beginning of the study)				
Higher versus lower (years)	1 (33)	OR 1.07 (1.02 to 1.12)	No imprecision	LOW

HR: hazard ratio, OR: odds ratio, RR: relative risk
[a] Studies were judged to be seriously imprecise if their effect estimate crossed the null line

Table 29: Clinical evidence summary: Site of onset

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)				
Bulbar versus limb	4 (3425)	HR 1.44 (1.08 to 1.92)	No imprecision	VERY LOW
Lower extremity versus upper extremity	1 (189)	HR 1.17 (0.66 to 2.07)	Serious imprecision[a]	VERY LOW
Bulbar versus upper extremity	1 (154)	HR 1.82 (0.99 to 3.33)	Serious imprecision[a]	VERY LOW
Respiratory versus upper extremity	1 (94)	HR 6.51 (2.72 to 15.6)	No imprecision	VERY LOW
Mortality or tracheostomy (all participants had non-invasive ventilation from the beginning of the study)				
Bulbar versus limb	1 (33)	OR 1.71 (0.6 to 4.9)	Serious imprecision[a]	VERY LOW

HR: hazard ratio, OR: odds ratio
[a] Studies were judged to be seriously imprecise if their effect estimate crossed the null line

Table 30: Clinical evidence summary: Diagnostic delay

Risk factors/outcomes	Number of studies (participants)	Pooled effect with 95% CIs OR effect and CI in median study, and range of effect values	Imprecision	GRADE
Mortality/mortality or tracheostomy (time to event)				
Longer versus shorter (months)	5 (2065)	HR 0.98 (0.97 to 1)	No imprecision	VERY LOW
7.1–10.6 versus ≤7 (months)	1 (2037[a])	HR 0.95 (0.82 to 1.09)	Serious imprecision[b]	VERY LOW
10.7–17 versus ≤7 (months)	1 (2037[a])	HR 0.81 (0.7 to 0.93)	No imprecision	LOW
>17 versus ≤7 (months)	1 (2037[a])	HR 0.56 (0.48 to 0.66)	No imprecision	LOW
1-year mortality				
7–12 versus 0–6 (months)	1 (121)	OR 0.42 (0.15 to 1.17)	Serious imprecision[b]	VERY LOW
13–24 versus 0–6 (months)	1 (97)	OR 0.44 (0.14 to 1.4)	Serious imprecision[b]	VERY LOW
≥25 versus 0–6 (months)	1 (78)	OR 0.07 (0.01 to 0.48)	No imprecision	VERY LOW
Mortality				
>2 versus <2 (years)	1 (1398)	RR 0.46 (0.36 to 0.58)	No imprecision	VERY LOW

HR: hazard ratio, OR: odds ratio
[a] This is the total number of participants in the study rather than the numbers in the groups being compared
[b] Studies were judged to be seriously imprecise if their effect estimate crossed the null line

8.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

8.5 Evidence statements

Clinical

Prognostic tool review

- One study of 326 people developed a prognostic tool that predicted poor prognosis (<25 months survival) and good prognosis (>50 months survival) with positive predictive values ranging from 60.1% to 85.7% and negative predictive values ranging from of 93.3% to 100% (Low quality)

Risk factor review

ALS functional rating scale/ALS functional rating scale revised

- Three studies of 2404 people with MND showed, in multivariable analysis, that a higher revised ALS functional rating scale (ALSFRS-R) at diagnosis was a significant predictor of longer survival (Low quality).
- One study of 176 people with MND showed, in multivariable analysis, that the ALS functional rating scale score (ALSFRS) at diagnosis was varied in its ability to predict one-year mortality. This was dependent on the ranges of scores being compared (Very Low quality).

Forced vital capacity

- Four studies of 1811 people with MND showed, in multivariable analysis, that a higher forced vital capacity at diagnosis was likely to be a predictor of survival (HR 0.98 [0.97 to 1]) (Very Low quality).
- One study of 254 people with MND showed, in multivariable analysis, that a forced vital capacity <80 (% predicted) at diagnosis versus ≥80 (% predicted) was a significant predictor of shorter survival (Very Low quality).

Weight

- Two studies of 147 people with MND showed, in multivariable analysis, that weight change prior to diagnosis or being underweight at diagnosis (BMI <18.5) was a significant predictor of shorter survival (Very Low quality).
- One study of 176 people with MND showed, in multivariable analysis, that a BMI change prior to diagnosis was varied in its ability to predict one-year mortality. This was dependent on the magnitude of weight loss being compared (Very Low quality).

Age

- Six studies of 3463 people with MND showed, in multivariable analysis, that older age at diagnosis was a significant predictor of shorter survival (Very Low quality).
- One study of 153 people with MND showed, in multivariable analysis, that age at diagnosis was varied in its ability to predict one-year mortality. This was dependent on the ranges of ages being compared (Very Low quality).
- One study of 33 people with MND on NIV showed, in multivariable analysis, that older age at diagnosis was a significant predictor of shorter survival (Low quality).

Site of disease onset

- Four studies of 3425 people with MND showed, in multivariable analysis, that bulbar onset MND versus limb onset MND was a significant predictor of shorter survival (Very Low quality).
- One study of 267 people with MND showed, in multivariable analysis, that site of onset was varied in its ability to predict survival. This was dependent on the sites of onset being compared (Very Low quality).
- One study of 33 people with MND on NIV showed, in multivariable analysis, that bulbar onset MND versus upper extremity onset MND was not a significant predictor of survival (Very Low quality).

Diagnostic delay (time from first developing symptoms to time of diagnosis)

- Six studies of 3463 people with MND showed, in multivariable analysis, that longer diagnostic delay was a significant predictor of longer survival (Very Low quality).
- Two studies of 2213 people with MND showed, in multivariable analysis, that a diagnostic delay was varied in its ability to predict survival or one-year mortality. This was dependent on the lengths of delays being compared (Very Low quality).

Economic

- No relevant economic evaluations were identified.

8.6 Recommendations and link to evidence

Recommendations	**Prognostic factors** **18. When planning care take into account the following prognostic factors, which are associated with shorter survival if they are present at diagnosis:** • **Speech and swallowing problems (bulbar presentation).** • **Weight loss.** • **Poor respiratory function.** • **Older age.** • **Lower Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS or ALSFRS-R) score.** • **Shorter time from first developing symptoms to time of diagnosis. [new 2016]**
Research recommendation	**2. Is the ALS Prognostic Index an accurate predictor of survival in people with MND under NHS care in England and/or Wales?**
Relative values of different outcomes	The GDG considered survival to be the critical outcome for this question. Accurate estimates of survival by clinicians enable people with MND to plan effectively for their future and augment their quality of their life for that period.
Trade-off between clinical benefits and harms	**Prognostic tools** One externally validated tool (ALS Prognostic Index) for predicting survival in people with MND was identified. It predicted survival from symptom onset based on information that could be gathered at the first patient encounter. The external validation indicated that those placed by the tool in the high risk group had a positive predictive value of 73.3% for survival less than 25 months from symptom onset and a negative predictive value of 93.3% for survival more than 50 months from symptom onset. Those in the low risk category had a positive

	predictive value of 59.1% for survival of more than 50 months from symptom onset and a negative predictive value of 100% for survival less than 25 months from symptom onset. **Risk factors** The review found that the risk factors specified by the GDG in the protocol were all predictors of mortality in people with MND. The site of MND onset was a significant predictor of survival. Those with bulbar onset as opposed to limb onset were found to have reduced survival. Older age at diagnosis, weight loss between 6 months before diagnosis and diagnosis, and shorter duration from first symptoms to diagnosis were predictors of reduced survival. A higher forced vital capacity at diagnosis was likely to be a predictor of survival with a meta-analysis of 5 studies giving a hazard ratio of 0.98 (0.97 to 1). This was supported by a further study which found that a forced vital capacity of less than 80% predicted at diagnosis was a significant predictor of shorter survival. In addition to these single factors, a lower ALS functional rating score (revised and not revised) at baseline was a predictor of reduced survival.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. Informal discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations. The recommendations for this review focus on how to best estimate survival and leaves the interpretation of how this will influence any management changes to the clinician's discretion.
Quality of evidence	**Prognostic tools** The included paper was graded as Low quality evidence due to the study being observational in nature. **Risk factors** All outcomes reported were graded as either Low or Very Low quality. This was due to all studies being observational cohorts and risk of bias due to selection bias. In addition, many outcomes displayed serious imprecision.
Other considerations	The GDG discussed the value of a tool to predict survival in people with MND. They agreed that such a prediction would be very useful to a person with MND in terms of their ability to plan for their future. Health professionals could also utilise such predictions to create better care plans for people with MND. The GDG considered that such a tool might not have to predict survival to within weeks or months to be of use; a prediction within a year would still be of great value. The GDG considered the ALS Prognostic Index (ALS-PI) to be a potentially useful tool for predicting survival in people with MND. The GDG agreed that accurate predictions of survival within 25-month intervals would have a benefit. It would support healthcare professionals to care more effectively for people with MND. This could be realised through accessing the right care at the right time in the disease progression. Examples of this would be accessing specialist palliative care, and equipment provision appropriate to the person's disease progression. Moreover, an accurate prediction of survival would enable a person with MND to plan for their future and prepare for the end of their life. However, the GDG felt that the tool needed to be validated in a UK cohort of patients who were receiving NHS care before it could be recommended. Therefore the GDG decided that it would be appropriate to make a research recommendation to validate the ALS-PI in an MND population under NHS care. The ALS-PI requires a test of executive dysfunction; this was evaluated through 3 executive tasks in the study. The GDG indicated that the assessment of

executive dysfunction in the tool was more extensive than would be possible in routine clinical settings. Therefore the GDG stated that a study to validate the tool should include examination of a simpler form of cognitive testing.

The GDG considered that if no prognostic tool could be recommended, it was important to highlight the significant prognostic factors associated with survival.

The GDG discussed the significance of length of time between symptom onset and diagnosis as a prognostic indicator. This is not related to service provision but to the individual patient presentation. Studies which attempt to stage MND indicate that many people are diagnosed when more than one area has become affected. Shorter time to diagnosis can therefore be caused by more severe initial symptoms, more rapid involvement of different areas or the nature of the area affected. People with bulbar symptoms seem more likely to present earlier due to the nature of the symptoms.

In addition to the prognostic factors which emerged from the review, the GDG discussed decline in respiratory function as a possible predictor of survival. The review indicated that poor respiratory function (forced vital capacity) at diagnosis was likely to be a predictor of shorter survival but none of the studies included in the review investigated decline in respiratory function and the GDG agreed that the effects of such a decline could plausibly be ameliorated by a patient's acceptance of NIV.

The GDG agreed that diagnostic delay, age at onset and poor respiratory function at diagnosis are recognised prognostic factors. These are on a continuum and the guideline group agreed that it was not possible to provide particular cut-off points. Currently these factors assist clinical judgement in considering individual prognosis.

This review looked at clinical prediction and did not include factors such as genetics. Currently some gene mutations are associated with familial MND and it is possible that in the future identification of further genetic changes will be important in predicting prognosis.

Research recommendation

The GDG made a high-priority research recommendation for validation of the ALS-PI in the UK with specific study required for method of evaluation of cognitive function. For further details please see Appendix N: Research recommendations.

9 Organisation of care

9.1 Introduction

People with MND need input from a variety of different specialists and services. The consequences of motor neurone diseases are diverse and individuals have problems with physical function, breathing, cognition and emotion, nutrition and communication. People's needs are complex and usually involve health and social care professionals in responding to these needs. The situation is compounded by often rapid change, with individuals having little time to adjust to one aspect of the illness before another presents. People are at high risk of suffering from a lack of coordination between services.

This chapter includes 2 reviews: the first on coordination of care and the second on frequency of assessment of people with MND.

9.2 Review question: 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?

For full details see the review protocol in Appendix C.

Table 31: PICO characteristics of review question

Population	• Adults (aged 18 and over) with MND
Intervention(s)	• MDT care • MDT care with a care coordinator • Usual care • Usual care with a care coordinator
Comparison(s)	Compared to each other
Outcomes	Critical: • Survival • Health-related quality of life – patient and carer • Number of unplanned hospital admissions Important: • Reduction in 'crisis management interventions' • Hospital length of stay • ALSFRS scale
Study design	• RCTs with people with MND • If no RCTs will search for cohort studies with people with MND

9.3 Clinical evidence

One RCT was included in the part review which looked at whether the addition of a care coordinator to an MDT improves outcomes for people with MND[24]. One systematic review[89] was identified for MDT care compared to usual care, however no RCTs were found. We therefore searched for cohort studies of which 6 were found[6,19,22,22,112,113,122,131], 3 of which were included in the Cochrane review. These are summarised in Table 32 and Table 33 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 34, Table 36 and Table 37). See also the study

selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

The GDG selected the most clinically important confounders which were to be controlled for in the cohort studies prior to examining the evidence. These included type of MND, age at onset of symptoms, NIV use, services/resources and social situation. Further possible important confounders included site of onset of symptoms, riluzole use, cognitive impairment and frontotemporal dementia. We included results that adjusted for these confounders rather than the unadjusted results. Not all studies adjusted for these confounders and this is detailed below.

Table 32: Summary of systematic reviews and RCTs included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Creemers 2014[24]	Multidisciplinary care plus case management by a co-ordinator versus multidisciplinary care alone	Patients with ALS	ALSAQ-40; ALSFRS-R; Caregiver Strain Index	
Ng 2011[89]	Multidisciplinary care versus routinely available local services or lower levels of intervention	Patients with ALS or MND	Primary outcomes: QOL (SF-36); VAS on life satisfaction and well-being. Secondary outcomes: outcomes that related to impairment, for example FVC; outcomes that related to disability or limitation in activity, for example ALSS and ALSFRS; outcomes that related to restriction in participation, and environmental or personal context, or both, for example Caregiver Strain Index (CSI), Utrecht Coping List (UCL); survival; hospitalisation such as readmissions and hospital length of stay; cost-effectiveness of care; adverse events.	No RCTs were included in this review

Table 33: Summary of cohort studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Aridegbe 2013[6]	Multidisciplinary care versus general neurology Specialist care provided by a core team of neurologists, specialist nurses, a respiratory physiologist, physiotherapists and a dietitian and an extended team of research nurses, occupational therapists, speech and language therapists and social workers versus General neurology clinics – neurologists whose primary interest was not MND.	Patients with MND	Survival time from onset of symptoms; survival time from diagnosis	Cox multivariate analysis for survival from symptom onset for clinic, age at symptom onset, el-Escorial category, site of onset, PEG use. From survival from diagnosis: clinic, age at diagnosis, diagnostic delay, el-Escorial category, site of onset. Variables chosen for the analysis were determined by a set of one-way univariate analyses. Only variables which had a significant relationship with survival were chosen for the analysis.
Chio 2006[19]	Multidisciplinary care versus general neurology Interdisciplinary team – followed up by tertiary ALS centres versus Interdisciplinary team – followed up by general neurological clinics	Patients with ALS	Survival time from onset of symptoms; mean hospital stay	Ran a cox multivariate analysis using the following variables: FVC<80% at diagnosis, PEG, age, attending a tertiary centre for ALS, bulbar onset, riluzole treatment, sex, delay in diagnosis and NIV use. The paper also reports mean hospital stay but this was not derived from a regression so assume this does not control for confounders.
Cordesse 2015[22,22]	Multidisciplinary care plus coordinator versus multidisciplinary care Community care network – 4 coordinators of care, one psychologist and	Patients with ALS	Survival time from diagnosis	Before and after study. Only ran a multivariate analysis on site of onset and initial slope of deterioration. Univariate analysis was conducted for survival for age, gender, site of onset, initial slope of deterioration, NIV,

Study	Intervention and comparison	Population	Outcomes	Comments
	one physiotherapist. In addition to: five neurologists, one pneumologist, one gastroenterologist, 2 speech therapists, one physiotherapist, 2 specialised nurses, one dietitian and 3 social workers versus Community care network without coordinator			gastrostomy and coordinated care.
Traynor 2003[122]	Multidisciplinary care versus general neurology Core MDT of neurologists, specialist nurses, physical, occupational, and speech therapists and a pulmonologist, nutritionist, psychologist and social worker. A representative of the IMNDA also attended the clinic versus General neurology clinics – neurologists whose primary interest was not MND. Not staffed by ancillary service professionals or by an IMNDA liaison.	Patients with ALS	Survival time from diagnosis	Only ran a multivariate analysis on variables that were significantly different between MDT and general care cohorts: general neurology clinic, bulbar onset disease, delay in diagnosis and age at diagnosis. Riluzole use was not included due to dependence on whether the individual attended an MDT.
Rooney 2015[112,113]	Multidisciplinary care versus general neurology (plus coordinator for some participants [Northern Ireland group] and none for others [Republic of Ireland group]) MDT clinic: neurologist with specialist expertise in ALS, a specialist ALS	Patients with ALS	Survival time from diagnosis	Multivariable analysis adjusting for time from first symptom onset to diagnosis, age at diagnosis, site of onset, sex, use of riluzole, use of gastrostomy and use of NIV. Coordinator in MDT arm, other arm some participants had and others didn't – both from 2 different locations (Northern Ireland and Republic of

Study	Intervention and comparison	Population	Outcomes	Comments
	nurse and a neuromuscular MDT including a physiotherapist, occupational therapist, speech and swallow therapist, and dietitian versus Care network with ALS Care Network Coordinator with a nursing background. A multidisciplinary ALS clinic, comparable to that of Republic of Ireland, was not set up until the end of the study period Combined with General neurology clinics without MDT care.			Ireland).
Zoccolella 2007[131]	Multidisciplinary care versus general neurology Multidisciplinary ALS clinic – neurologist with expertise in ALS, a pulmonologist, a nutritionist, a psychologist and physical and speech therapists versus General neurology clinics – neurologist whose primary interest was not ALS	Patients with ALS	Survival time from diagnosis	Cox proportional regression model for: clinic, age, sex, EEC (El Escorial criteria/category) at diagnosis, time from onset to diagnosis (diagnostic delay), riluzole use, PEG, NIV.

Table 34: Clinical evidence summary: Multidisciplinary care plus case management versus multidisciplinary care alone – RCT

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDT plus case management versus MDT alone (95% CI)
ALSAQ-40 Scale from: 0 to 100 (higher is worse outcome)	57 (1 study) 12 months	Very low[a,b] due to risk of bias, imprecision	–	The mean ALSAQ-40 in the control groups was 19.1 (SD 14.7)	The mean ALSAQ-40 in the intervention groups was 3.7 higher (4.37 lower to 11.77 higher)
ALSFRS-R Scale from: 0 to 48 (higher is better outcome)	53 (1 study) 12 months	Very low[a,b] due to risk of bias, imprecision	–	The mean ALSFRS-R in the control groups was 25.1 (SD 11.5)	The mean ALSFRS-R in the intervention groups was 1.1 lower (6.77 lower to 4.57 higher)
CSI Scale from: 0 to 13 (higher is worse outcome)	53 (1 study) 12 months	Very low[a,b] due to risk of bias, imprecision	–	The mean CSI in the control groups was 7.9	The mean CSI in the intervention groups was 0.6 higher (1.06 lower to 2.26 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 35: Confounders for cohort studies

CONFOUNDERS (in order of importance)
Type of MND (for example, presence/absence of bulbar symptoms)
Age at onset of symptoms (main prognostic determinants for survival)
NIV (may effect survival)
Services with coordinated care may tend to have better financially supported/resourced professional services
Social situation (for example if patient lived alone)
Possible other confounders:
Cognitive impairment

CONFOUNDERS (in order of importance)
Riluzole (may effect survival)
Site of onset of symptoms (main prognostic determinants for survival)
Frontotemporal dementia

Table 36: Clinical evidence summary: Multidisciplinary care plus coordinator versus multidisciplinary care alone – before-and-after study

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MDT	Risk difference with MDT plus coordinator (95% CI)
Survival time from diagnosis (maximum 8 years follow-up) – Cordesse 2015	2452 (1 study)	Very low[a] due to risk of bias	HR 0.55 (0.44 to 0.69)	–	See comment[b]

[a] 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

[b] Hazard ratio was adjusted and therefore absolute numbers could not be calculated

Table 37: Clinical evidence summary: Multidisciplinary care versus general neurology – cohort studies

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDT versus general neurology (95% CI)
Survival time from onset of symptoms – Aridegbe, 2013	417 (1 study)	Very low[a] due to risk of bias	HR 0.58 (0.46 to 0.73)	–	See comment[d]
Survival time from diagnosis (5 years) – Aridegbe, 2013	417 (1 study)	Very low[a] due to risk of bias	HR 0.51 (0.41 to 0.63)	–	See comment[d]
Survival time from diagnosis (6 years) – Rooney 2015	719 (1 study)	Very low[a] due to risk of bias	HR 0.59 (0.49 to 0.71)	–	See comment[d]

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MDT versus general neurology (95% CI)
	(1 study)	due to risk of bias, imprecision	(0.48 to 0.96)	–	See comment[d]
Survival time from diagnosis (1 year) – Zoccolella, 2007	126 (1 study)	Very low[a,b] due to risk of bias, imprecision	HR 0.91 (0.44 to 1.88)	–	See comment[d]
Survival at 4 years from the diagnosis (4 years) – Zoccolella, 2007	126 (1 study)	Very low[a,b] due to risk of bias, imprecision	HR 1.4 (0.88 to 2.23)	–	See comment[d]
Median survival from onset – Chio, 2006	221 (1 study)	Very low[a,b] due to risk of bias, imprecision	–	Median 775 days	Median of 305 days more for the intervention group than the control group, p=0.008
Mean duration of hospital stay – Chio, 2006	221 (1 study)	Very low[a,b] due to risk of bias, imprecision	–	–	The mean duration of hospital stay in the intervention groups was 6.6 lower (12.47 to 0.73 lower)

[a] 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

[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

[c] Downgraded by 2 increments as unable to analyse imprecision as median survival times reported

[d] Hazard ratio was adjusted and therefore absolute numbers could not be calculated

9.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Original cost-effectiveness analysis

Model overview/methods

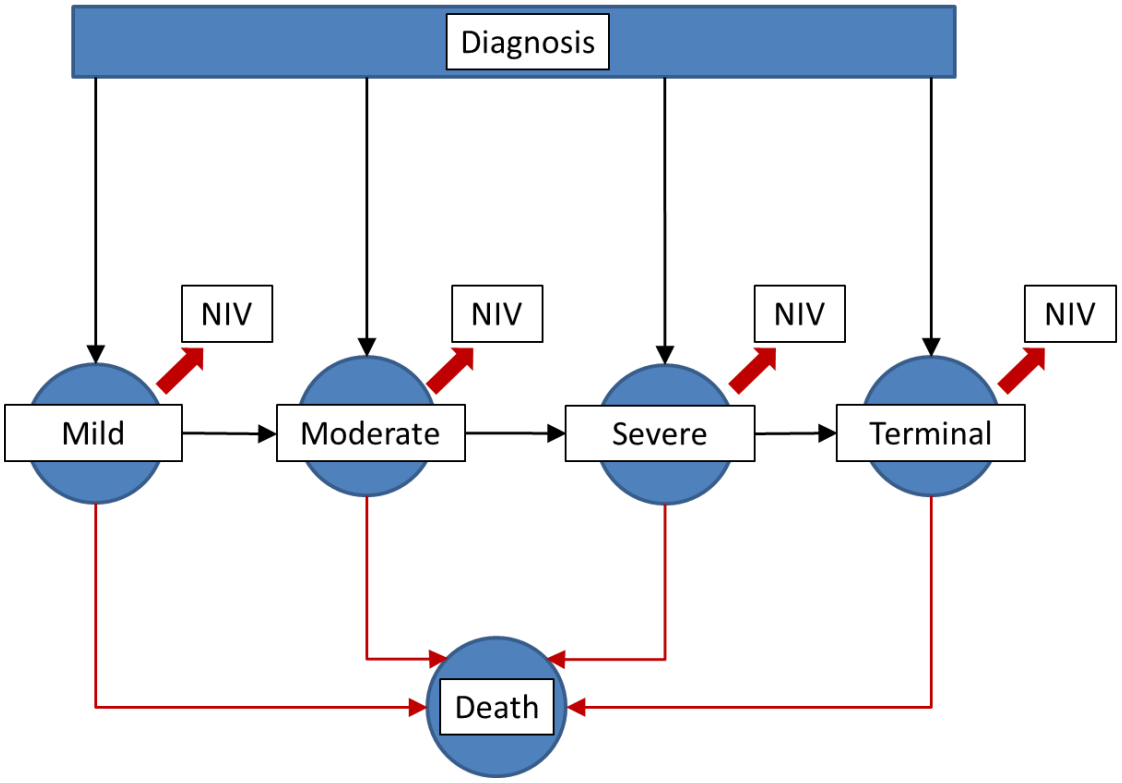
Comparators

Only 2 comparators were considered in this economic evaluation:

- General care – currently when an individual is diagnosed with MND, the majority will continue to be reviewed in a general neurology clinic. The neurologist running this clinic would usually have a primary interest that is 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 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 specialists within an MDT could vary, there was no clinical evidence that specifically evaluated the effectiveness of each additional specialist in an MDT. Therefore the MDT composition in the model is the same as that used in the clinical studies.

Figure 3: Model structure



As shown in Figure 3 above, 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 et al.[111,111] 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 receives MDT care and the state they are diagnosed in. Individuals who begin the model in the mild state for example live longer than those who are diagnosed in the moderate state. Any survival benefits from Riluzole and NIV, which have different usage rates depending on the type of care received, have also been captured. Finally, at any point within 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. More detail on the parameters and sources used to inform this model can be found in Appendix M.

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 is agreed.

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 reoccurring 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. Within the model there are three types of event that can happen to the individual with MND: disease progression, NIV use and death.

Incremental cost of MDT care versus cost of usual care

The cost of MDT care was calculated by the GDG using expert consensus. The MDT was costed to match the healthcare professional composition in the Abridge study used from the clinical review, as this formed the clinical evidence of the model and also represents current NHS care. The GDG identified 2 components of the MDT that required healthcare professional's time. Firstly, there was the time associated with keeping up-to-date with patient records. Secondly, there was a dedicated time spent with the patient. The timings dedicated to each activity are given below.

Table 38: 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)
Specialist nurse	£42.00	6 (5–30)	20 (10–30)
Physiotherapist (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 39: 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

The total cost of MDT care combining the costs in Table 38 and Table 39 is £1,275. The GDG agreed that if the individual was not part of an MDT they would likely receive 2 neurological outpatient visits per year which were costed 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 healthcare professionals will also be involved with the individual outside of MDT care and these costs have been considered in the model. As these costs will also be incurred in 'general' care they are not shown above. For example, if an individual needs a device to allow them

to communicate then they will be referred to the speech and language therapist regardless of whether they are receiving MDT care. Further details can be found in Appendix M.

Base case results

The results in Table 40 below 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 the cost of the MDT alone 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 40: Probabilistic base case results

Intervention	Average costs per patient	Average health outcomes
General care	£4,598	0.49
MDT	£14,394	0.86
Difference	£9,796	0.37
ICER	£26,672 per QALY	

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 detailed in Appendix M. Firstly, there are strong reasons to believe that the quality of life of individuals with MND has been undervalued in this model. When patient-elicited quality of life measures are used, as shown in sensitivity analyses detailed in Appendix M, the ICER falls to £17,387 and £20,791 per QALY respectively. Secondly, as detailed in Vandenberg[123,124], there are good reasons to believe that MDT care could also improve quality of life. When a small increase in quality of life is attached to individuals receiving MDT care the ICER falls to £20,469 per QALY. 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.

The results also 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. If the model is re-run with the cost of MDT being 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 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).[32,32]

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 carer quality of life that are not incorporated into the analysis. Therefore taking into account the sensitivity of the model results in relation to changes in quality of life 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.

Limitations and discussion of results

The main 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. 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 not all confounders can be controlled for. It is worth noting that across 4 different studies in 4 different populations the results were mostly the same. Although Zoccolella[131] 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.

This limitation and others have been evaluated and assessed in sensitivity analyses, detailed in Appendix M. They show that 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.

The full economic write-up which fully details all assumptions and model inputs can be found in Appendix M.

9.5 Evidence statements

Clinical

- Very Low quality evidence from 1 RCT comprising 57 participants demonstrated a clinical benefit of multidisciplinary care alone compared to multidisciplinary care plus case management for the ALSAQ-40. The evidence was at very serious risk of bias and showed serious imprecision.
- Very Low quality evidence from 1 RCT comprising 57 participants demonstrated no clinical difference between multidisciplinary care alone compared to multidisciplinary care plus case management for ALSFRS-R. The evidence was at serious risk of bias and showed serious imprecision.
- Very Low quality evidence from 1 RCT comprising 57 participants demonstrated no clinical difference between multidisciplinary care alone compared to multidisciplinary care plus case management for CSI. The evidence was at serious risk of bias and showed serious imprecision.
- Low quality evidence from 1 before-and-after study comprising 2452 participants demonstrated a clinical benefit of multidisciplinary care plus coordinator versus multidisciplinary care alone. The evidence was at very serious risk of bias but showed no serious imprecision.
- Very Low quality evidence from 1 cohort study comprising 417 participants demonstrated a clinical benefit of multidisciplinary care compared to general neurology for survival time from onset of symptoms. The evidence was at very serious risk of bias but showed no serious imprecision.

- Very Low quality evidence from 3 cohort studies comprising 1480 participants demonstrated a clinical benefit of multidisciplinary care compared to general neurology for survival time from diagnosis. The evidence was at very serious risk of bias but showed no serious imprecision.
- Very Low quality evidence from 1 cohort study comprising 126 participants demonstrated no clinical difference between multidisciplinary care and general neurology for survival time from diagnosis at 1 year and 4 years. The evidence was at very serious risk of bias and showed very serious imprecision.
- Very Low quality evidence from 1 cohort study comprising 221 participants demonstrated a clinical benefit of multidisciplinary care versus general neurology for median survival from onset and mean duration of hospital stay. The evidence was at very serious risk of bias and it was not possible to assess the imprecision.

Economic

- No relevant economic evaluations were identified.
- An original cost-utility analysis found that 'multidisciplinary team' care was not cost-effective compared to 'general care' for managing individuals with MND at a £20,000 per QALY threshold (ICER: £26,672 per QALY gained).

9.6 Recommendations and link to evidence

Recommendations	**Organisation of care** **19. Provide coordinated care for people with MND, using a clinic-based, specialist MND multidisciplinary team approach. The clinic may be community or hospital based. [new 2016]** **20. 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 and coordination 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** • **provide coordinated care for people who cannot attend the clinic, according to the person's needs. [new 2016]** **21. The multidisciplinary team should assess, manage and review the following areas, including the person's response to treatment:** • **Weight, diet, nutritional intake and fluid intake, feeding and swallowing (see Chapter 16 and Chapter 17).** • **Muscle problems, such as weakness, stiffness, cramps (see Chapter 13).** • **Physical function, including mobility and activities of daily living (see Chapter 15).** • **Saliva problems, such as drooling of saliva (sialorrhoea) and thick, tenacious saliva (see Chapter 14).**

	• **Speech and communication (see Chapter 18).** • **Cough effectiveness (see Chapter 20).** • **Respiratory function and respiratory symptoms (see Chapter 19) and Non-invasive ventilation (see Chapter 21).** • **Pain and other symptoms, such as constipation.** • **Cognition and behaviour (see Chapter 7).** • **Psychological support needs (see Chapter 10).** • **Social care needs (see Chapter 11).** • **End of life care needs (see Chapter 12).** • **Information and support needs for the person and their family members and/or carers (as appropriate) (see Chapter 6). [new 2016]** **22. 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.** • **A healthcare professional with expertise in palliative care (MND palliative care expertise may be provided by the neurologist or nurse in the multidisciplinary team, or by a specialist palliative care professional). [new 2016]** **23. The multidisciplinary team should have established relationships with, and prompt access to, the following:** • **Clinical psychology and neuropsychology.** • **Social care.** • **Counselling.** • **Respiratory ventilation services.** • **Specialist palliative care.** • **Gastroenterology.** • **Orthotics.** • **Wheelchair services.** • **Assistive technology services.** • **Alternative and augmentative communication (AAC) services.** • **Community neurological care teams. [new 2016]**
Research recommendation	**Is a network-based model as effective as a clinic-based model to deliver multidisciplinary care to people with MND?**
Relative values of	The GDG identified survival, unplanned hospital admissions and health-related quality of life (for patient and carers) as critical outcomes. Hospital length of stay,

different outcomes	reduction in 'crisis management interventions' and ALSFRS-R scale were important outcomes.
Trade-off between clinical benefits and harms	No harms were identified. The GDG considered that the evidence indicated the benefit of multidisciplinary team (MDT) care. The benefits noted were an increase in survival time and increased uptake of interventions for MDT care. The GDG noted from the studies that people who were not receiving care from an MDT team were less likely to be receiving NIV.
Trade-off between net health effects and costs	No economic evaluations were found that evaluated the cost-effectiveness of multidisciplinary team (MDT) care, therefore an original economic model was constructed. Based on the clinical review, MDT increased survival by 8 months but also increased use of NIV and Riluzole. The economic model evaluated the trade-off between this clinical benefit and the additional costs associated with MDT care such as additional staff time, increased use of NIV and Riluzole plus the additional costs of general MND care associated with increased survival. The base case model results showed that the additional costs and QALYs of MDT care compared with usual care were £9,796 and 0.37 respectively, and the incremental cost-effectiveness ratio was £26,672 per QALY relative to usual care. However, the model was built incorporating a variety of conservative assumptions: that is, assumptions that highly biased against the most effective intervention (MDT care). Firstly, the cost of MDT care was simply added on to the average costs associated with treating an individual with MND: that is, the usual care costs. There are a variety of components of the MDT that would replace usual care costs, such as staff contact. Therefore in the model, it is assumed that staff contact time is added on to what is currently done, whereas in reality there will be some overlap, meaning for example that an individual will no longer see the speech and language therapist once a year in addition to the times they see them as part of the MDT clinic. Secondly, the model assumes no cost savings generated from MDT care. Evidence from the clinical review suggests that MDTs may reduce costs through reducing unscheduled healthcare utilisation for example. This was shown in the study by Chio et al.[19,20] This study was not formally considered in the model as the data were observational and uncontrolled for any potential confounders. The model also overestimates the cost of MDT care by assuming that every healthcare professional sees the individual with MND at every visit, when in reality this is unlikely to be the case. Thirdly, the model assumes no quality of life improvement for patients in the MDT arm. When this assumption was relaxed only slightly, by improving quality of life by 0.05, then the ICER associated with MDT relative to usual care becomes £20,469 per QALY. A sensitivity analysis showed that reducing the survival benefit from MDT, within a reasonable limit, played a small role in the cost-effectiveness of MDT care. The reason for this is that by living longer the NHS will incur more costs from continued treatment of the individual with MND. In the model, the continued survival benefit falls mainly on individuals who reach the 'terminal' state, which has a quality of life of 0.27 and a cost of £5,605. Therefore, extended life in these patients is not cost-effective at a £20,000 per QALY threshold. To evaluate this, the model was run assuming that the MDT itself created no additional costs to the NHS; the only costs incurred were those associated with additional survival. The ICER of MDT care

	dropped to £19,045 per QALY meaning it was only just cost-effective. A sensitivity analysis was also conducted that increased the cost of the MDT by 50%: the resulting ICER was £30,828 per QALY. Given the considerable increase in cost and small change in cost-effectiveness relative to the base case, this shows that the cost of the MDT itself is not the largest driver of cost-effectiveness in the model. The GDG noted that quality of life, as assessed by EuroQol-5 dimension (EQ-5D), was highly likely to produce underestimates for individuals with MND due to the ceiling/floor effect of EQ-5D (that is, since there are only 3 responses for each domains, extreme values are common). It is likely that individuals with MND would fall into the lowest EQ-5D states when in reality their quality of life could be much higher. One example of this is that the use of a wheelchair means that MND patients state they are confined to bed in the questionnaire when in reality their movement is much greater than this. Studies identified in the systematic review for quality of life values show a huge disparity between general population and patient-elicited quality of life scores. Under the model's current assumptions, any intervention that extends life in an MND cohort is unlikely to be cost-effective even if it only costs a small amount. If an intervention has an ICER below £30,000 and above £20,000 it can be considered a cost-effective intervention if it is believed that health-related quality of life has been inadequately captured. Given the highly conservative assumptions made in this analysis that bias against interventions that extend survival in an MND cohort, MDT can be considered a cost-effective intervention. This is highlighted in the sensitivity analyses which showed that the models results were highly sensitive to changes in quality of life.
Quality of evidence	One RCT examining the addition of a care coordinator to an MDT team was found (Creemers 2014).[23,24] The GDG had concerns about the relevance of the study to the UK as they considered MDT care in a Dutch setting to differ from how care is organised in the UK. One before-and-after study found a clinical benefit of multidisciplinary care plus coordinator versus multidisciplinary care alone for survival from time of diagnosis. However, the GRADE quality rating was Very Low and it only adjusted for site of onset and initial slope of deterioration. The other studies found were cohort studies, looking at multidisciplinary care versus no multidisciplinary care. The outcomes were survival time from diagnosis, and survival time from onset of symptoms in 1 study (Aridegbe 2013)[6,6]. All outcomes were graded as Very Low quality. The Zoccolella (2007)[131,131] and Chio[19,20] studies took place in an Italian setting, which the GDG considered may differ from the UK and the composition of the MDT was very different compared to the other two cohort studies. In the Zocolella (2007)[131,131] study the GDG noted that a very small number of individuals received NIV. The Traynor study (2003)[122,122] was conducted in the Republic of Ireland however they only ran a multivariate analysis on variables that were significantly different between MDT and general care cohorts. Riluzole use was not included due to dependence on whether the individual attended an MDT. The GDG acknowledged that the Aridegbe study[6,6], which was conducted in the UK, showed a clinical benefit of the MDT even after adjustment for NIV and riluzole use. The Rooney (2015)[112,113] study also showed a clinical benefit after adjustment for use of riluzole, use of gastrostomy and use of NIV. However, the intervention had a coordinator in the MDT arm, but in the non-MDT arm some participants had a

	coordinator and others did not and included a mix of two different locations. Although the studies identified were cohort studies, the direction and magnitude of benefit for survival was similar in Aridegbe (2013)[6,6],Traynor (2003)[122,122] and Rooney (2015).[112,113] The GDG considered that the model of care in these studies was capable of being translated more widely in a UK setting. They noted that the models included an MDT in a clinic setting with arrangement for close collaboration and integration with care in the community. The GDG considered that the clinic-based setting ensured the development of close collaborative working and acknowledged that this was likely to be possible in other arrangements.
Other considerations	The GDG based their recommendations on the clinical and health economic evidence. The evidence indicated that clinic-based, specialist MND multidisciplinary teams with involvement of professionals who see people in their homes was clinically- and cost-effective. This clinic could be in the community or hospital-based. The GDG were aware that this model of care is not the current model of care in all areas but were convinced by the evidence. They developed a research recommendation to explore other models of care. The GDG considered that the main tasks required of the MDT are regular planned reviews of the person with MND, and establishment of communication between professionals involved in the care of the person with MND, including integration of those seeing the person in the community. The evidence was of review at 2–3 month intervals, which the GDG considered appropriate for most people with MND. The GDG recognised that integration of care between clinic and community could be carried out in different ways but did not consider that the evidence allowed them to make a specific recommendation. The evidence for the MDT included coordination as an integral part of the work of the MDT. The evidence showed no specific benefit from having an independent, additional coordinator to an MDT. The only RCT study with a coordinator showed that the MDT alone had a clinical benefit for ALSAQ-40 compared to MDT plus coordinator, and no clinical difference for ALSRFS-R and Caregiver Strain Index. One before-and-after study found a clinical benefit of multidisciplinary care plus trained coordinators versus multidisciplinary care alone for survival, but it only adjusted for site of onset and initial slope of deterioration. Furthermore, the intervention group also included a psychologist and a physiotherapist in addition to the 4 coordinators. The GDG considered that the extra coordinators were similar to the coordination within the MDTs of the other cohort studies. The GDG were not confident in the results as the participants had a maximum follow-up of 8 years, yet were predicting survival to 20 years which seems at odds with known life expectancy in an MND population. As the cohorts were not concurrent there may have been other changes in management over 10 years, and other differences leading to bias. The GDG wished to ensure that care for the person with MND was coordinated but did not wish to specify who should coordinate it as this may differ for different geographical locations. The GDG also emphasised that the MDT need to consider care for people who are no longer able to attend clinic but whose care continues to need coordination. The GDG listed the areas they agreed were important to assess, manage and regularly review. The detail required will vary according to individual patient need with different areas taking precedence at different times. The core areas to assess included: weight, nutritional intake, fluid intake, feeding, eating and swallowing; saliva control; cough effectiveness; respiratory function and symptoms; muscle problems such as weakness, stiffness, cramps; physical function, including mobility and activities of daily living; pain; speech and communication; cognition and behaviour; psychological support needs; social care needs; end of life needs; information and support needs for the person and their family and/or carers (as

appropriate).

The GDG considered the evidence and their experience of services in deciding who to recommend as constituting the core MDT. They recognised that both the method of working, that is, a clinic based model, and the professionals involved are likely to contribute to the beneficial effect of this model of care. The studies were largely similar in terms of staff model, with only slightly different memberships. For example, Aridegbe (2013) has a social worker as part of the extended team while Rooney (2015) does not include a social worker. Ascertaining the benefit of individual members requires further study and the GDG considered it more appropriate at present to recommend core MDT based on the evidence reviews. The core MDT and extended team are those who are likely to be important in the care of many people with MND although the list is not exclusive or exhaustive. The core team consists of those professionals who will be required for assessment and review of most people with MND while the other services and practitioners listed need to be accessible but their involvement may be more targeted.

The teams in the evidence review included specialist nurses. The GDG recognised that specialist nurses may fulfil a number of roles such as provision of information, planning end of life care and coordination.

The care of people with MND is largely palliative, that is it involves the management of symptoms and holistic care including dealing with end of life issues. Expertise in dealing with palliative care for people with MND will be held by neurologists with an interest in MND, and specialist nurses in the studies in the evidence review also had these skills. The GDG recognised that not all neurologists or nurses may have these skills and additional specialist palliative care health professionals may need to be part of the core MDT to ensure this expertise is available.

The GDG considered it essential that the core MDT have the expertise to regularly assess respiratory function and that this did not require a respiratory physician. Close liaison and prompt access to respiratory ventilation services is required for consideration and delivery of NIV. The GDG were aware that whilst this service is provided predominantly by respiratory medicine physicians and teams, there are some areas where anaesthetic departments provide this input.

Social services involvement will be necessary for almost all patients but may be via their local social services department. The GDG recognised that not all clinic-based MDTs will be able to have all these professionals involved but that they should aspire to fulfil these requirements as the cost-effectiveness analysis indicated that this model of care is cost-effective. They also acknowledged that individual patients, depending on personal preference and geographical location, may decline this type of service.

The core MDT and the services listed where prompt access is required outline services specific to MND care. People with MND and their families and carers will also require ongoing involvement of local services such as their GP and district nursing services. The importance of these local services increases towards end of life.

Research recommendation

The GDG discussed that health professionals work in ways such as in networks which may not meet the multidisciplinary care model as we have described it. The GDG agree that other models of care may be similarly effective and have therefore developed a research recommendation to promote research to assess the

	effectiveness of alternative models. For further details please see Appendix N: Research recommendations.

9.7 Review question: What is the optimum frequency of assessment required to assess disease progression of MND?

For full details see the review protocol in Appendix C.

Table 41: PICO characteristics of review question

Population	Adults (aged 18 and over) with MND Strata: People with cognitive impairment will be considered a separate subgroup People with frontotemporal dementia will be considered as a separate subgroup
Intervention	Time points as specified by the studies
Comparison	Compared to each other
Outcomes	Critical: • Health-related quality of life • Patient/carer/healthcare professional satisfaction with the process
Study design	Randomised controlled trials If no randomised controlled trials are available we will look for abstracts of RCTs and cohort studies (sample size limit n=20)

9.8 Clinical evidence

No relevant clinical studies comparing different frequencies of assessment were identified.

9.9 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

9.10 Evidence statements

9.10.1 Clinical

- No clinical evidence was found.

9.10.2 Economic

- No relevant economic evaluations were identified.

9.11 Recommendations and link to evidence

Recommendations	**24. Tailor the frequency of the multidisciplinary team assessments to the person's symptoms and needs, with more or less frequent assessments**

	as needed. [new 2016] **25. Ensure arrangements are in place to trigger an earlier multidisciplinary team assessment if there is a significant change in symptoms identified by the person, family members and/or carers (as appropriate), or healthcare professionals. [new 2016]** **26. 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]** **27. 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]** **28. 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, ongoing assessments. Priority should be given to ensuring continuity of care and avoiding untimely case closure. [new 2016]** **29. Consider referral to a specialist palliative care team for people with current or anticipated significant or complex needs, for example, psychological or social distress, troublesome or rapidly progressing symptoms and complex future care planning needs. [new 2016]** **30. For guidance on the use of riluzole for people with MND, see the NICE technology appraisal guidance on the use of riluzole (Rilutek) for the treatment of motor neurone disease. [new 2016]**
Relative values of different outcomes	The review searched for RCTs where available, or cohort studies in the absence of RCTs. The GDG were interested in the following outcomes: health-related quality of life; patient/carer/healthcare professional satisfaction with the process.
Trade-off between clinical benefits and harms	No relevant clinical studies comparing different frequencies of assessment were identified.
Trade-off between net health effects and costs	No relevant economic evidence was identified. The GDG considered the cost implications of altering the time commitments of the MDT. The cost of an 'average' length MDT visit along with the extra time spent outside of the meeting reviewing notes was found to be £127. The GDG considered that tailoring the number of assessments to the individual would have an ambiguous effect on costs. In some cases it would mean an individual being assessed more frequently than current practice; in other circumstances, where disease progression is slow and there are fewer symptoms to manage, it may mean less frequent assessments. In the cases where an individual receives more frequent assessments, the GDG felt this would be a cost-effective use of resources as it would allow for timely symptom management that would improve health outcomes and cut down on unscheduled healthcare utilisation.
Quality of evidence	No relevant clinical evidence was identified.
Other considerations	The GDG used the evidence for coordination of care to inform these

	recommendations. The GDG agreed that an appropriate guide for frequency of MDT assessment is every 2-3 months, but that more or less frequent review should take place according to patient need. The GDG recognised the variety of symptoms and needs of people with MND and that frequency of assessment should be tailored to the person. They agreed it is also important for mechanisms to be in place where significant changes in symptoms, cognition or behaviour could trigger an earlier review. The format and structure of the review may need to be adapted according to the needs of the person with MND; for example additional time may be required when seeing people with communication problems or people with cognitive or behavioural problems. The GDG were aware that people with MND may have involvement with many health and social care professionals. They considered it important that key decisions were shared. These might include decisions to arrange gastrostomy or to commence NIV. While people who work closely with people with MND will be aware of the likely trajectory of the disease, it is inevitable that people with MND will see professionals who do not have this knowledge. There is a danger that, for example, a social worker may close a case without realising that the person's condition is likely to deteriorate within a short time and that reassessment is likely to be required. The GDG considered that this aspect of MND needs to be emphasised when people with MND are seen by professionals outside the core team. The GDG agreed on the importance of specialist palliative care input for people with MND. While almost all people with MND are likely to require input from palliative care teams, people whose symptoms are difficult to manage or likely difficult to manage, for example those with rapidly progressing symptoms may require early referral to palliative care due to the complexity, and in some cases rapidity, of their disease progression. The evidence review on end of life care found that some carers thought that palliative care was not available until too late to be of most benefit. Riluzole use was not reviewed within the guideline as it is covered by the NICE technology appraisal guidance (TA20) on the use of riluzole (Rilutek) for the treatment of Motor Neurone Disease.

10 Psychological support

10.1 Introduction

Psychological distress is an understandable and natural response to a diagnosis of motor neurone disease (MND). Patients at every stage can find themselves dealing with difficult and distressing issues that may well need professional psychological support. The psychological needs of their carers also need addressing.

People use a variety of resources to respond to this distress, including their own inner resources and emotional support from carers, family and friends. For some patients, however, the level and nature of their psychological distress is such that they would benefit from professional support.

10.2 Review question: What psychological support is needed for people with MND and their families and carers?

For full details see review protocol in Appendix C.

Table 42: PICO characteristics of review question

Population and setting	• Adults (aged 18 and over) with MND, their families and carers
Topic of interest	• To identify the psychological support needs of people with MND and their families and carers
Context(specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	Potential themes identified by the GDG that would be relevant for inclusion in this review included: • Coping with the diagnosis • Managing family relationships • Change in identity/roles • Sexuality • Psychological factors associated with employment (employment support is included in the 'Social care support' review) • Management of anxiety and depression • Respite care
Review strategy	Qualitative studies were sought for inclusion in this review. Studies will be analysed using thematic analysis. Results will be presented as a narrative, and diagrammatically where appropriate. 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.

10.3 Clinical evidence

Thirty four studies were included in the review;[4,11-15,41,43-46,54-59,61,65,69,70,75,79,91,93,94,96-98,101,107] these are summarised in Table 43 below. Themes and sub-themes from the studies are detailed in Table 44. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 45, Table 46, Table 47, Table 48, Table 49, Table 50, Table 51, Table 52). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

The evidence is derived from studies of psychological issues that the person with MND and their families and carers had, in order to ascertain what their psychological support needs would be.

Table 43: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (1:1 interviews, focus groups, partner interviews, semi-structured interviews)				
Aoun 2012[4]	Semi-structured interviews	Bereaved spouses of patients with MND	To explore the experiences of MND family carers through to bereavement, including whether experiences differ according to prolonged grief status and what the implications for service delivery are	This study was also included in the 'Planning for end of life' review
Bolmsjo 2001, Bolmsjo 2001a, Bolmsjo 2003[11-13]	Semi-structured interviews	Patients with MND and relatives of people with MND	To explore patients' and carers' experiences of MND, including patient discussion of existential issues, and a comparison of experiences between patients and carers	Patients' interviews were not recorded and analysis is based on interviewer notes during the interview. Pre-specified topics were used to guide the interview schedule and analysis. This study was also included in the 'Planning for end of life' review.
Brown 2008[15]	Narrative interviews	People with MND	Explored patients' experiences and how they talk about living and coping with MND	
Cipolletta 2014[21]	Semi-structured interviews	People with ALS	Explored the experience of family members who live with ALS patients until their death	
Fanos 2008[41]	Interviews	People with ALS	To explore the meaning of hope in individuals with ALS	Patients' interviews were not recorded and analysis is based on interviewer notes during the interview
Foley 2014, Foley 2014B[43,44]	Interviews	Patients with ALS	To explore and develop a theory about the processes underlying ALS patients'	This study was also included in the 'Planning for end of life' review

			engagement with health services, including an emphasis on issues surrounding loss and control that emerged from the data	
Gent 2009[45]	Interviews	Carers of people with MND	To explore the experiences of MND carers to identify the coping strategies adopted and the potential implications for service provision	This study was also included in the 'Social care support' review
Gibbons 2013[46]	Interviews	People with MND	To investigate the lived experience of fatigue in patients with MND	
Herz 2006[54]	Focus groups	Carers of people with MND	To explore the experience and perceptions of carers of people with MND	This study was also included in the 'Planning for end of life' and 'Social care support' reviews
Hocking 2006A;[56] Hocking 2006;[55] Brott 2007[14]	Semi-structured interviews	People with MND	To explore the experience of living with MND	This study was also included in the 'Information and support at diagnosis' review
Hogden 2012[58]	Semi-structured interviews	People with ALS	To explore patient experiences of ALS, and to identify factors influencing decision-making in the specialised multidisciplinary care of ALS	
Hogden 2012A[57]	Semi-structured interviews	Health professionals and advisors from MND New South Wales	To explore clinician perspectives on patient decision-making in multidisciplinary care for ALS, to identify factors influencing decision-making	This study was also included in the 'Information and support at diagnosis' review
Hogden 2013[59]	Semi-structured interviews	Carers of people with MND	To explore carer participation in decision-making, to identify carer roles, and determine the facilitators and barriers to carer participation in decision-making	This study was also included in the 'Social care support' review

			for ALS multidisciplinary care	
Hughes 2005[61]	Semi-structured interviews	People with MND and their carers and health professionals	To look at the lives, experiences of services and suggestions for change in people living with MND	This study was also included in the 'Information and support at diagnosis' review
King 2009[65]	Interviews	People with ALS or MND	To present a model that explicates the dimensions of change and adaptation as revealed by people who are diagnosed and live with ALS/MND	
Locock 2009[70]	Narrative interviews and semi-structured interviews	People with MND and their carers	Examines the relevance of the concepts of biographical disruption and repair to MND	
Locock 2010[69]	Secondary analysis of 2 interview studies (Brown 2008 and Locock 2009)	People with MND and their family carers	To explore attitudes to peer support among people with MND and their family and carers	
McKelvey 2012[75]	Semi-structured interviews	Carers of people with MND	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	This study was also included in the 'Social care support' review
Mistry 2013[79]	Semi-structured interviews	People with MND	To explore how each participant's individual understanding of MND, their feelings, and their sense of self and identity were affected after their diagnosis. Also to explore the movement from receiving a diagnosis through to coping	This study was also included in the 'Recognition and referral' review

			strategies.	
O'Brien 2004A[91]	Semi-structured interviews	People with MND	Exploring the desire for information about MND and the experiences in seeking and obtaining such information in people with different stages of progression	
O'Brien 2011[93]	Narrative interviews	People with MND, current carers and former carers of family members with MND/ALS.	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	This study was also included in the 'Information and support at diagnosis' review
O'Brien 2012[94] O'Brien 2012b[92]	Narrative interviews	People with MND and carers of people with MND	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.	Two papers with an overlap in the data used; carers' interviews were incorporated in the analysis for both papers, while patients' interviews incorporated in the analysis in only 1 of the papers. This study was also included in the 'Social care support' review.
Oh 2013[95]	Semi-structured interviews	Wives who care for their husbands with ALS	To explore and capture the lived experiences of wives providing care to husbands with ALS in South Korea	
Oh 2014A[96]	Semi-structured interviews	People with ALS	Explored the illness experiences from the perspectives of patients with ALS in the sociocultural context of South Korea	
Olsson 2012[97]	Semi-structured	People with ALS	To explore what	

	interviews		factors facilitate and hinder the manageability of living with ALS	
Oyebode 2013[101]	Semi-structured interviews	Partners of people with MND	Explore the experience of living with, and caring for, a partner with MND	
Ozanne 2013[98]	Semi-structured interviews	Patients with ALS	To explore how patients with ALS find meaning despite the disease	Subsample of participants recruited as part of a larger study. This study was also included in the 'Planning for end of life' review.
Preston 2012[107]	Semi-structured interviews	Former carers and relatives of deceased patients who had MND	To explore carers' attitudes and experiences of using the Preferred priorities for care (PPC) document to plan future care	This study was also included in the 'Planning for end of life' review
Taylor 2011a;[118] Taylor 2014[119,120]	Narrative interviews	People with MND and carers of people with MND	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	This study was also included in the 'Social care support' review
Whitehead[126]	Narrative interviews	Patients with MND, current and former carers of people with MND	To explore MND patients' and carers' experiences of the final stages of the disease	This study was also included in the 'Planning for end of life' review

Evidence

10.3.1.1 Themes and sub-themes derived from the evidence

Table 44: Themes and sub-themes

Main theme	Sub-themes
Coping with the diagnosis	Receiving the diagnosis – first reaction
	Subsequent feelings after diagnosis – making sense of it
	Support after the diagnosis
Understanding the disease	Sources of information
	Information-seeking behaviour
	Filtering of information
Acceptance	Finding meaning in life
	Acceptance of the disease
	Coping strategies
	Gaining control
	Maintaining self-esteem
Coping with a changed life	Perception of loss
	Maintaining previous 'normality' for as long as possible
	Adjusting to a new 'normality'
	Living for the moment
	Hope
	Looking to the future
	Family considerations
Change in relationship	Change in identity/role
	Reduction in intimacy
	Importance of touch

Main theme	Sub-themes
Carers	Information required
	New responsibilities of carers
	Changed life of the carer
	Burden for the carer
	Patients feeling like a burden
	Carers' emotions
	Coping emotionally
	Counselling
	Respite care
	Carers' role in decision-making
Sources of support	Family support
	Support groups
	Support from services
	Professionals view of services provided
Decision-making	Continuous decisions
	The importance of family in making decisions
	Decisions for the present
	Health professionals' response to decision-making
	Barriers to decision-making
	Cognitive and behavioural change

Table 45: Summary of evidence: Theme 1 – Coping with the diagnosis

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Receiving the diagnosis – first reaction					
5 (Mistry 2013;O' Brien 2011; Hogden 2012; Oh 2014A; Foley 2014)	Interviews	There were diverse reactions to learning they had the condition. Patients felt shock and devastation when they realised they had been diagnosed with a life-threatening condition. Some had feelings of falling or being in a dream state. Others had sorrow, fear, loneliness and stress. Their previous thoughts prior to diagnosis that it would be treatable were destroyed by the 'bomb shell'. Whereas some said it confirmed their own conclusions and they were relieved to have a name and understand where their symptoms were coming from, some could not comprehend the implications at the time of diagnosis. Their reaction influenced readiness to learn about the condition and participate in receiving care and decision-making. Some were unable to take in the information after the diagnosis as they were so shocked, needing time to process a terminal condition, how it would change their lives and digest the feeling of loss before receiving help from healthcare services.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Subsequent feelings after diagnosis – making sense of it					
7 (Hogden 2012; Locock 2009; Oh 2014A; Mistry 2013; Fanos 2008; Ozanne 2013;	Interviews	After diagnosis most people tried to understand how or why they had MND. Some felt they were being punished, and felt it was unfair. Many tried to find meaning in their suffering. They hoped to move to a position of acceptance. Many found it difficult to accept the diagnosis due to lack of a known cause. They were frustrated that health professionals could not inform them of personal survival times and disease trajectories. Responses became complex and nuanced as they came to understand the meaning of the diagnosis. Feeling a 'breaking off', like it is a 'death sentence' and life was in effect already over and they had been denied a future. Some imagined life was already over, wishing they were dead or 'just to disappear'. It became more real after meeting	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
King 2009)		other advanced patients.			
Sub-theme 3: Support after the diagnosis					
2 (O'Brien 2011; Hocking 2006)	Interviews	Some people felt they had inadequate support after diagnosis. They felt that people should know the follow-up arrangements and have a point of contact. Information needs varied but insufficient explanation was often given. They also had to tell their family which was difficult.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 46: Summary of evidence: Theme 2 – Understanding the disease

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Sources of information					
6 (Oh 2014A; Hogden 2012; Hogden 2012A; Hughes 2005; Hocking 2006;	Interviews	Most patients initially had not heard of ALS or had limited information since it is a rare disease. Patients therefore gained information from a variety of sources, including health professionals, MND Associations, internet sources, online communities, empirical evidence, support groups and the media. Knowing who to trust regarding seeking, receiving and following advice was important but patients were often given conflicting information. Some felt the need for improved information and communication between professionals and users with some patients unsure where to	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Cipolletta 2014)		get information from. Not getting the right information at the right time led some to look for information for themselves, for example in booklets, leaflets, and from MND stories in the media and the internet.			
Sub-theme 2: Information-seeking behaviour					
3 (Hughes 2005; O'Brien 2004 Hogden 2012)	Interviews	Different people had different information-seeking requirements, often related to how well they had accepted their illness, how long ago they were diagnosed or the stage of the disease. Thus it could also fluctuate over time. If they had not yet come to terms with their diagnosis they were often reticent about seeking information. Some just coped day-to-day with the illness and thought it detrimental to have information on what might not occur. Some patients actively sought information from various sources, usually early on in the illness. Some were selective in their information seeking and did not want a full understanding of the implications of the illness at diagnosis, others had access to information but did not always use it, and some had someone screen out unsuitable material, purposefully gathered information on issues concerning them at that time. A further category, 'information avoiders', did not actively seek information but were not entirely ignorant about the illness. They avoided information due to fear of occurrences that weren't happening to them.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Filtering of information					
2 (Hogden 2012; O'Brien 2004)	Interviews	Some, typically the 'information avoiders', always required someone to screen information as they were anxious about exposure to information about MND. Media coverage and unscreened information was a constant threat which could be distressing, therefore they needed someone to filter the information, usually the carer/family member. They often avoided newspapers and television. Professionals also felt a	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
		responsibility to filter information to the client as they knew they would be exposed to a number of different sources of information which could be confusing and of various quality, therefore they provided guidance on the range of evidence-based information available. They were wary of crushing patients' hope but thought poor quality information, which gave unrealistic expectations, compounded their difficulty in accepting the inevitable nature of MND.			

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 47: Summary of evidence: Theme 3 – Acceptance

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Finding meaning in life					
3 (Ozanne 2013; Bolmsjo 2003; Cipolletta 2014)	Interviews	Acceptance of the situation (not the disease) made it easier to find meaning. Different things gave people meaning in life, such as leading an active life, spending time in nature, working, spending more time with family (particularly children and grandchildren).These activities created feelings of freedom, happiness and strength. Help from outside (from family, hospital, social services or personal assistants) was necessary to make life meaningful and reassured participants that help was there if they needed it. Feeling needed and giving help to others also	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		helped participants find meaning.			
Sub-theme 2: Acceptance of the disease					
8 (Hughes 2005; Foley 2014; Hogden 2012; Hogden 2012A; Locock 2009; Oh 2014A; Mistry 2013; Cipolletta 2014)	Interviews	People at all stages of MND and ages discussed the need to accept the illness, however there were varying degrees of acceptance. It was a balancing act for most between avoiding dwelling too much on their situation but facing and accepting symptom progression. Some people ignored their illness as much as they could. Many who were able to come to terms with the diagnosis expressed a positive outlook and could reframe the situation as an opportunity to make the most out of the time they have left. Many who had accepted the progression of their disease still had feelings of frustration. Patients had difficulty adjusting to deterioration as the disease progressed; they had to get used to fact that they would become more dependent on healthcare professionals as this occurred. However, some felt they would avoid having to live to an old age with the associated loss of independence. Age was an important factor in acceptance of the disease and of death, with many older people who had had a long life and fulfilled their ambitions accepting the disease more than younger people (50 years or younger). Those who would 'lose out on parenthood' were less accepting than those who had raised children. There was greater acceptance in those over a year since diagnosis.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Coping strategies					
4 (Bolmsjo 2003; Hughes	Interviews	Professionals recognised that individuals had many different emotions and coping strategies. Coping with deterioration involved denial, resilience or a focus on maintaining current routines and lifestyle. Religion or spirituality did not feature	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
2005; King 2009; Hogden 2012)		strongly. Outlook on life overlapped with reported coping strategies. Those who had a positive outlook looked for positive meaning as a way of coping and although they still expressed fear and loss, they showed resilience and remained engaged in normal life through the use of active strategies for adapting to change, for example using alternative support structures or using humour. Some tried to control their muscle twitching to gain a sense of control. Others used more passive strategies and would let things happen without thinking about the consequences. They may perceive change as unremarkable so that it does not mean as much to them, or use it as a form of denial when it is too hard to cope. They may also pretend that the change is not there. This was sometimes positive as the person could focus on what was important in life and coping with disease outcomes. It was often used to protect self-esteem. Whichever strategy was effective depended on personal criteria, beliefs, values and understandings. 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. Regardless of ther person's adaption strategies, their decisions and choices were never complete due to constant change.			
Sub-theme 4: Gaining control					
4 (Foley 2014; King 2009; Hocking 2006; Locock	Interviews	People need to feel in control of their lives. The loss of functions that come with disease progression could make people feel like their MND was in control, which could elicit pessimistic assessments about life, such as feelings of hopelessness. Therefore patients often felt a strong need to find ways to exert control. This could be in control of their care, including engagement with services and choice of	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
2009)		treatment, by being part of decision-making and exerting control over their life in order to promote feelings of self-worth and personal integrity. Some found that by staying positive, planning ahead, reasserting a sense of normality, resolving ways to incorporate a change into daily living, or learning to live with altered circumstances allowed them to maintain their independence and control over their lives for as long as possible.			
Sub-theme 5: Maintaining self-esteem					
2 (King 2009; Olsson 2012)	Interviews	Distress and frustration impacted on people's sense of well-being, affecting their self-worth and undermining self-esteem, for example frustration with tasks that they can't do anymore. Their personal image of being able-bodied, strong and independent was continually challenged. They may be embarrassed at slurring their speech or using a wheelchair in public, which may make them stay at home (inclusion). Protecting a public image was important for sustaining self-esteem. Some were threatened by change, but others were okay or relished it as a challenge. Skills were developed to deal with challenges by tackling public issues (helping others). Some set new goals in life that could be achieved (coping). Positive reactions advanced participants' self-esteem and self-worth as they regained a sense of self and achievement.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 48: Summary of evidence: Theme 4 – Coping with a changed life

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Perception of loss					
6 (Foley 2014; Ozanne 2013; King 2009; Fanos 2008; Oh 2014A; Cipolett a 2014)	Interviews	Patients had a perception of continual loss and often experienced hopelessness about the future. Losses included the physical change, their ability to engage in important aspects of their life and activities, their identity, their feeling of control over their lives, and their future. Loss in physical function caused despair at the resultant loss of content in life. This caused feelings of hopelessness, uncertainty, fear of losing more abilities (walking, communication) and fear of a steady decline in function and health. For some there was a process of mourning their lost abilities, therefore taking pleasure in new ones appeared to be very important in maintaining hope.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Maintaining previous 'normality' for as long as possible					
6 (Hughe s 2005; Hogden 2012; Locock 2009 ; Oh 2014; Oh 2014A; Ollson 2012)	Interviews	People sought to restore a sense of normality in different ways. They often tried to find ways to do continue with their lives as normal for as long as possible, even if they fatigued earlier. Continuing work was important for some, although some wished to retire and focus on more valued aspects of their lives. Continuing to drive was important for continuity of identity. Going into a wheelchair was often a negative turning point, and was to be resisted as long as possible. When old activities became impossible people searched for new alternatives to keep a 'normal life' going and to distract themselves from thinking about the future.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Adjusting to a new 'normality'					
8	Interviews	Patients were no longer part of the same social groups and	Applicability of evidence	Applicable[a]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
(Hughes 2005; Hogden 2012; Locock 2009; Oh 2014; Oh 2014A; Olsson 2012;Fanos 2008; Gibbons 2013)		their goals of life and health had changed. Social relationships were sometimes limited to meeting and interacting with other patients. Days felt long and they had too much time to think. It was difficult to find meaningful content in daily life. Patients were often fatigued which lead to frustration. Patients wanted to accept the diagnosis and its progression, so they could make the most of their remaining time and move onto practical concerns. Some found it difficult to adjust to the diagnosis, mostly as they did not know what caused it. Those who could adjust started re-assessing goals and aims quickly. Patients had to deal with the fact that they were not able (or would not be able) to partake in the activities they had previously. They had to make practical adjustments to their lifestyle in order to retain their independence. As they got used to living with MND, changes became routine and adjustments were continually made. Many re-prioritised so they could maximise time with family and framed goals differently. Getting help from outside could help them to adapt to their new normality and be less dependent on their family. Computer technology, such as virtual socialising, helped with this new normality. Wheelchairs helped with mobility. Many said their perspective had changed; instead of enjoying participating in activities with loved ones, they were now able to enjoy watching their play.	Theme saturation/sufficiency	Saturated[b]	
Sub-theme 4: Living for the moment					
4 (Ozanne 2013;	Interviews	Many started cramming all the things they had previously wanted to do in the rest of their lives into a smaller amount of time. Trips and holidays were important. Some had a	Applicability of evidence Theme	Applicable[a] Saturated[b]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Locock 2009; Fanos 2008; Olsson 2012)		changed attitude to life, with new value attached to just 'being', living for the moment, the preciousness of each day, and 'the small things'. They could focus on the important things in life in the here and now rather than plan in advance. Many found it easier to live in the present and not plan things in advance and found happiness in the small things. The disease showed them what was important in life. Acceptance and living in the present reduced the pain of thinking about the disease and the future.	saturation/sufficiency		
Sub-theme 5: Hope					
3 (Ozanne 2013; Brown 2004; Fanos 2008)	Interviews	Hope was important for a lot of people. Hope for a cure, of misdiagnosis, for the disease stopping or that it wouldn't become much worse, of surviving over a particular time, of regaining lost capacities and being able to do lost activities, or that their illness would not progress too rapidly so they could remain active and independent for as long as possible. Others hoped that research would lead to improvement and ultimately a cure. Many called on an existing belief in a higher power, for a miracle or cure, a better afterlife or comfort in heaven seeing lost loved ones. Many reported hope of relinquishing former capacities and developing new ones. The was a delicate balance of managing hope and not going too far in the direction of sadness or happiness, but rather controlling their emotions today. Sustaining what remains positive in life by looking at what can be achieved rather than what is no longer possible was underpinned by hope, although knowing that survival may be an ambitious desire.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High
Sub-theme 6: Looking to the future					
2 (Hogden 2012;	Interviews	There were paradoxical attitudes and changed perceptions towards the future. Under one third identified plans for their future care needs or needs of their families. People	Applicability of evidence Theme	Applicable[a] Not saturated[b]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Oh 2014A)		experienced a sense of loss of the normal future they once had. Images of new futures were limited; some felt their future would be very hard so did not think about it.	saturation/sufficiency		
Sub-theme 7: family considerations					
5 (Foley 2014; Ozanne 2013; Hogden 2012; Locock 2009; Fanos 2008)	Interviews	Patients wanted to know how the disease would progress for the sake of their family. They wished to limit the impact of their illness on their loved ones. Many people with children were overwhelmed by the prospect that they would die before raising their children. Missing out on important events, not seeing their children succeed in adulthood or seeing grandchildren grow up, losing out on retirement with their partner, caused despair. However, parenthood could also give them feelings of hope and energy to resist ALS.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 49: Summary of evidence: Theme 5 – Change in relationships

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Change in identity/role					
7 (Aoun 2012; Oyebod	Interviews	Carers discussed how their role had changed from wife/husband to nurse/carer. This was a significant change in their identity and that of their partner. People often felt	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
e 2013; Oh 2013; Locock 2009; Hughes 2005; Oh 2014A; Cipolletta 2014)		that there was a child-parent dynamic and there was a loss of role in the household. People felt that being dependent on their partner for personal care was like being a child, and felt bad that the roles had been reversed. Partners found it hard to deal with their partner's cognitive impairment.			
Sub-theme 2: Reduction in intimacy					
6 (Aoun 2012; Taylor 2011; Oyebode 2013; Oh 2013; Locock 2009; Cipolletta 2014)	Interviews	Carers experienced role reversal and felt that having to carry out a lot of personal tasks and spend time caring led to exhaustion and less time or desire for intimacy. Special equipment could restrict intimacy by affecting quality and frequency of touch. Specialised beds meant that couples were no longer in the same bed or room. Communication devices also impacted on expression of sexuality and gender, especially if they generated a voice of the opposite gender. Changes to the patient's strength and their fragility were noted, including respiratory and physical disability. Cognitive changes led to feelings of a child-parent dynamic. Strained relationships sometimes led to marital breakdown. Some couples however were unchanged or felt stronger. Some felt that it had brought them together more. Patients felt that health professionals did not speak to them about sexuality or intimacy.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High
Sub-theme 3: importance of touch					
2 (Taylor	Interviews	Patients felt that touch was important emotionally and for maintaining their relationship. However some were unable to	Applicability of evidence Theme	Applicable[a] Not saturated[b]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
2011; Oyebode 203)		suggest ways to overcome restricted intimacy. Some carers did overcome the physical and emotional barriers, which was beneficial to maintaining a connection. Loss of sexual and physical contact was a common source of sadness.	saturation/sufficiency		

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 50: Summary of evidence: Theme 6 – Carers

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Information required					
1 (O'Brien 2012)	Interviews	Carers wanted greater information about the disease and its expected progression and what services might be available for their needs, and who they should contact to initiate services. Some lacked clarity about the role and responsibilities of health and social care professionals. The burden of caring made it difficult to seek this information out on their own.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: New responsibilities of carers					
7 (Aoun 2012; O'Brien 2012; Bolmsjo 2003;	Interviews	This involved a lot of new tasks including taking over the responsibilities their partner used to deal with, such as finances, as well as taking on the various tasks involved in caring for their partner. Some provided personal care, others did not. Carers helped patients to get out of the house to live their lives. They provided emotional support for discussion of	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Gent 2009; Hogden 2013; McKelvey 2012; Hughes 2005)		the patient's changing needs, facilitated communication between patient and health professionals, and supported decision-making in their care. They sourced and synthesised information and filtered it for the patient. Often provided physical and practical assistance for appointments and services and helped to coordinate appointments and services. The role was found to be both physically and emotionally draining; if the carer was a partner they also had sleep disruption due to turning their partners over and night-time PEG feeding. Day care was also exhausting as it involved physically moving the person. Tiredness leads to anxiety which impacted on their mood.			
Sub-theme 3: Changed life of the carer					
4 (Bolmsjo 2003; O'Brien 2012; Hocking 2006; McKelvey 2012)	Interviews	As participants' lives changed so did their families'. The caring role gave them limited freedom. Some wished to maintain a sense of normality and retain some control over their personal lives. They would try to do the same activities as before. Many found a change in their ability to maintain relationships and interact socially.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 4: Burden for the carer					
4 (Herz 2006; Hughes 2005; O'Brien 2012; Oyebode 2013)	Interviews	The emotional cost to the carer was more than the physical burden, with the emotional impact extending long after the death of their loved one. The deterioration in health and increasing burden on the carer was described as a 'downhill spiral' or like 'drowning'. There was also a financial burden; some felt they were good with finances but others expressed need for greater financial support.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		Carers tried to continue to care for their loved one and attempted to continue without additional support for as long as possible. Most worried about leaving partners at home in case anything happened to them, so watched them and some avoided going out. They felt they had to be mentally strong for both the person with MND and themselves, and did not want to show negative feelings in front of the person with MND. Those with more advanced MND were no longer able to find practical solutions and this had an emotional impact on carers.			
Sub-theme 5: Patients feeling like a burden					
3 (Ozanne 2013; Hogden 2012; Foley 2014)	Interviews	Patients were disappointed at being dependent on others. Feeling like they were a burden on others caused feelings of guilt and sometimes resulted in patients exerting control over their healthcare to make things easier for their families. Patients didn't want to be a burden to their family but were resigned to the fact that they would be more dependent on them. They struggled between seeking to alleviate family concerns and needing more assistance from their family.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 6: Carers' emotions					
1 (Herz 2006; Locock 2009; Bolmsjo 2003; Oyebode 2013)	Interviews	Carers expressed many emotions: they had love and respect for their loved ones, and some felt caring for them was seen as a test and expression of this. Carers had to deal with a series of, often fast-paced, losses. The sudden cutting-off of their anticipated future and change to their lives made them struggle with feelings of anger, fear, denial, helplessness and hopelessness. Some carers found the future distressing and didn't want to think or talk about it. Uncertainty in how long individuals survive was a source of sadness. They resented the disease.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 7: Coping emotionally					
2 (Aoun 2012; Oyebode 2013; Gent 2009)		Carers had various coping strategies such as having a positive approach to caring, focusing on the present, emphasising remaining capabilities, counting their capabilities and problem-solving together. Some felt that MND gave them time to make decisions and have time together. Some carers felt they needed to vent their emotions while others switched off their emotions to manage their caring responsibilities. Some coped by socialising more which gave them a sense of normal life continuing, however some did not wish or manage to do this. Management of time was important so they could continue with their interests and social activities.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Not saturated[b]	Moderate
Sub-theme 8: Counselling					
2 (Bolmsjo 2003; O'Brien 2012)	Interviews	Whereas some patients did not want to confide in others, carers felt a need to do so. Many carers felt unable to talk to friends and family about the impact it was having on them. They thought that accessing formal counselling would be helpful, particularly post-bereavement. Those who had gone to counselling had positive experiences. Some had difficulty in accessing counselling and had a lack of knowledge of how to access it.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Not saturated[b]	Moderate
Sub-theme 9: Respite care					
3 (Aoun 2012; Herz 2006; O'Brien 2012; Oyebode 2013)	Interviews	Some carers were dissatisfied with the level of respite care available. Former (not current) carers discussed the need for respite for emotional release and replenishment. Respite care was perceived as a positive opportunity to have a break from the caring role. Those hesitant were reassured when respite services had specialist experience of caring for patients with MND. There was some variability across locations in ability to access respire services; carers wished	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Not saturated[b]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		for both advanced and short-term booking for respite services. Some felt guilty when patients were unwilling to agree to respite.			
Sub-theme 10: Carers' role in decision-making					
1 (Hogden 2012A)	Interviews	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 wellbeing of the carer at risk. Clinicians reported instances where carers had a negative influence on decision-making discussions, such as a gate-keeping role blocking access between the health professional and the patient. An MDT model of care enhanced their role-in decision-making, when supported by access to ALS research information and clinician education websites.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 51: Summary of evidence: Theme 7 – Sources of support

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Family support					
4 (Foley 2014;	Interviews	Patients discussed the importance of social support from friends, family, the medical team and even their pets. Some	Applicability of evidence	Applicable[a]	High
			Theme	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Fanos 2008; Oh 2014A; Ozanne 2013)		patients felt there was a balance between drawing support and providing support to loved ones. Friends and family gave patients meaning and strength through presence and support and accepting them as individuals. Most talked about grasping the value of family since they had the disease.	saturation/sufficiency		
Sub-theme 2: Support groups					
4 (Foley 2014; Fanos 2008; Oh 2014A; Ozanne 2013)	Interviews	Although this was not true for everyone, many found that identifying peers could be important in exchanging information about the management of ALS. Support groups were a way of getting advice on aspects of disability, home adaptation and claiming benefits. Some enjoyed advising others. They enjoyed the interaction and sharing their experiences. Some enjoyed the camaraderie and found that it normalised their identity. However it was hard to see others at further stages of the disease, and to see them deteriorate, as there were no inspiring examples of recovery. Some wanted to attend face-to face groups but could not due to other reasons. Practical access problems, working, fatigue, difficulties travelling and problems interacting face-to-face, worried about getting to toilet, managing drinking or eating or unfamiliarity of the environment, aimed more at bereaved spouses, or did not like the mix of carers and MND patients were some reasons. Some chose isolation as they did not like groups or did not want to share personal information, or felt that they had nothing in common apart from MND and that it could reinforce difference and exclusion from normality.	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Saturated[b]	High
Sub-theme 3: Support from services					
5 (Bolmsjo 2003;	Interviews	Generally patients trusted health professionals, and had a strong desire to trust them. However they were less likely to trust non-empathetic professionals. They trusted those who	Applicability of evidence Theme	Applicable[a] Saturated[b]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Foley 2014; Herz 2006; Hughes 2005; Hogden 2012)		were knowledgeable, personable in approach, and provided reassurance about their care. They felt reassured when they felt in control of their care. They felt there was an overall lack of knowledge and understanding of MND and its impact on people, which impacts on their experiences of services. Many found that professionals were distant and divorced and therefore did not want to approach them with questions. Many were unsure about the services they were entitled to, especially when first diagnosed. Patients found that MDT clinical ALS services were a supportive decision-making environment, and expressed confidence in the ALS teams because of expertise, specialised knowledge and dedicated ALS services. They appreciated the print and internet resources given about the nature and progression of ALS, and the available clinical and support services for symptom management. They had regular appointments to discuss healthcare and psychosocial issues and to plan for anticipated care needs. The MDT was viewed as the main source of assistance outside of family.	saturation/sufficiency		
Sub-theme 4: Professionals view of services provided					
1 (Hughes 2005)	Interviews	Professionals identified a need for increased knowledge about MND, through improved education and training, for their colleagues. They also thought they 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. There was a need for support from people with an	Applicability of evidence Theme saturation/sufficiency	Applicable[a] Not saturated[b]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
		understanding of MND: not necessarily professionals.			

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 52: Summary of evidence: Theme 8 – Decision-making

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Continuous decisions					
1 Cipolletta 2014	Interviews	Family members felt that difficult decisions and crossroads were continuous, for example dealing with NIV, euthanasia or family management.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 2: The importance of family in making decisions					
2 (Foley 2014; Hogden 2012)	Interviews	Family was the most important aspect in patients' decision-making. Family (or absence) of was often the main reason for opting in or out of services, to prolong life or not and also for decisions on symptom management. Having their backing for decisions was important and looking out for their loved one could restrict them making the decisions they wanted to make in their care. Being a parent was the main factor in how they made decisions about their care. They opted in or out of services depending on how their children responded to health care services in their lives. Wishing to minimise disruption to children's lives had conflicting emotions of engaging with services that could sustain their lives. Very few made decisions independently, preferring to share decision-	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		making with others, for example family or health professionals. Those with no family had more freedom in decision-making about their care.			
Sub-theme 3: Decisions for the present					
1 (Hogden 2012)	Interviews	Regardless of coping strategy their decision-making was guided by a focus on the present, rather than thinking about the future. Maintaining current wellbeing was a higher priority than proactive engagement in decision-making for disease progression. Decision-making was complicated by the reluctance to plan for the future. Coping with the present was preferable to contemplating the future.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 4: Health professionals' response to decision-making					
1 (Hogden 2012A)	Interviews	Clinicians aimed to guide the patient and carer through decisions in a timely manner using evidence-based information on the options regularly discussed. They saw it as a cyclical process, responding to recurrent change as the person's condition deteriorated.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 5: Barriers to decision-making					
1 (Hogden 2012A)	Interviews	Clinicians perceived barriers to be: patient acceptance of the diagnosis, the types of information patients sourced, and the patient-carer relationship. Poor family dynamics and problems with acceptance and insight impacted on their relationship with the patient. They reported little control over these issues, but aimed to respond to the changing needs of the patient as best as they could. 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. Some sought assistance too late when their condition was unmanageable (critical windows perhaps lost). Crisis management strategies were seen as a last resort for	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		those who were unable to come to terms with the changes to their life.			
Sub-theme 6: Cognitive and behavioural change					
1 (Hogden 2012A)	Interviews	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.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

10.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

10.5 Evidence statements

10.5.1 Clinical

Coping with the diagnosis

- Patients could not always comprehend the full implications at the time of diagnosis. They required more time to process the diagnosis before receiving healthcare services. Patients stated that an understanding of MND helped them move towards acceptance. Frustration was expressed about health professionals not being able to give survival times or disease trajectories. Many felt that their lives were already over and that they had received inadequate support post-diagnosis.

Understanding the disease

- It was noted that because MND is a rare disease few healthcare professionals had adequate knowledge, resulting in patients receiving information from a variety of sources, sometimes contradictory. Some reported not knowing where to get information from and some asked others to filter information for them. Information-seeking behaviour differed by person, and could be seen as related to acceptance of their illness, length of diagnosis, stage of disease or fluctuating depending on changes caused by MND. Healthcare professionals also felt a responsibility to filter information to patients because they were aware of the impact the information could have.

Acceptance

- Patients felt that if they accepted their situation it was easier to find meaning in life. All participants identified the need to accept the disease, but they varied in their ability to do so. Acceptance was recognised as being harder for patients as the disease progressed, as they had to get used to being more dependent on others. Age and raising children were important factors relating to acceptance.
- Patients reported a variety of coping strategies: denial, resilience, a focus on maintaining current routines and lifestyle. Coping strategies were based on beliefs, values and understanding of the disease. The failure or success of adaptation strategies was directly linked to stress levels and wellbeing. Overall people needed to feel in control of their lives and find ways to exert this control. The distress and frustration caused by lifestyle restrictions impacted on a person's sense of wellbeing, self-worth and self-esteem.

Coping with a changed life

- Many patients experienced continual loss from a variety of factors: physical change, previous life, their future, their identity. This caused feelings of hopelessness, and uncertainty and concern regarding the loss of further functions in the future. Some went through a process of mourning their lost abilities. Taking pleasure in new activities was important in maintaining hope. Many wished to maintain their normal lives for as long as they could and found different ways to do this. When activities were no longer possible, new activities were undertaken in order to keep a 'normal life' and to distract from the future.
- Some patient's social life was limited only to meeting other patients. Accessing external help was identified as being important to enable the enjoyment of activities. Often participants started to

live for the moment, focusing on what was important in the here and now rather than planning ahead, with hope being important for many. There were paradoxical attitudes about looking towards the future: many did not want to plan for the future as they found it hard that they had lost their expected future. Many worried about how the disease would impact on their loved ones, especially their children, when they died.

Change in relationship

- Many participants spoke of how MND had changed their romantic relationships. There was a change in role, from wife/husband to nurse/carer. The manifestation of a change in role resulted in less time or desire for intimacy. Specialist equipment and changes in strength were also noted as restricting intimacy. Patients stated that health and social care professionals tended not to speak to them about sexuality or intimacy. Touch was identified as being important emotionally to maintain relationships, however some found the barriers too difficult to overcome. Loss of sexual and physical contact was a common cause of sadness.

Carers

- Carers felt they needed more information about MND and the services available. They acknowledged that they had to carry out more personal tasks as they had to take over those of their partner, provide personal care, and provide general support for the person with MND. This impacted on the family and carer's life. They reported having limited freedom, wishing for a sense of normality and a desire to retain some control over their personal lives.
- There was an emotional cost to the carer while caring. They reported often feeling overwhelmed and noticed their own health deteriorating. Many tried to go on without additional support for as long as possible, often feeling it was a test and expression of their love. They felt the need to be strong for both themselves and the person with MND, and not show negative feelings in front of their loved one. In turn, people with MND reported feeling like they were a burden and felt guilty about depending on others, often causing them to make decisions to make things easier for their families.
- Carers reported various coping strategies such as: having a positive approach to caring, focusing on the present, emphasising remaining capabilities, appreciating the time they had together and socialising. Some wished to vent their emotions while others switched off their emotions to get on with the practicality of caring. Management of time was an important factor in continuing their normal life.
- Carers felt a need to confide in others but were unable to talk to friends and family about the impact that caring was having on them. They thought that accessing formal counselling would be helpful, particularly post-bereavement and some reported having positive experiences of counselling. However, it was reported that some respondents had found difficulty in accessing counselling or did not know how or where to access it.
- Some participants were dissatisfied with the level of respite care that was provided. Former carers discussed the need for respite for emotional release and replenishment, whereas current carers did not. They acknowledged that respite care had given them a positive opportunity to have a break from caring. And were reassured when respite services had specialist experience of caring for patients with MND. There was variability in access to respite care which was dependent upon location. Carers noted that it would be useful to have advanced and short-term booking of respite services. Some carers expressed that they had felt guilty when the person with MND was unwilling to agree to respite.
- It was evident that decisions regarding the care of the patient had a considerable influence on carers' quality of life. However, it was noted that often patients and carers did not agree on care decisions. Sometimes carers acted as a gate-keeper, blocking the health professionals' access to the patient. Carers positively reported that an MDT model of care enhanced their role in decision-making when supported by access to research and educational websites.

Patients

Sources of support

- Patients found support from friends, family, the medical team (and even pets) as being very important. There was often a balance between drawing support and providing support to loved ones. It was reported that friends and family gave patients meaning and strength through their presence, support and acceptance of them as individuals. Patients stated that they appreciated family more since having the disease.

Support groups

- There was variability regarding whether patients liked support groups or not. Some participants found that it was a good place to exchange information on the management of MND, and that it was an opportunity to advise others or just a good place to interact. Others acknowledged that it was difficult to see others at further stages of the disease. Some reported that they could not attend due to practical access problems and others did not like the mix of carers, people with MND and/or bereaved spouses.

Healthcare professionals

- Generally, patients reported that they wanted to trust health professionals, but they were less likely to trust non-empathetic professionals, trusting those who were knowledgeable, personable, and able to provide reassurance about their care. It was reported that there was a sense of a lack of knowledge and understanding of MND and the impact it has on one's life amongst healthcare providers. Patients reported that they were unsure of the services they were entitled to. Some patients found that an MDT service was a supportive decision-making environment which they liked due to their expertise, specialised knowledge and dedicated MND services. They had regular appointments to discuss healthcare and psychosocial issues and to plan for anticipated care needs. Professionals felt they required more MND knowledge and felt that better coordination of services and information exchange between professionals was required to ensure consistency of care.

Decision-making

- Family members felt that difficult decisions and crossroads were continuous.
- Family was the most important factor in a patient's decision-making process; they were the main reason for opting in or out of services, prolonging life or not and/or for symptom management decisions. Some patients chose not to make decisions independently, preferring to share this process with others such as family or healthcare providers.
- Regardless of coping strategy, decision-making was mainly guided by a focus on the present rather than the future. Maintaining current wellbeing was a higher priority as coping with the present was preferable to contemplating the future. Health professionals aimed to guide the patient and carer though decisions, in a timely manner, with evidence-based information. The health professional saw it as a cyclical process, responding to recurrent change as the person's condition deteriorated.
- Clinicians perceived the barriers to decision-making as: patient acceptance of the diagnosis, the types of information patients sourced, and the patient-carer relationship. They had little control over these issues but could respond to the changing needs of the patient as best as they could. Timing was important in decision-making and care could be hampered by lack of motivation or limited insight into their condition. Crisis management strategies were seen as the last resort for those who were unable to come to terms with the changes to their life.
- As cognitive and behavioural changes were not routinely assessed in the clinics, identification of patients at risk of impaired decision-making skills was not systematic or standardised. More specific and detailed knowledge of these changes could improve healthcare professionals' approach with the patient and carers.

10.5.2 Economic

- No relevant economic evaluations were identified.

10.6 Recommendations and link to evidence

Recommendations	**Psychological support** **31. During multidisciplinary team assessments and other appointments, discuss the psychological and emotional impact of MND with the person and ask whether they have any psychological or support care needs. Topics to discuss may include the following:** • **Their understanding of MND and how it affects daily living.** • **Accepting and coping with the diagnosis and prognosis, including concerns and fears about dying.** • **Their ability to continue with current work and usual activities.** • **Adjusting to changes in their life and their perception of self.** • **Changes in relationships, familial roles and family dynamics.** • **Sexuality and intimacy.** • **Concerns about their family members and/or carers.** • **Decision-making. [new 2016]** **32. Offer the person information about sources of emotional and psychological support, including support groups and online forums. If needed, refer the person to counselling or psychology services for a specialist assessment and support. [new 2016]** **33. During multidisciplinary team assessments and other appointments, discuss the psychological and emotional impact of MND with family members and/or carers (as appropriate), and ask whether they have any psychological or social care support needs. Topics to discuss may include the following:** • **Their understanding of MND and how it affects daily living.** • **Accepting and coping with the diagnosis and prognosis, including concerns and fears about the person with MND dying.** • **Adjusting to changes in their life.** • **Changes in relationships, familial roles and family dynamics, including their change to a carer role (if appropriate).** • **Sexuality and intimacy.** • **Involvement in decision-making.** • **Impact on other family members and/or carers.** • **Their ability and willingness to provide personal care and operate equipment. [new 2016]** **34. Offer family members and/or carers (as appropriate) information about respite care and sources of emotional and psychological support, including support groups, online forums and counselling or psychology services. [new 2016]**

Relative values of different outcomes	This qualitative review aimed to analyse the needs and experiences of people with MND, their families and carers to find the most appropriate ways of providing emotional and psychological support. Information from interviews and focus groups was synthesised into themes and sub-themes through thematic analysis.
Trade-off between clinical benefits and harms	Recognising the psychological needs of people with MND and their families and carers and providing appropriate psychological and emotional support is unlikely to be harmful. Exploring these issues can be difficult and needs to be done sensitively and with regard to individual people's response to their diagnosis.
Trade-off between net health effects and costs	No economic evidence was identified for this review question. A discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations.
Quality of evidence	Qualitative studies were sought for inclusion in this review. Studies were analysed using thematic analysis and results were presented as a narrative. The methodological quality of each study was assessed using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome. The themes were graded as Moderate or High quality. While many studies did not report the background of the investigator there were a number of studies contributing to each theme and many of the themes were saturated.
Other considerations	The GDG used the themes in the evidence and their experience to develop recommendations. The evidence in the area of social care also contributed to the discussion and development of these recommendations. Additionally, the GDG were informed by a co-opted expert in neuropsychology. The main themes from the evidence review were used by the GDG in outlining the important areas to consider regarding the psychological needs of people with MND and their families and carers: coping with the diagnosis, understanding the disease, acceptance, coping with a changed life, change in relationship, carers, sources of support, and decision-making. The GDG were aware of the importance of psychological and emotional issues for all other areas of disease management, noting that acceptance of the disease helped people cope with all aspects of symptom management. The GDG highlighted that discussions about sex, touch and intimacy are of particular importance as these conversations are often avoided by healthcare professionals in the experience of people with MND and their carer(s). The GDG recognised that healthcare professionals who deliver psychological support must adapt the content and delivery of this support to the needs of the person with MND. Everyone has different requirements for support, and therefore the interactions must be led by the person. The evidence revealed that feeling in control of one's life was important to people with MND. The studies showed that people's psychological and emotional needs may change, particularly as the disease progresses. Regular discussion and review is therefore required to assess changing support requirements. The GDG felt the key aspects to assess were: the person's understanding of MND and how it affects daily living; their acceptance of and ability to cope with the disease, its progression and the prospect of dying; their ability to continue with current work and usual activities; adjustments they must make to their life and their perception of self; changes in relationships, familial roles and family dynamics; issues with sexuality and intimacy; concerns about their family members and/or carers; and their ability to make decisions. This list is not exhaustive and not all people will have needs in these areas. The GDG distinguished informal emotional support and counselling from formal

	psychological support in their recommendations. Many people with MND and their families can be helped with informal support, including involvement with support groups and charities such as those associated with the MND Association. The most appropriate psychological intervention(s) will depend on the nature and severity of the individual's problems, any history of previous psychological problems and the quality of social support available. A range of psychological interventions can be offered by both the statutory and voluntary sectors. Health and social care professionals offering day-to-day care provide much general psychological support to patients and carers. They play a key role in psychological assessment, and in the prevention and amelioration of distress. Practitioners should however be alert to the requirement for formal psychological assessment and support, and the need to refer to psychological and neuropsychological services. More specialised services include counselling, clinical and health psychology, and liaison psychiatry may be available as an integral part of MND services or may be part of generic mental health services, primary care services or specialist palliative care. The GDG considered it important to ensure that the person's family members' and/or carer's psychological and emotional needs are recognised and reviewed regularly. Family members face significant changes in their role as they are coping both with the reality of reduced life expectancy for a loved one but also with requirements to provide increasing care and physical support. Their needs may also change as the disease progresses. The GDG felt that the key aspects to assess were: their understanding of MND and how it affects daily living; their acceptance of and ability to cope with the disease, its progression and the prospect of dying; adjustments they must make to their life; changes in relationships, familial roles and family dynamics, including their change to a carer role; issues with sexuality and intimacy; their involvement in decision-making and their ability and willingness to provide personal care and deal with equipment. There can be a presumption that family members will take on caring duties and there is a need to recognise that this may not be something that all family members are able to do as they are also dealing with significant change to their circumstances. The GDG highlighted the need for appropriate treatment for people suffering from depression. This can be found in CG91 NICE guideline 'Depression in adults with a chronic physical health problem: Treatment and management'.

11 Social care support

11.1 Introduction

The diagnosis and management of MND takes place primarily within health services. However, the reality of that diagnosis and its effect on the physical health of the individual is lived out by the person and their family and carers outside healthcare settings. MND provides challenges to basic functions such as eating, communication and mobility. Social care is involved in providing practical support to people to improve their quality of life and maintain their independence. Social care services are provided by local authorities and people who require social care need to have a formal assessment. Since April 2015, carers are also entitled to a carer's assessment to ensure their needs are met. The needs of each individual patient will be specific to that patient and their situation. While there are known variations in patterns of disability developed by people with MND, there is significant overlap in problems faced by people with MND and their families and/or carers. This review was carried out to inform recommendations about issues faced by people with MND and their families/carers. The recommendations will also be informed by reviews in other sections where there is overlap.

11.2 Review question: What are the social care support needs of people with MND and their families and carers?

For full details see review protocol in Appendix C.

Table 53: PICO characteristics of review question

Population and setting	• Adults (aged 18 and over) with MND, their families and carers • Families and carers of adults with MND
Topic of interest	To identify the social care support needs of people with MND and their families and carers
Context (specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	Potential themes identified by the GDG that would be relevant for inclusion in this review included: • Financial support • Employment support • Transport • Support with eating • Support with dressing/washing • Support to engage with social activities • Adaptations at home • Appropriate housing
Review strategy	Qualitative studies were sought for inclusion in this review. Studies will be analysed using thematic analysis. Results will be presented as a narrative, and diagrammatically where appropriate. 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.

11.3 Clinical evidence

Six studies, reported in 7 papers, were included in the review;[45,54,59,75,92,94,118] these are summarised in Table 54 below. The themes identified in this review are summarised in Table 55. Evidence from

these studies is summarised in the clinical evidence summary below (Table 56 and Table 57). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, and excluded studies list in Appendix K.

Table 54: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (1:1 interviews, focus groups, partner interviews, semi-structured interviews)				
Gent 2009[45]	Interviews	Carers of people with MND	To explore the experiences of MND carers to identify the coping strategies adopted and the potential implications for service provision	This study was also included in the 'Psychological support' review
Herz 2006[54]	Focus groups	Carers of people with MND	To explore the experience and perceptions of carers of people with MND	This study was also included in the 'Psychological support' and 'Planning for end of life' reviews
Hogden 2013[59]	Interviews	Carers of people with MND	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 multidisciplinary care	This study was also included in the 'Psychological support' review
McKelvey 2012[75]	Interviews	Carers of people with MND	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	This study was also included in the 'Psychological support' review
O'Brien 2012[94] O'Brien 2012b[92]	Interviews	People with MND and carers of people with MND	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	Two papers with an overlap in the data used; carer interviews were incorporated in the analysis for both papers, while patient interviews are in the analysis in only 1 of the

			of barriers to the uptake of social services in the UK.	papers. This study was also included in the 'Psychological support' review.
Taylor 2011a[118]	Interviews	People with MND and carers of people with MND	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	This study was also included in the 'Psychological support' review

Evidence

11.3.1.1 Themes and sub-themes derived from the evidence

Table 55: Themes and sub-themes

Main theme	Sub-themes
Social care needs	Equipment
	Personal care
	Support with eating
	Support to engage in life
	Financial support
	Respite
	Training
Delivery of social care	Information
	Person-centred care
	Continuity of care
	Specialist care

Table 56: Summary of evidence: Theme 1 – Social care needs

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Equipment					
4 (Gent 2009; Herz 2006; Taylor	Interviews and focus groups	Participants discussed how the provision of equipment (for example wheelchair, recliner chair, profiling bed) can improve the quality of life of both patient and carers by improving outdoor mobility and transfers. Carers discussed how equipment allowed them to better care for their loved	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
2001a; McKelvey 2012)		one irrespective of their own ill health. Some carers suggested that the provision of equipment extended the time patients were able to be cared for at home. Participants also discussed the importance of communication devices to allow patients to maintain their social roles, relationships and quality of life. However, patients and carers discussed the importance of adjustments to equipment to allow for intimacy and sexual expression between patients and their partners; for example, communication devices generating a same-gender, non-computerised voice and for hospital beds to be placed in a room where partners can also sleep.			
Sub-theme 2: Personal care					
1 (Gent 2009)	Interviews	Some patients with MND require support with personal care. Some family carers feel uncomfortable providing this.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 3: Support with eating					
1 (Gent 2009)	Interviews	Some patients require support with eating, including selecting and preparing meals and support to eat independently.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 4: Support to engage in life					
2 (Hogden 2013, McElvey 2012)	Interviews	Participants discussed how it was important for both patients and carers to continue to engage in social activities and maintain their other roles and responsibilities. Carers discussed how their caring role interfered with their other responsibilities, such as maintaining employment and caring for children and grandchildren. Participants also discussed how they experienced some barriers to leaving the house and engaging in social activities; for example, access to friends' houses and other establishments.	Applicability of evidence	Partially applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 5: Financial support					
2 (Herz 2006, O'Brien 2012)	Interviews and focus groups	Carers expressed feeling financial strain due to the economic burden of caring for their loved one. Carers expressed a desire for greater funding to provide support and equipment to allow patients to be cared for at home for longer.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 6: Respite					
3 (Gent 2009, Herz 2006, O'Brien 2012)	Interviews and focus groups	Carers discussed how respite was seen as an opportunity to take a break from the caring role and to allow emotional replenishment and relaxation.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 7: Training					
1 (O'Brien 2012)	Interviews	Carers expressed a desire for training in manual handling to ensure their safety and the safety of their loved one and to ensure that their loved one was cared for properly.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 57: Summary of evidence: Theme 2 – Delivery of social care

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Information					
1	Interviews	Participants discussed uncertainty about what services they	Applicability of evidence	Applicable[a]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
(O'Brien 2012)		require, what support is available, and what they are entitled to. Participants also discussed a lack of awareness about who they need to contact to access support. Carers discussed how the burden of caring could interfere with their ability to look for information and felt that informational support could be provided.	Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Person-centred care					
2 (McKelvey 2012; O'Brien 2012)	Interviews	Participants discussed the importance of patients being involved in decisions about their care. Participants also discussed how care was not always available when patients needed it. Participants discussed how both advanced and late booking of respite care would be useful.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Continuity of care					
1 (O'Brien 2012)	Interviews	Participants discussed a lack of continuity in care, with little consistency in care teams. Participants felt that social services were sometimes poorly organised.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 4: Specialist care					
1 (O'Brien 2012)	Interviews	Participants discussed how those who organised the initiation of care and home carers were unfamiliar with the problems encountered by people with MND. Carers discussed how they felt more reassured about referring their loved ones to respite centres with experience of caring for people with MND.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

11.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

11.5 Evidence statements

Clinical

- Six qualitative studies in 7 papers were included in the review, from which 2 main themes were identified: social care needs and delivery of social care. The following sub-themes were identified: equipment, personal care, support with eating, support to engage in life, financial support, respite, training, information, person-centred care, continuity of care, and specialist care.

Social care needs

- Participants discussed how the provision of equipment (for example wheelchair, recliner chair, profiling bed) can improve the quality of life of both patient and carers by improving outdoor mobility and transfers. Participants expressed the importance of adjustments to equipment to allow for intimacy and sexual expression between patients and their partners, for example, communication devices generating a same-gender, non-computerised voice and for specialised beds to be placed in a room where partners can also sleep.
- Some patients required support with eating, including selecting and preparing meals and support to eat independently.
- Participants discussed how it was important for both patients and carers to continue to engage in social activities and maintain their other roles and responsibilities. Participants expressed the importance of communication devices to allow patients to maintain their social roles, relationships and quality of life. Participants also discussed how they experienced some barriers to leaving the house and engaging in social activities; for example, access to friends' houses and other establishments.
- Carers expressed feeling financial strain due to the economic burden of caring for their loved one and how their caring role interfered with their other responsibilities, such as maintaining employment and caring for children and grandchildren. They expressed a desire for greater funding to provide support and equipment to allow patients to be cared for at home for longer.
- Carers discussed how respite was seen as an opportunity to take a break from the caring role and to allow emotional replenishment and relaxation. Respite centres with experience of caring for people with MND were reassuring for carers and they expressed that advanced and late booking of respite care would be useful.
- Carers expressed a desire for training in manual handling to ensure their safety and the safety of their loved one.

Delivery of social care

- Participants discussed uncertainty about what services they require, what support is available, and who they need to contact to access support. Carers discussed how the burden of caring could interfere with their ability to look for information and they felt information and support should be provided routinely to them.

- Participants discussed the importance of patients being involved in decisions about their care and that care was not always available when patients needed it.
- Participants indicated a lack of continuity in care with little consistency in care teams, and felt that social services were sometimes poorly organised. It was felt that those who organised the initiation of care and home carers were unfamiliar with the problems encountered by people with MND.

Economic

- No relevant economic evaluations were identified.

11.6 Recommendations and link to evidence

Recommendations	**35. A social care practitioner with knowledge of MND or rapidly progressive complex disabilities should discuss the person's needs and preferences for social care, and provide information and support for them to access the following:** • **Personal care, ensuring there is continuity of care with familiar workers, so that wherever possible, personal care and support is carried out by workers known to the person and their family members and/or carers (as appropriate).** • **Equipment and practical support (see Chapter 15).** • **Financial support and advice (for example, money management, how to access carers' and disability benefits and grants, continuing healthcare funding and funeral expenses).** • **Support to engage in work, social activities and hobbies, such as access to social media and physical access to activities outside their home.** • **Respite care. [new 2016]** **36. Be aware that as MND progresses, people may develop communication problems and have difficulty accessing support or services. For example, they may be unable to access a call centre. Ensure people are given different ways of getting in touch with support or services, and a designated contact if possible. [new 2016]**
Relative values of different outcomes	This qualitative review aimed to analyse the social care support needs and experiences of people with MND, their families, and carers. Information from interviews and focus groups was synthesised into themes and sub-themes through thematic analysis.
Trade-off between clinical benefits and harms	Correct identification and delivery of social care needs would be of benefit to people with MND and their carers. Significant difficulties in practical matters are likely without this.
Trade-off between net health effects and costs	No economic evidence was identified for this review question. A discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations.
Quality of evidence	The methodological quality of each study was assessed using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome. The themes were graded between Low and High with saturation being a key determinant of quality rating.
Other considerations	The GDG used the evidence and their own experience of care for people with MND to develop these recommendations.

The social impact of MND is considerable. People affected by MND can have a rapidly changing range of needs for social care and support at different stages of the patient pathway. The breadth of support that may be required from professional social care is extensive. These include help with personal care, such as bathing and dressing; help inside and outside the home, such as cleaning and shopping; advice on work and employment issues and assistance to secure financial support and benefits such as applications for the blue badge scheme for parking, Motability, car adaptations; practical aids, including house adaptations, installation of grab rails, wheelchairs, augmentative and alternative communication (AAC) and other equipment; help to care for children and other dependants (such as older relatives); and carer respite.

The recommendations in this section do not cover all areas of requirement for social care involvement for people with MND. The recommendations in the section on equipment and adaptations are also particularly relevant for social care and can be found in Chapter 15. Referral for an assessment to social care and referral of carers for a carer's assessment is discussed in Section 6.6.

The GDG highlighted that people with MND require ongoing assessment and monitoring of their social care needs. The needs of people with MND change rapidly and proactive care is needed to ensure that care and equipment are available when required. The GDG expressed the importance of cases being kept open to allow speedy and appropriate assessment if circumstances change and considered it an important part of coordination of care to achieve this. While this is relevant to all services, the GDG considered it a particularly important message for social care professionals.

The GDG agreed that ideally small social care teams are needed to ensure that there is continuity of care provision from people who are aware of the specific needs of the person with MND. However, there can be situations where different carers visit who are unaware of the specific care needs of the person with MND, and this is difficult for families who may need to be present to explain the provision of care. Lack of continuity in this way is an added burden for carers and a source of stress rather than support. There can be an expectation that family members will take on caring tasks but this should not be presumed when assessments of needs are made.

The GDG agreed that it is important for people with MND and their families to continue in their work and social roles and relationships and engage in life activities as much as possible. Both physical and online access may be important and should be available to people with MND.

The GDG stated that equipment provided to the person with MND needs to be appropriate to their individual circumstances and their physical, cognitive, behavioural and communication needs. Some patients may refuse certain equipment and this should be respected, but the issues that may arise as a result of refusal may need to be explained. Support is needed in making choices, and careful explanation of the issues in the provision of equipment is necessary. In addition, the consequences of adaptations to the home environment for carers should be considered and equipment needs to be removed in a timely manner following death.

Access to respite care was considered important by the GDG, with a need for flexibility between planned and crisis respite. Respite care can involve extra care being provided within the person's home so that their family member does not have to fulfil a caring role. Respite more usually refers to provision of care in an inpatient setting where the person with MND is admitted for a short period of time to give

	their family member a break. At present the provision of respite may differ according to locality and GDG members reported that in their areas the length of respite care varied from 1–6 weeks per year. The GDG also noted that people with MND may develop communication problems and that this may impact on their ability to access support and services. This can be anticipated and it should not be presumed that people with MND will be able to use a telephone or continue to be able to use the communication method they used when initially seen. For this reason they should be provided with alternative ways of contacting services.

12 Planning for end of life

12.1 Introduction

MND may present in different ways and prognosis is variable but the majority of people with MND die within 2–3 years of diagnosis. Discussions about end of life are difficult but honest and sensitive communication about the diagnosis, likely timescales, how the disease might progress and the support available may be helpful to the person with MND and their families and carers.

The recommendations in this chapter are informed by an evidence review of patient and carer experiences of support and communication about end of life issues. The effect of MND on a patient's ability to communicate may mean that planning for end of life has to be considered early in the course of illness.

12.2 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?

For full details see the review protocol in Appendix C.

Table 58: Characteristics of review question

Population and setting	• Adults (aged 18 and over) with MND, their families and carers
Topic of interest	Communication and support to help people with MND, their families and carers anticipate and prepare for end of life
Context (specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	Potential themes identified by the GDG that would be relevant for inclusion in this review include: • Access to MND specialists (for example doctor, nurse, respiratory consultant, palliative care specialist) • Advance care planning • Advance refusal of treatment (including DNACPR) • 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
Review strategy	Qualitative studies were sought for inclusion in this review. Studies will be analysed using thematic analysis. Results will be presented as a narrative, and diagrammatically where appropriate. 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.

12.3 Clinical evidence

Methods

We searched for qualitative studies exploring patients' and carers' perceptions of their experiences of having MND as well as studies exploring the communication and support they wanted to receive to help them anticipate, and prepare for, end of life.

Twelve papers reporting 9 qualitative studies were included in the review;[43,44] [4,11,54,107,110,126] [12,13,53,98] these are summarised in Table 59 below. Themes identified from the studies are summarised in Table 60. Key findings from these studies are summarised in the modified clinical evidence summary tables (Table 61, Table 62 and Table 63). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, and excluded studies list in Appendix K.

Of the studies identified, 7 studies used one-to-one interviews as their collection method, and 2 studies used focus groups. One study was with patients with MND, 4 studies were with current and/or former carers of people with MND, and 3 studies were with both patients and carers.

Summary of included studies

Table 59: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (1:1 interviews, focus groups, partner interviews, semi-structured interviews focus groups, etc.)				
Aoun 2012[4]	Semi-structured interviews	Bereaved spouses of patients with MND	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.	This study was also included in the 'Psychological support' review.
Bolmsjo 2001, Bolmsjo 2001A, Bolmsjo 2003[11-13]	Semi-structured interviews	Patients with MND and relatives of people with MND	To explore patients' and carers' experiences of MND, including patient discussion of existential issues, and a comparison of	Patients' interviews were not recorded and analysis is based on interviewer notes during the interview. Pre-specified topics

			experiences between patients and carers.	were used to guide the interview schedule and analysis. This study was also included in the 'Psychological support' review.
Foley 2014, Foley 2014B[44 43]	Interviews	Patients with ALS	To explore and develop a theory about the processes underlying ALS patients' engagement with health services, including an emphasis on issues surrounding loss and control that emerged from the data.	This study was also included in the 'Psychological support' review.
Hagena 2014[53]	Focus group followed by interviews	Patients with MND, current and former carers of people with MND	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.	
Herz 2006[54]	Focus groups	Carers of people with MND	To explore the experience and perceptions of carers of people with MND	This study was also included in the 'Psychological support' and 'Social care' reviews.
Ozanne 2013[98]	Interviews	Patients with ALS	To explore how patients with ALS find meaning despite the disease	Subsample of participants recruited as part of a larger study. This study was also included in the 'Psychological support' review.
Preston 2012[107]	Semi-structured interviews	Former carers and relatives of deceased patients who had MND	To explore carers' attitudes and experiences of using the PPC document to plan future care	This study was also included in the 'Psychological support' review.

Ray 2014[110]	Semi-structured interviews	Carers of people with MND	To explore family caregivers' perspectives on dying and the death event of their relative with MND	Secondary analysis of data taken from 2 previous qualitative studies
Whitehead 2012[126]	Narrative interviews	Patients with MND, current and former carers of people with MND	To explore MND patients' and carers' experiences of the final stages of the disease	This study was also included in the 'Psychological support' review.

Evidence

12.3.1.1 Themes and sub-themes derived from the evidence

Table 60: Themes and sub-themes

Main theme	Sub-themes
Information	Information about death Information about end of life care
Choice and control	Choice and control Advance care planning
Support	Need for additional support Importance of specialist care Timing of palliative care Psychological support Support to create a positive death Bereavement support

12.3.1.2 Evidence summary

Table 61: Summary of evidence: Theme 1 - Information

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Information about death					
4 (Ozanne 2013; Whitehead 2012; Bolmsjo 2003; Ray 2014)	Interviews	Patients and carers discussed anxiety over the uncertainty surrounding death in MND. Patients and relatives expressed a wish for greater certainty around disease prognosis and the estimated time of death. Patients also expressed fears about how they would die, and receiving the information that most patients with MND will fall asleep before death reduced some anxiety. A minority of bereaved carers who felt that the death of their loved one was unexpected also discussed feeling unprepared about how to recognise the symptoms of death. As the disease progressed carers often wanted more information than patients.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Information about end of life care					
3 (Foley 2014; Whitehead 2012; Hagena 2014)	Interviews	Some participants felt they needed more information about treatment and care options to be able to make decisions about end of life care. This was important to reduce anxiety about the future, as well as to help them make decisions about their future care.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 62: Summary of evidence: Theme 2 – Choice and control

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Choice and control					
4 (Whitehead 2012; Bolmsjo 2003; Ray 2014; Foley 2014)	Interviews	Patients discussed how having choice and control over their treatment was extremely important. Patients and carers discussed how they wanted to be involved in decisions, including the decision about where death will occur, the use of life-sustaining treatment, and the ability to choose treatments with consideration of maintaining their identity and dignity.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Advance care planning					
3 (Whitehead 2012; Preston 2012; Ray 2014)	Interviews	Outlining people's thoughts about end of life care was useful to represent patients' wishes. Those patients who made advance care plans and their carers reported that they found this process reassuring. Where a healthcare professional supports patients to complete an advance care plan, participants expressed a preference that this should be someone with whom the patient has an established relationship. Some carers suggested that advance care documents should be drawn up when patients are able to communicate their wishes and sign the document. However, some patients and carers found it difficult to raise this topic, and some chose to delay discussion of advance care. Carers discussed how it was extremely distressing when advance care plans were not adhered to, and stressed the importance of all staff being aware of and adhering to advance care plans.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

Table 63: Summary of evidence: Theme 3 - Support

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Need for additional support					
2 (Whitehead 2012; Herz 2006)	Interviews and focus groups	Carers discussed how the availability of support towards the end of life was variable and they expressed a need for greater support during this time. Limited GP involvement, poor access to care and a lack of continuity of care were common complaints. Additional support was perceived as important to manage the health complications arising at this time, and may relieve carers from their caring role to allow greater emotional intimacy with their loved ones.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Importance of specialist care					
3 (Bolmsjo 2003, Herz 2006, Whitehead 2012)	Interviews and focus groups	Carers discussed the importance of staff, including GPs and home carers, having specialist training in palliative care to be able to fully meet the physical and emotional needs of patients at the end of life. One carer reported greater burden when patients were being cared for by inexperienced staff, and carers found it helpful when specialist staff were available to manage increasing physical complications and take responsibility for medical decisions that less experienced staff felt unqualified for.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Timing of palliative care					
2 (Herz	Interviews	Some carers discussed how palliative care was not	Applicability of	Applicable[a]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
2006, Bolmsjo 2003)		available until too late to be of most benefit. These carers suggested that palliative care should be arranged earlier, so that healthcare staff are able to build a rapport with patients before the time of death.	evidence		
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 4: Psychological support					
3 (Whitehead 2012, Ray 2014; Hagena 2014)	Interviews and focus groups	Most patients and carers did not express a desire for psychological support to help them prepare for death. Although anticipation of death was associated with psychological distress, patients and carers felt that talking about their feelings about the end of life would increase emotional distress and undermine their ability to 'keep going'.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 5: Support to create a positive death					
2 (Whitehead 2012; Bolmsjo 2003)	Interviews	Carers discussed how support from healthcare professionals could help to create a positive experience during death. Carers emphasised the importance of having a period of calm before death, where they were able to say goodbye to their loved ones. This should include effective pain management. In hospital, the provision of a private room can create intimacy. Carers felt that where patients had choice and control over their death, this allowed for a more positive dying experience.	Applicability of evidence	Applicable[a]	High
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 6: Bereavement support					
2	Interviews	Few carers reported receiving bereavement support.	Applicability of	Applicable[a]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
(Whitehead 2012; Aoun 2012)		Some carers discussed how the involvement of healthcare services vanished at the death of their loved one, and they felt that they were left to manage their bereavement alone.	evidence		
			Theme saturation/sufficiency	Saturated[b]	

12.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

12.5 Evidence statements

Clinical

Information

- Patients and carers discussed anxiety about the uncertainty surrounding death in MND and expressed a desire for greater certainty about disease prognosis and the estimated time of death. They also expressed fears about how they would die. Furthermore, some participants felt they needed more information about treatment and care options to be able to make decisions about end of life care. This was important to reduce anxiety about the future, as well as to help them make decisions about their future care.

Choice and control

- Patients discussed how having choice and control over their treatment was extremely important. Areas where patients and carers expressed particular interest in decision-making included where death would occur, the use of life-sustaining treatment, and choosing treatments with consideration of their identity and dignity. The process of making advance care plans was reported to be reassuring by both patients and carers. Where a healthcare professional is to support patients to complete an advance care plan, participants expressed a preference that this should be someone with whom the patient has an established relationship. Some carers suggested that advance care documents should be completed when patients are able to communicate their wishes and sign the document. Carers discussed how it was extremely distressing when advance care plans were not adhered to, and stressed the importance of all staff being aware of and adhering to advance care plans.

Support

- Carers discussed how the availability of support towards the end of life was variable. Additional support was perceived as important to manage the health complications arising at this time, and may relieve carers from their caring role to allow greater emotional intimacy with their loved ones.
- Carers expressed the importance of staff, including GPs and home carers, having specialist training in palliative care to be able to fully meet the physical and emotional needs of patients at the end of life. Carers found it helpful when specialist staff were available to manage increasing physical complications and take responsibility for medical decisions that less experienced staff felt unqualified for.
- Carers discussed how palliative care was not available until too late to be of most benefit. It should be arranged earlier, so that healthcare staff are able to build a rapport with patients before the time of death.
- Most participants did not express a desire for psychological support to help them prepare for death. Although anticipation of death was associated with psychological distress, patients and carers felt that talking about their feelings about the end of life would increase emotional distress and undermine their ability to ‘keep going’.

- Carers said support from healthcare professionals could help to create a positive end of life experience through facilitating a period of calm before death, where they were able to say goodbye to their loved ones. This should include effective pain management and allowing patients choice and control over their death. In hospital, the provision of a private room can create intimacy.
- Few carers reported receiving bereavement support. Some carers discussed how the involvement of healthcare services vanished at the death of their loved one, and they felt that they were left to manage their bereavement alone.

Economic

- No relevant economic evaluations were identified.

12.6 Recommendations and link to evidence

	Planning for end of life **37. 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]** **38. Be prepared to discuss end of life issues whenever people wish to do so. [new 2016]** **39. Provide support and advice on advance care planning for end of life. Topics to discuss may include:** • **What could happen at the 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.** • **How to ensure advance care plans will be available when needed, for example, including the information on the person's Summary Care Record.** • **When to involve specialist palliative care.** • **Areas that people might wish to plan for, such as:** i. **what they want to happen (for example, their preferred place of death)** ii. **what they do not want to happen (for example, being admitted to hospital)** iii. **who will represent their decisions, if necessary** iv. **what should happen if they develop an intercurrent illness. [new 2016]**
Recommendations	**40. 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] **41. Offer people the opportunity to talk about, and review any existing, ADRT, DNACPR orders and Lasting Power of Attorney when interventions such as gastrostomy and non-invasive ventilation are planned. [new 2016]** **42. 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 carer responsibilities and spend time with the person with MND. [new 2016]** **43. Towards the end of life, ensure there is prompt access to the following, if not already provided:** • **A method of communication that meets the person's needs, such as an AAC system.** • **Specialist palliative care.** • **Equipment, if needed, such as syringe drivers, suction machines, riser–recliner chair, hospital bed, commode and hoist.** • **Anticipatory medicines, including opioids and benzodiazepines to treat breathlessness, and antimuscarinic medicines to treat problematic saliva and respiratory secretions. [new 2016]** **44. Offer bereavement support to family members and/or carers (as appropriate). [new 2016]**
Relative values of different outcomes	This qualitative review aimed to analyse the needs and experiences of people with MND, their families, and carers to find the most appropriate ways of communicating and supporting them in anticipating and preparing for end of life. Information from interviews and focus groups was synthesised into themes and sub-themes through thematic analysis.
Trade-off between clinical benefits and harms	Planning for end of life care could increase support, choice and control at the end of life for people with MND and their families. Ensuring understanding of available legal directives would be of benefit to healthcare professionals, people with MND and their families and carers.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. A discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations. Earlier referral to specialist palliative care may increase costs to the NHS, however this is reserved for those with very complex needs and ensuring timely referral will improve the level of support the palliative team can provide.
Quality of evidence	The methodological quality of each study was assessed using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome. Studies were grouped by theme and sub-theme. Information about death was rated as Moderate quality evidence; information about end of life care as High quality; choice and control as Moderate quality; advance care planning as Low quality; need for additional support as Low quality; importance of specialist care as Moderate quality; timing of palliative care as Moderate quality; psychological support as Low quality; support to create a positive death as Low quality and bereavement support as Moderate quality.
Other considerations	The evidence review informed recommendations on planning for end of life. This review also informed recommendations about information and support for people at

diagnosis (Section 6.6).

The GDG agreed that people should be given the opportunity to talk about end of life, including their concerns, and they need to be given information about how they might influence and control this through various legal means and directives. These conversations should be allowed to happen at any time but there are particular times when the topics should be raised, such as when discussing NIV.

The GDG emphasised that the conversations and decisions about end of life care must be led by the person with MND. The optimum timing and content of information and support for end of life care and advance care planning will differ. The evidence showed that some people with MND and their carers felt that identifying the 'end of life' phase for the person with MND should be undertaken earlier. However, not all people with MND want to discuss sensitive issues about end of life care at an early point in disease progression. It is important for the clinician to understand the wishes of the person when offering support and information on all aspects of end of life care, but it may be important to emphasise that it is easier to make decisions while communication and cognition have not been affected.

The evidence review indicated that as the disease progresses, the information needs of people with MND, and that of their families, could be different. Sensitivity is required by health and social care professionals when considering these needs.

In the evidence review, people with MND, their family and/or carers expressed fears about how the person with MND would die. The GDG agreed that professionals need to be open to this common anxiety and a discussion about it.

The GDG discussed the importance of creating advance care plans to ensure that people with MND receive the care they wish if they lose capacity. The GDG stated that advance care plans are wide-ranging and can apply to the treatment of, for example, chest infections, as well as withdrawal of ventilation. The GDG were aware that some people wish to discuss interventions such as tracheostomy and ventilation and their potential use. Those people with MND who were expected to lose cognition or the ability to communicate were mentioned as a priority group for advance care planning discussions. The GDG highlighted 4 areas that people with MND might wish to plan for: their preferred place of death, anything they do not want to happen, who will represent their decisions, and what should happen if they develop an intercurrent illness.

The GDG considered that discussions about advance care planning should include legal aspects so that people are aware of what the different types of plans are. These should include 'Do Not Attempt Resuscitation (DNACPR)' orders, 'Lasting Power of Attorney' (LPA) as well as 'Advance Decisions to Refuse Treatment' (ADRT). A system is needed which ensures that advance plans are available when required, such as adding it to their Summary Care Record. The GDG felt that discussion on when to involve specialist palliative care should be made as part of the discussion on advance care planning.

One of the problems for people dying with MND can be a lack of coordination between services who deliver end of life care and the MDT they see for diagnosis and review. People who are at home will need involvement from their GP and other community services and information must be coordinated between these services.

The GDG agreed that family and carers may require additional support as end of life approaches. They stated that family and informal carers often needed to have a reduction in their caring responsibilities to allow them to grieve and say goodbye.

	This might include for example additional carers at night. In the evidence review, carers discussed how the availability of support towards the end of life was variable. The evidence indicated that families and carers often do not receive bereavement support and the GDG stated that it should be offered to them. Other practical support the GDG considered essential was the provision of anticipatory medicines to relieve symptoms at the end of life. GDG members spoke of the distress to the person with MND, their family and/or carers when this medication was not available. The GDG noted that the reviews did not cover conversations involving treatment withdrawal. The healthcare professional should allow these conversations to take place with the person with MND. Recommendations on stopping NIV can be found in Sections 21.10 and 21.18. These recommendations do not cover pain management, symptom management and family support in the last days of life. Please refer to 'Care of dying adults in the last days of life (NICE guideline NG31) for further recommendations on support during the last 3 days of life.

13 Pharmacological and non-pharmacological management for muscle problems

13.1 Introduction

MND causes degeneration of motor neurones. This results in a variety of muscle-related signs and symptoms. The common muscle symptoms are fasciculations (uncontrollable muscle twitching under the skin visible to the eye but not causing movement), muscle cramps due to stiff muscles, muscle stiffness, spasticity and spasms due to increased muscle tone and the wasting and weakness of muscles. These can all cause distress and problems for the person with MND, including pain, and need careful assessment and treatment. Weakness in the muscles that control breathing, the chest wall and the diaphragm can lead to breathlessness and problems with breathing. Interventions for problems with breathing are considered in Chapters 19 and 21.

The guideline looked for evidence for pharmacological and non-pharmacological management of these muscle symptoms. Evidence and recommendations on equipment appropriate for people with MND can be found in Chapter 15.

13.2 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?

For full details see review protocol in Appendix C.

Table 64: PICO characteristics of review question

Population	• Adults (aged 18 and over) with MND who have muscle cramps and/or muscle stiffness and/or muscle weakness
Intervention(s)	• 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(s)	Compared to each other, placebo, or nothing
Outcomes	Critical: • Quality of life (EQ5D, SF-36, SF-12, SEQUOL) (continuous) • Reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle strength, Medical Research Council [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) • Patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) (continuous) (critical outcomes for people at the end of life)

	• Adverse effects of treatment (drowsiness, treatment-related reduction in mobility, treatment-related reduction of functional ability) (dichotomous)
Study design	Order of preference for study designs for each intervention: • Systematic reviews of RCTs which meet our PICOs • Randomised controlled trials Where no RCTs are available, we will consider: • Abstracts of RCTs • Non-randomised trials: prospective or retrospective cohort studies of 20 participants

Evidence from indirect populations was not considered for this question because the GDG did not consider any other populations to be generalisable to MND in terms of muscle-related symptoms.

13.3 Clinical evidence

This review includes one RCT[33] from a Cochrane review[8] for muscle cramps. One other RCT from the Cochrane was excluded on the basis of the dosage of baclofen used in the trial, and was not analysed further. Other studies in the Cochrane review did not meet the PICO for this review question. Two further studies were found for gabapentin compared to placebo.[77,78] No other RCTs or cohort studies were identified for the other drugs.

Three studies were included in the final review[33,77,78] and are summarised in Table 65 below. One study[33] compared the effectiveness of memantine with placebo for functional disability in people with ALS. The Gabapentin studies investigate arm muscle strength in a phase II and phase III trial from the same authors.

Further information on which side effects were measured was not reported. Outcome data from the studies were extracted and forest plots were generated in Review Manager. Evidence for outcomes from this study are summarised in the GRADE evidence profiles. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 65: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
DE CARVALHO 2010[33]	Memantine versus placebo • Patients were prescribed riluzole 50 mg twice daily if not already on riluzole 1 month prior to trial start • Memantine was titrated in 5 mg weekly increments from starting dose 5 mg to 10 mg twice daily.	Adults with clinically probable, laboratory-supported probable or definite ALS	SF-36 MRC (muscular strength) ALSFRS	RCT
MILLER 1996[77]	Gabapentin versus placebo	Adults with clinical or laboratory-supported probable or definite ALS	Arm megascore decline (rate of decline per day); maximal voluntary contraction (MVC) rate of decline; cramps; drowsiness; weakness	RCT – Phase II trial

Study	Intervention/comparison	Population	Outcomes	Comments
MILLER 2001[78]	Gabapentin versus placebo	Adults with clinical or laboratory-supported probable or definite ALS	Arm megascore decline (rate of decline per week); MVC rate of decline; drowsiness; ALSFRS; SF-12	RCT – Phase III trial

Table 66: Clinical evidence summary: Memantine versus placebo

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects Time frame is 12 months	
				Risk with placebo	Risk difference with memantine (95% CI)
Health-related quality of life SF-36 SF-36 score (range 0–100).	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean health-related quality of life SF-36 in the control groups was 40.7	The mean health-related quality of life SF-36 in the intervention groups was 3.4 lower (10.42 lower to 3.62 higher)
MRC (muscle strength) (scale 0–160)	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean MRC (muscle strength) in the control groups was 105.7	The mean MRC (muscle strength) in the intervention groups was 4.3 higher (13.15 lower to 21.75 higher)
ALSFRS Final scores (scale 0–40)	63 (1 study)	LOW[a,b] due to risk of bias, imprecision	–	The mean ALSFRS in the control groups was 20.6	The mean ALSFRS in the intervention groups was 0.4 lower (4.57 lower to 3.77 higher)

[a] *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*
[b] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 67: Clinical evidence summary: gabapentin versus placebo

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentin (95% CI)
Median arm megascore decline (per day/per week)	353 (2 studies)	VERY LOW[a,b,c] due to risk of bias, imprecision	Not estimable	See comment[b]	See comment Phase II trial data: The median arm megascore decline in the gabapentin group was: -0.0025 per day in the gabapentin group; the median arm megascore decline in the placebo group was: -0.0040 per day Phase III trial data: The median arm megascore decline in the gabapentin group was: -0.0198 per week in the gabapentin group ;the median arm megascore decline in the placebo group was: -0.0209 per week

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentin (95% CI)
MVC median rate of decline (per week)	353 (2 studies)	VERY LOW[a,b,c] due to risk of bias, imprecision	Not estimable	See comment[b]	Phase II trial data: The median MVC rate of decline in the gabapentin group was: -0.017 per week; the median arm megascore decline in the placebo group was: -0.028 per week. Phase III trial data: The median MVC rate of decline in the gabapentin group was: -0.020 per week; the median arm megascore decline in the placebo group was: -0.021 per week.
Drowsiness	353 (2 studies)	MODERATE[a] due to risk of bias	RR 2.64 (1.61 to 4.33)	Moderate	
				106 per 1000	174 more per 1000 (from 65 more to 353 more)
Weakness	149 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 2.07 (0.84 to 5.09)	Moderate	
				86 per 1000	92 more per 1000 (from 14 fewer to 352 more)
Cramps	149 (1 study)	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 3.54 (0.78 to 16.14)	Moderate	
				29 per 1000	74 more per 1000 (from 6 fewer to 439 more)
ALSFRS (scale 040; higher is better)	128 (1 study)	MODERATE[a] due to risk of bias			The mean ALSFRS at 36 weeks in the intervention groups was 0.7 higher (1.13 lower to 2.53 higher)
SF-12 (scale 0–100; higher is better)	128 (1 study)	LOW[a,c] due to risk of bias,			The mean SF-12 in the intervention groups was 0.17 higher (0.04 lower to 0.38 higher)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with gabapentin (95% CI)
		imprecision			

[a] *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*
[b] *Unable to analyse data as medians given and incompletely reported*
[c] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*
[d] *Not decrease in muscle cramps*

13.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, typical treatment costs relevant to the treatments in the studies included in the clinical review are provided to aid consideration of cost-effectiveness.

Table 68 provides the annual acquisition cost of the therapeutics included in the clinical review. Drug posology is based on included RCTs, the British National Formulary or advice from GDG members. Unit prices have been sourced from the NHS electronic drug tariff (NHS Business Services Authority), which provides an average cost of medicines when prescribed in a primary care setting. Exceptions are indicated. The cost of drug administration and monitoring is excluded.

Economic considerations

Health-related quality of life was an outcome of 2 trials of gabapentin versus placebo (De Carvalho 2010 and Miller 2001). Miller 2001 reported results of the SF-12 questionnaire but omitted information regarding the mental health component, so cannot be mapped to EQ-5D scores for cost-utility evaluation. There was no clinical benefit of gabapentin versus placebo in health-related quality of life as reported by De Carvalho (SF-36).

Table 68: Unit costs for pharmacological treatments of muscle weakness, stiffness and cramps

Drug class	Drug name	Preparation	Dose (mg/day)	Annual drug acquisition cost
NMDA antagonists	Memantine hydrochloride	Tablets	20[a]	£900
		Oral solution		£8,227[b]
Skeletal muscle relaxant	Baclofen	Tablets	60	£49
		Oral solution		£439
	Dantrolene sodium	Capsules	225	£354
	Tizanidine	Tablets	36	£470
	Quinine sulphate	Tablets	200	£26
Benzodiazepines	Diazepam	Tablets	10	£10
		Oral solution		£1,742
		Ampoules		£168
		Rectal solution		£501
	Clonazepam	Tablets	4	£36
		Oral solution		£2,197
	Midazolam	Ampoules	20	£116[b]
GABA analogues/ uptake inhibitors	Gabapentin	Capsules	3600[c]	£152
		Tablets		£636
		Oral solution		£10,074
Botulinum toxins	Botulinum toxin Type A	Ampoules	100 units (0.25 injections/ month)	£415[d]

Unit costs and dosages are sourced from the NHS electronic drug tariff (NHS Business Services Authority) and British National Formulary, respectively; except:

(a) Sourced from De Carvalho *et al.* 2010
(b) Sourced from CMU eMIT June 2014 (DH CMU = Department of Health Commercial Medicines Unit)
(c) Sourced from Miller *et al*. 1996
(d) Sourced from MIMs online June 2014

13.5 Evidence statements

Clinical

Memantine versus placebo

- One study compared memantine versus placebo.[33] The duration of treatment was 12 months. The evidence showed that there was no clinical benefit at the end of treatment in terms of quality of life, muscle strength, or functionality. The evidence was generally of Low or Very Low quality.

Gabapentin versus placebo

- Two studies compared gabapentin versus placebo.[77,78] The duration of treatment was 6 months, with a follow-up of 1 month. The evidence showed there were clinical harms for drowsiness, weakness and cramps for gabapentin. The rest of the evidence showed no clinical difference. The evidence was of Very Low quality.

Economic evidence

- No relevant economic evaluations were identified.

13.6 Recommendations and link to evidence

Recommendations	**Pharmacological treatments for muscle problems** **45. Discuss the available treatment options for muscle problems. Take into account the person's needs and preferences, and whether they have any difficulties taking medicine (for example, if they have problems swallowing). [new 2016]** **46. Consider quinine[a] as first-line treatment for muscle cramps in people with MND. If quinine is not effective, not tolerated or contraindicated, consider baclofen[a] instead as second-line treatment. If baclofen is not effective, not tolerated or contraindicated, consider tizanidine[a], dantrolene[a] or gabapentin[a]. [new 2016]** **47. Consider baclofen, tizanidine, dantrolene[a] or gabapentin[a] to treat muscle stiffness, spasticity or increased tone in people with MND. If these treatments are not effective, not tolerated or contraindicated, consider referral to a specialist service for the treatment of severe spasticity. [new 2016]** **48. Review the treatments for muscle problems during multidisciplinary team assessments, ask about how the person is finding the treatment, whether it is working and whether they have any adverse side effects. [new 2016]**
Relative values of different outcomes	Health-related quality of life (EQ5D, SF-36, SF-12, SEQUOL), reduction of muscle weakness (hand-held dynamometry for muscle power, Oxford scale for muscle

[a] At the time of publication (February 2016), these medicines did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	strength, MRC score), reduction of increased tone (Ashworth scale, MRC score or hand-held dynamometry for muscle power) and reduction of muscle cramps (Ashworth scale, MRC score) were critical clinical outcomes. Mobility (functional independence measure, ALS functional rating score), patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) and adverse effects of treatment (drowsiness, treatment-related reduction in mobility, treatment-related reduction of functional ability) were important clinical outcomes.
Trade-off between clinical benefits and harms	**Muscle weakness** One study was identified that considered muscle weakness and found no difference between memantine and placebo for health-related quality of life, muscle weakness or ALSFRS scores. Two studies were included which looked at the effectiveness of gabapentin versus placebo on muscle weakness. Both studies found no significant differences between gabapentin and placebo. These studies were considered to be indirect to this review as they did not consider the intervention as a treatment for muscle weakness, but as a measure to slow down the progression of muscle weakness. Higher doses than would be considered in clinical practice had been used. The GDG did not recommend the use of a pharmacological treatment for muscle weakness in people with MND. **Muscle cramps** There was evidence to suggest that gabapentin is associated with a higher level of muscle cramps when used to treat muscle weakness. However, the GDG commented that this study was conducted in a particular population of people with muscle weakness and used a higher dose of gabapentin than would be used in clinical practice. As such, the GDG did not feel that it was appropriate to base a recommendation on this evidence and chose to make a consensus-based recommendation on the pharmacological treatment of muscle cramps. **Muscle stiffness, spasticity or increased tone** No evidence was identified on the use of pharmacological treatments for muscle stiffness, spasticity or increased tone in people with MND. The GDG did not consider it appropriate to use evidence from an indirect population to answer this question, and chose to make a consensus-based recommendation on the pharmacological treatment of muscle stiffness, spasticity or increased tone.
Trade-off between net health effects and costs	No economic evaluations were identified. For people with muscle weakness the clinical evidence did not show a clinical benefit of pharmacological intervention versus placebo, therefore pharmacological intervention is unlikely to be cost-effective. For people with cramps, the GDG gave a consensus that baclofen, dantrolene, tizanidine, gabapentin and quinine may provide a beneficial effect. Of these drugs, quinine has a considerably lower cost of £26, followed by Baclofen at £49–£439 (depending on method of administration). Tizanidine, dantrolene and gabapentin have higher costs but are similarly priced to each other. The GDG considered the significant difference in cost and lack of clinical evidence when recommending lines of treatment. They noted that oral solution preparations may be higher cost than tablet or capsule preparations, so should be used only in people with a clinical necessity. For people with muscle spasticity, stiffness or increased tone, the GDG gave a consensus that dantrolene, baclofen, tizanidine, and gabapentin may provide a beneficial effect. They noted that oral solution preparations of baclofen and gabapentin are higher cost and so should only be used in people with a clinical

	necessity. Given the small difference in cost, the GDG considered these options to be equally cost-effective. Outside of these treatments the GDG felt that referral to a specialist was necessary to ensure symptoms are appropriately managed.
Quality of evidence	Overall, the evidence identified was graded as Low to Very Low quality. One small study was identified that looked at memantine versus placebo and this was graded as Low to Very Low quality. The GDG noted that 2 studies were identified which considered the use of gabapentin to stop the progression of muscle weakness rather than for the treatment of muscle weakness. The study also used a dose that was considered by the GDG to be clinically inappropriate.
Other considerations	In the absence of evidence the GDG made consensus recommendations for possible treatments for muscle symptoms. These symptoms are common in people with MND and can be distressing so the GDG agreed it was important to provide some guidance despite the lack of evidence. They based their recommendations on knowledge of how these drugs might be of use and on clinical experience. Although the GDG considered that the pathophysiology in MND differs from other neurological diseases and they could not use choose an indirect population for the evidence review, they were aware of the evidence included in the NICE Multiple Sclerosis guideline (CG186) for treatment of spasticity in that population. The GDG were aware that most of these drugs are not licensed for use in people with MND. They highlighted the importance of ensuring that all pharmacological treatments are titrated appropriately. The group noted that all pharmacological treatments should be titrated to the maximum tolerated dose, according to the needs of the individual. The GDG stated that the approach to titration should be dependent upon the individual's ability to tolerate the drug, side effects resulting from treatment and the needs of the individual. The GDG emphasised that these are symptomatic treatments and should be judged on their ability to improve symptoms and stopped if they do not result in improved quality of life for the patient. **Cramps** The GDG considered that treatment with quinine is standard clinical practice for the alleviation of cramps but highlighted the limited evidence. The GDG felt that, given the impact of pain caused by cramps to the individual, it was appropriate to develop a recommendation suggesting that healthcare professionals consider using quinine as a first-line treatment, followed by baclofen if quinine is not tolerated or contraindicated. Third-line treatments to consider were dantrolene, tizanidine or gabapentin. The GDG had experience of use of these drugs in clinical practice. **Muscle stiffness** The GDG considered that current practice for muscle stiffness, spasticity or increased tone was treatment with a range of pharmacological interventions, including baclofen, dantrolene, tizanidine, gabapentin or botulinum toxin. The GDG developed a consensus-based recommendation supporting the use of these treatments for the alleviation of muscle stiffness, spasticity or increased tone. The GDG considered that focal spasticity not responding to other treatments might benefit from more specialist care where botulinum toxin could be considered. They did not consider that this was currently a common treatment option and agreed not to include a recommendation for use of botulinum toxin. The GDG recognised that medication for stiffness and spasticity could lead to increased weakness and reduced mobility, and careful monitoring is essential. **Other** The GDG identified that people with MND may experience a combination of muscle stiffness and cramps. Treatment should be considered on the basis of individual

	symptoms. The GDG noted that it was important to regularly review any treatment provided for muscle weakness, stiffness or cramps in people with MND to ensure that the needs of the individual are met and that benefit from the intervention is gained. Choice may also be influenced by the formulation of drugs and which formulation suits the patient. The GDG felt that it was important to discuss the treatment options with the patient and carers. For example, consideration of how treatments are administered is important, as some people with MND are not able to swallow oral solutions and it may be necessary to provide these in alternative forms. The GDG discussed the need for further research for the pharmacological management of muscle symptoms. They did not prioritise the pharmacological treatments of muscle symptoms for the development of a research recommendation in this guideline. They developed a research recommendation for non-pharmacological management of muscle symptoms as they considered this more likely to inform clinical practice in a shorter time frame (see Section 13.11).

13.7 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?

For full details see the review protocol in Appendix C.

Table 69: PICO characteristics of review question

Population	Adults with MND with muscle cramps and fasciculations, increased tone (including spasticity, muscle spasm or stiffness), and/or muscle weakness, wasting or atrophy
Intervention(s)	• Physical therapy (manual techniques, massage, exercise, stretching and positioning–range of movement exercises, endurance and strength training) • Electrotherapy adjuncts (transcutaneous electrical nerve stimulation [TENS], ultrasound, intramuscular manual therapy-trigger point dry needling for relief of muscle spasms and contractions, functional electrical stimulation [FES], transcranial magnetic stimulation [TMS]) • Orthoses, splinting and casting
Comparison(s)	Usual care or placebo/sham
Outcomes	Critical: • Reduction of increased tone, muscle cramps and muscle weakness (Ashworth scale for spasticity, hand-held dynamometry for muscle power, Oxford scale for muscle strength/MRC score) • Health-related quality of life (for example EQ5D, SF-36, SF-12, SEQUOL) Important: • Patient/carer reported outcomes (pain [VAS], reduction of muscle stiffness, reduction of muscle cramps, reduction of fatigue) (critical outcome for people at the end of life) • Mobility (functional independence measure, ALS functional rating score) • Adverse effects of treatment (drowsiness, treatment-related increase in weakness, treatment-related reduction in mobility, treatment-related reduction of functional ability)
Study design	Order of preference for study designs for each intervention: • Systematic reviews of RCTs which meet our PICOs • Randomised controlled trials Where no RCTs are available, we will consider: • Abstracts of RCTs

- Non-randomised trials: prospective or retrospective cohort studies of 20 participants

13.8 Clinical evidence

Three studies were included in the review;[30,35,37] these are summarised below. The 3 included studies were also included in 3 Cochrane systematic reviews.[7,31,40]

Two studies compared the effectiveness of either resistance exercise[30,31] or range of motion exercise[37,37] with usual care. One study compared the effectiveness of transcranial magnetic stimulation versus placebo.[35]

No relevant clinical studies for orthoses or splints were identified.

Data were extracted and analysed in Review Manager. As there was only 1 study each for the included interventions, no further analysis was performed. Evidence was assessed for quality using GRADE.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 71, Table 72 and Table 73). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 70: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Dal Bello-Haas 2007[30,31]	Resistance exercise versus usual care • Resistance exercise programme: once-daily upper limb and lower limb stretch exercises plus range of motion exercise against gravity. Compliance monitored throughout study. • Usual care: once daily upper limb and lower limb stretch exercises. Compliance monitored throughout study.	ALS	SF-36 at 6 months; Fatigue severity scale (FSS) at 6 months; ALSFRS at 6 months.	
Drory 2001[37,37]	Range of motion exercise versus usual care • Exercise programme: 15 minute exercise programme for upper limbs, lower limbs and trunk, performed twice daily at home. Adherence checked every 2 weeks via telephone.	ALS	SF-36 at 3 months; MRC at 3 months; ALSFRS at 3 months; VAS (pain) at 3 months.	

Study	Intervention/comparison	Population	Outcomes	Comments
	• Usual care: no extra physical activity other than usual daily life requirements. Adherence checked every 2 weeks via telephone.			
Di Lazzaro 2009[35]	TMS versus placebo • All patients were taking riluzole at admission • TMS: repetitive TMS of two hemispheres sequentially at 1-minute intervals. Motor cortex of each side stimulated for 5 consecutive days every month for 12 consecutive months. • Placebo/sham rTMS: performed using same stimulator connected to butterfly coil MCF-P-B-65 which has no stimulating effect on cortex but produces similar auditory and tactile sensations as real coil.	ALS	MRC (muscle strength); ALSFRS-R.	

Table 71: Clinical evidence summary: Resistance exercise versus usual care

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with resistance exercise (95% CI)
SF-36 physical function at 6 months (range 0–100)	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 physical function at 6 months in the control groups was 14	The mean SF-36 physical function at 6 months in the intervention groups was 7.1 higher (1.31 to 12.89 higher)
SF-36 physical role at 6 months (range 0–100)	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 physical role at 6 months in the control groups was 4.9	The mean SF-36 physical role at 6 months in the intervention groups was 1.2 higher (0.1 lower to 2.5 higher)
SF-36 pain at 6 months (range 0–100)	18 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 pain at 6 months in the control groups was 10.3	The mean SF-36 pain at 6 months in the intervention groups was 0.2 higher (1.09 lower to 1.49 higher)
SF-36 general health at 6 months (range 0–100)	18 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 general health at 6 months in the control groups was 16.4	The mean SF-36 general health at 6 months in the intervention groups was 0.4 higher (3.49 lower to 4.69 higher)
SF-36 vitality at 6 months (range 0–100)	18 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 vitality at 6 months in the control groups was 14.8	The mean SF-36 vitality at 6 months in the intervention groups was 0.8 higher (3.04 lower to 4.64 higher)
SF-36 social function at 6 months (range 0–100)	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 social function at 6 months in the control groups was 7.7	The mean SF-36 social function at 6 months in the intervention groups was 1.1 higher (0.47 lower to 2.67 higher)
SF-36 emotional state at 6 months (range 0–100)	18 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 emotional state at 6 months in the control groups was 4.7	The mean SF-36 emotional state at 6 months in the intervention groups was 0.4 higher (0.77 lower to 1.57 higher)
SF-36 mental health at 6 months (range 0–100)	18 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 mental health at 6 months in the control groups was 24	The mean SF-36 mental health at 6 months in the intervention groups was 0.6 lower (3.28 lower to 2.08 higher)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with resistance exercise (95% CI)
ALSFRS at 6 months ALSFRS (range 0–40)	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean ALSFRS at 6 months in the control groups was 28.1	The mean ALSFRS at 6 months in the intervention groups was 5.7 higher (1.29 to 10.11 higher)
FSS (range 0–63)	30 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean FSS in the control groups was 42.9	The mean FSS in the intervention groups was 0.2 lower (11.38 lower to 10.98 higher)
Maximal voluntary isometric contraction (MVIC) –upper extremity MVIC megascore	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean maximum voluntary isometric contraction–upper extremity in the control groups was -10.2	The mean maximum voluntary isometric contraction– upper extremity in the intervention groups was 0.1 higher (3.78 lower to 3.98 higher)
MVIC –lower extremity megascore	18 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	–	The mean maximum voluntary isometric contraction–lower extremity in the control groups was -25.9	The mean maximum voluntary isometric contraction – lower extremity in the intervention groups was 6.2 higher (0.21 lower to 12.61 higher)

[a] *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*
[b] *Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs*

Table 72: Clinical evidence summary: Range of motion (ROM) versus usual care

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with ROM exercise (95% CI)
SF-36 at 3 months (range 0–100)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean SF-36 at 3 months in the control groups was 80	The mean SF-36 at 3 months in the intervention groups was 2.7 higher (3.1 lower to 8.5 higher)
MRC (muscle strength) (range 0–160)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean MRC (muscle strength) in the control groups was 87.3	The mean MRC (muscle strength) in the intervention groups was 10.9 lower (23.56 lower to 1.76 higher)
Ashworth scale (range 0–4)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean Ashworth scale in the control groups was 0.75	The mean Ashworth scale in the intervention groups was 0.55 lower (0.96 to 0.14 lower)
ALSFRS at 3 months (range 0–40)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean ALSFRS at 3 months in the control groups was 22	The mean ALSFRS at 3 months in the intervention groups was 6.7 higher (0.38 to 13.02 higher)
FSS at 3 months (range 0–63)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean FSS at 3 months in the control groups was 44.5	The mean FSS at 3 months in the intervention groups was 12.1 lower (23.32 to 0.88 lower)
Pain (VAS) (range 0–10)	18 (1 study) 3 months	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean pain (VAS) in the control groups was 2.21	The mean pain (VAS) in the intervention groups was 1.12 lower (4.66 lower to 2.42 higher)

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

Table 73: Clinical evidence summary: TMS versus placebo

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MRC at 12 months (95% CI)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MRC at 12 months (95% CI)
MRC (range 0–160)	12 (1 study) 12 months; control group=2.5	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean MRC in the control groups was 2.5	The mean MRC in the intervention groups was 0.6 lower (1.59 lower to 0.39 higher)
ALSFRS-R (range 0–40)	12 (1 study) 12 months; control group=21.2	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean ALSFRS-R in the control groups was 21.2	The mean ALSFRS-R in the intervention groups was 1.9 higher (5.13 lower to 8.93 higher)

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

13.9 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, some relevant unit costs are provided to aid consideration of cost-effectiveness.

Frequently used staff

The hourly cost of hospital and community-based physiotherapists and occupational therapists are given in Table 74.[25,25]

Table 74: Unit costs of healthcare professionals

Healthcare professional and setting	Cost of 1 hour of client contact time at AfC salary band 6 (AfC band 7)
Hospital physiotherapist/occupational therapist	£45 (£54)
Community physiotherapist/occupational therapist	£43 (£52)

Face-to-face assisted manual therapy

Current manual techniques including stretching, positioning, endurance and strength training require approximately 2 days (16 hours) of time from both physiotherapist and occupational therapist time per patient per year (GDG estimate). This equates to an annual cost of approximately £1,400 when delivered by experienced therapists (based on hourly costs of staff given in Table 74).

Telephone assisted exercise therapy

A 'range-of-motion' muscle exercise program was evaluated versus care employing no stretching exercises (Drory 2001[37,37] – see clinical review). The program involved an initial consultation with an experienced physiotherapist and telephone support every 14 days. The cost of 1 year of this support, based on 15-minute calls (totalling 6 hours per annum) plus a 1-hour initial session, is £340 when delivered by an experienced physiotherapist (based on an equal weighting of hospital to community care, and physiotherapist to occupational therapist time, and based on hourly costs of staff given in Table 74).

Electrotherapy

Transcranial magnetic stimulation (TMS) is rarely used. Di Lazarro 2009[35] (also see clinical review) showed no evidence of clinical benefit for those with muscle weakness.

TENS devices may be provided on loan to patients and cost between £17 and £730 (NHS Supply Chain Catalogue April 2013[1]), however information from the GDG suggested the most commonly used model costs £30 (TPN 200 Plus).

Functional electrical stimulation (FES) is provided in the hospital setting. Using the example of treatment to the hand, an initial assessment costs £140 and treatments cost £300 per session, of

which five is an average (NICE clinical guideline 162: Stroke rehabilitation[83]). Therefore the cost of a standard treatment package using the MS2v2 system, lasting 6 months, is estimated to be £840.

Intramuscular trigger point dry needling for relief of muscle spasms, provided by a hospital or community physiotherapist (agenda for change salary band 6 or 7), requires 1 hour of professional time, costing £54 excluding the costs of travel.

13.10 Evidence statements

13.10.1 Clinical

Resistance exercise versus usual care

- One study compared resistance exercise versus usual care. The duration of treatment was 6 months. The evidence showed no clinical benefit at the end of treatment for resistance exercise in terms of: quality of life (SF-36), fatigue severity (FSS). The evidence showed a clinical benefit at the end of treatment for functionality (ALSFRS), with an increase in effectiveness of resistance exercise. The evidence was generally of Low or Very Low quality.

Range of motion exercise versus usual care

- One study compared range of motion exercise versus usual care. The duration of treatment was 3 months. The evidence showed no clinical benefit at the end of treatment for range of motion exercise in terms of: quality of life (SF-36) or muscle strength (MRC) or fatigue (FSS). The evidence showed a clinical benefit at the end of treatment for reduction of cramps (Ashworth), improvement of functionality (ALSFRS), and reduction of pain (VAS). The evidence was generally of Low or Very Low quality.

TMS versus usual care

- One study compared transcranial magnetic stimulation (TMS) versus placebo/sham. The duration of treatment was 12 months. The evidence showed no clinical benefit at the end of treatment for TMS in terms of muscle strength (MRC) or functionality (ALSFRS-R). The evidence was generally of Very Low quality.

13.10.2 Economic

- No relevant economic evaluations were identified.

13.11 Recommendations and link to evidence

Recommendations	**Exercise programmes** **49. Consider an exercise programme for people with MND to:** • **maintain joint range of movement** • **prevent contractures** • **reduce stiffness and discomfort** • **optimise function and quality of life. [new 2016]** **50. Choose a programme that is appropriate to the person's level of function and tailored to their needs, abilities and preferences. Take into account factors such as postural needs and fatigue. The programme**

	might be a resistance programme, an active-assisted programme or a passive programme. [new 2016] **51. Check that family members and/or carers (as appropriate) are willing and able to help with exercise programmes. [new 2016]** **52. Give advice to the person and their family members and/or carers (as appropriate) about safe manual handling. [new 2016]** **53. If a person needs orthoses to help with muscle problems, they should be referred to orthotics services without delay, and the orthoses should be provided without delay. [new 2016]**
Research recommendation	**3. 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?**
Relative values of different outcomes	The reduction of increased tone, muscle cramps and muscle weakness, and health-related quality of life, were considered to be critical outcomes. Patient- or carer-reported outcomes (including pain, reduction in muscle stiffness and muscle cramps, and reduction of fatigue) were important outcomes for people with MND but critical for people with MND who were at the end of life. Mobility and adverse effects of treatment (including drowsiness, treatment-related increase in weakness, treatment-related reduction in mobility and treatment-related reduction of functional ability) were also important outcomes. The GDG noted that, given the deterioration of muscle function in people with MND, any maintenance or improvement in function could be considered beneficial to the individual.
Trade-off between clinical benefits and harms	There was some evidence to suggest a clinical benefit of resistance exercise and range of movement exercise for the treatment of muscle weakness, cramps and stiffness on physical health and functioning scores. This was mainly a suggestion of benefit of resistance exercise compared to usual care for an increase in the ALSFRS scale at 6 months. The ALSFRS score at 3 months, Ashworth score and the FSS score at 3 months were improved in the range of movement group when compared to usual care. The GDG considered that the provision of passive movement exercise for people with MND who are unable to move themselves would be beneficial for the treatment of muscle weakness, cramps and stiffness. The GDG agreed that any improvement or maintenance of function is likely to represent a benefit to the individual as it is preventing deterioration in function. There are cost implications if muscle stiffness increases as this has a significant impact on further health needs: for example the development of pressure ulcers or hospital admissions resulting from falls. The GDG identified that there would also be benefits from increasing or maintaining daily function by improving the likelihood that the individual can stay within their own home.
Trade-off between net health effects and costs	No economic evidence was identified but unit costs of treatments were considered. The GDG noted that the potential long-term benefits of physical exercise to reduce deterioration of muscle function and subsequent loss in quality of life will outweigh the cost of providing these exercises. Therefore, physical therapy approaches are likely to be cost-effective. The GDG noted that electrotherapy adjuncts, such as repetitive transcranial magnetic stimulation (rTMS), are rarely used, relatively costly, and the clinical

	evidence is not compelling. Therefore, electrotherapy adjuncts are not likely to be cost-effective.
Quality of evidence	Overall there was Low to Very Low graded evidence in 2 RCTs for exercise versus usual care in a direct population. The sample size was very small and there were some concerns about the quality of one of the studies, particularly in relation to the baseline scores in physical function. However, there was some suggestion of a benefit in reduction of spasticity for a range of movement programme. The GDG felt it is likely that this improvement could help to improve daily functioning. One other very small study (graded as Very Low quality) of TMS versus placebo was found but there were no clinically significant findings. No evidence was found for other devices.
Other considerations	The GDG used the available evidence and their experience to develop recommendations. The GDG are aware that MND patients have been advised not to exercise because of concern that this could lead to overwork muscle damage and fatigue. However, deconditioning secondary to reduced activity is likely to compound the muscle weakness and deconditioning caused by MND which would impact on independence and quality of life. Over-exercise or competitive exercise may be ill-advised, and lead to fatigue that outweighs any other benefit. The GDG noted that passive movement and resistance exercises are usual practice in MND care. They were reassured by the evidence available and agreed to make a recommendation on the use of exercise. However, they considered that a large randomised trial was required to be able to make a stronger recommendation and therefore developed a research recommendation. The GDG considered the importance of tailoring the provision of exercise to specific symptoms, for example weakness and cramps. This can help to maintain and improve movement, which are both important to people with MND. The GDG discussed the importance of having willing family and/or carers to enable the person with MND to undertake the prescribed exercise programme. It should not be assumed that family members and carers are able to help in this way. The GDG considered that prescription of exercise programmes should be complemented with advice about safe manual handling for both the person with MND and their family and/or carer to prevent injury. The GDG were aware that may people with MND require orthoses to help with muscle symptoms and mobility. Orthoses may be helpful as a non-pharmacological intervention for muscle symptoms. Orthoses can be useful in positioning of limbs and may help symptoms such as cramp and spasm. As with recommendations for other aids and equipment, the GDG highlighted the necessity for the supply of orthoses to people with MND without delay. The use of adjunctive therapies such as transcutaneous electrical nerve stimulation (TENS) and functional electrical stimulation (FES) was discussed. The GDG reported that they were not aware of these being widely used within clinical practice for the maintenance of muscle function for people with MND. In addition, they did not feel there was adequate evidence available to recommend use of these devices. NICE has issued full guidance on functional electrical stimulation for drop foot of central neurological origin (IPG278). **Research recommendation** The GDG considered that there was continuing uncertainty about providing strong recommendations to people with MND to exercise and a large randomised controlled trial is required to inform future recommendations in this area. For

	further details please see Appendix N: Research recommendations.

14 Saliva management

14.1 Introduction

The development of difficulties with swallowing in MND is often accompanied by a disruption of the natural handling of saliva and its flow. Saliva may be sticky or watery and associated with pooling. Choking and or drooling (sialorrhoea) may follow and can present significant problems for people including at times being embarrassing. Issues with saliva present a significant management challenge for those involved in the care of MND and are described as affecting up to half of people with the condition.[117,117]

Management of problems with saliva requires a careful clarification of the issues: is there excessive saliva; is it causing drooling or choking; is the saliva watery or tenacious? Interventions include approaches to reduce the production of saliva, alter its character (for example making it thinner), and aid clearance.

In this chapter the different approaches in general use are considered; the professional involved in managing MND should be familiar with these and there should be local access to the different interventions.

14.2 Review question: What is the clinical- and cost-effectiveness of interventions for saliva management in people with MND?

For full details see review protocol in Appendix C.

Table 75: PICO characteristics of review question

Population	Adults (aged 18 and over) with MND Strata: • Patients with sialorrhoea (drooling of saliva) • Patients with thick, tenacious saliva • People with cognitive impairment including frontotemporal dementia and excessively watery saliva (sialorrhoea) • People with cognitive impairment including frontotemporal dementia and thick, tenacious saliva
Intervention(s)	For sialorrhoea: • Atropine (sublingual) • Benztropine • Hyoscine (oral or sublingual or patch) • Glycopyrrolate (sublingual or syringe driver, orally or via PEG) • Amitriptyline (tricyclic antidepressants [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 For 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(s)	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)
Study design	Randomised controlled trials If no randomised controlled trials are available we will look for abstracts of RCTs and cohort studies (sample size limit = 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)

14.3 Clinical evidence

Sixteen studies were included in the review;[3,5,9,16,18,62,66-68,72,76,99,128,130] these are summarised in Table 76 below.

No evidence was found evaluating interventions for treating thick, tenacious saliva in MND or indirect populations.

For the treatment of sialorrhoea, evidence was retrieved evaluating the efficacy of botulinum toxin, glycopyrrolate, and benztropine.

Evidence from these studies is summarised in the clinical evidence summary tables below (Table 77, Table 78, Table 79, Table 80, Table 81). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

One of these studies[19] compared the efficacy of botulinum toxin with placebo for the treatment of sialorrhoea in patients with MND. However, this study was evaluated to be at high risk of bias due to differences between the 2 groups in the main outcome at baseline. Consequently, papers evaluating botulinum toxin in indirect populations were included in the evidence review.

One Cochrane review that examined interventions for sialorrhoea in patients with MND[129] was included in the review but as it only included 1 paper[62], this was assessed and analysed separately. A further Cochrane review that examined interventions for sialorrhoea in children with cerebral

palsy[125] was found after the inclusion of indirect populations and was included in the review. However, as the review strategy involved analysing patients from indirect populations together, the papers in this review were extracted separately and analysed alongside other indirect populations.

Table 76: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Alrefai 2009[3]	Botulinum toxin (100 units split equally between parotid glands; 1 dose) versus placebo	Children with cerebral palsy	Carer-reported severity and frequency of drooling at 1 month	No ultrasound, no anaesthesia
Arbouw 2010[5]	Glycopyrrolate (Oral, 1 mg (5 ml) 3 times daily for 1 week) versus placebo	Adults with idiopathic Parkinson's disease	Patient-reported severity of sialorrhoea in last 3 days of the treatment week; change in motor symptoms in last 3 days of treatment week	Crossover study: washout period=1 week
Basciani 2011[9]	Botulinum toxin (3000 MU dose into the parotid and submandibular glands) versus no treatment	Children with cerebral palsy	Carer-reported severity and frequency of drooling at 4 weeks	Ultrasound and anaesthesia
Camp-Bruno 1989[16]	Benztropine (Mean dose= 3.8 mg/day for 2 weeks	Children, young people and adults with cerebral palsy (95%) and other degenerative nervous disease (5%)	Carer-reported severity of drooling; discontinuation of medication due to side effects	Crossover study: washout period=1 week (evidence of carry-on effects for 1–2 days)
Chinnapongse 2012[18]	Botulinum toxin (2500 units [0.5 ml], 1 dose) injected to the submandibular and parotid glands versus placebo	Adults with idiopathic Parkinson's disease	Change in drooling impact score at 4 weeks; change in severity and frequency of drooling using Drooling Frequency and Severity Scale (DFSS) at 4 weeks; aspiration pneumonia at 20 weeks; discontinuation of medication due to side effects at 20 weeks	No ultrasound, no anaesthesia
Jackson 2009[62]	Botulinum Toxin (2500 units, 1 dose) injected into the parotid and submandibular glands versus placebo	Adults with ALS	Patient reported symptom severity at 2 weeks; patient assessment of	Electromyography and anaesthesia if requested

Study	Intervention/comparison	Population	Outcomes	Comments
			saliva thickness at 2 weeks; caregiver reported symptom severity at 2 weeks; caregiver assessment of saliva thickness at 2 weeks; ALSFRS-R at 2 weeks; SEIQOL-DW at 2 weeks	
Lagalla 2006[66]	Botulinum toxin (100 units, 1 dose) injected into the parotid glands versus placebo	Adults with Parkinson's disease	Sialorrhea severity at 1 month; patient satisfaction with treatment at 1 month	No ultrasound
Lagalla 2009[67]	Botulinum toxin (4000 units (0.8 ml), 1 dose) injected into the parotid glands versus placebo	Adults with Parkinson's Disease	Sialorrhea severity at 1 month; patient satisfaction with treatment at 1 month	No ultrasound
Lin 2008[68]	Botulinum toxin (2 units/kg body weight, 1 dose (injected into 1 parotid gland and 1 contralateral submandibular gland) versus placebo	Children with cerebral palsy	Severity and frequency of drooling at 2 weeks	Guided by ultrasound
Mancini 2003[72]	Botulinum toxin (225 MU, one dose) injected into parotid and submandibular glands versus placebo	Adults with Parkinson's disease (70%) or multiple system atrophy (30%)	Severity and frequency of drooling at 2 weeks	Patients with moderate or severe swallowing difficulties
Mier 2000[76]	Glycopyrrolate (oral, 3 times daily for 8 weeks; dose increased weekly for 4 weeks and titrated by weight; range=0.6 mg –3 mg) versus placebo	Children with cerebral palsy (87%) or other developmental disorders	Severity of drooling at 8 weeks; discontinuation of medication due to side effects at 8 weeks	Crossover study: washout period=1 week
Ondo 2004[99]	Botulinum toxin (2500 units, 1 dose) injected into parotid and submandibular glands versus placebo	Adults with Parkinson's disease	Severity of drooling at 1 month; severity and frequency of drooling at 1	

Study	Intervention/comparison	Population	Outcomes	Comments
			month	
Walshe 2012[125]	Systematic review of interventions for sialorrhoea	Children with cerebral palsy		
Wu 2011[128]	Botulinum toxin (1 dose titrated by weight; range=30–50 U) injected into parotid and submandibular glands versus placebo	Children with cerebral palsy	Carer-reported severity of drooling at 1 month	After injection, all patients received a course of oromotor training by a speech therapist
Young 2011[129]	Systematic review of interventions for sialorrhoea	Patients with MND		
Zeller 2012[130]	Glycopyrrolate (oral solution, 3 times daily for 8 weeks. Dose increased weekly for 4 weeks and titrated by weight; mean=0.15 mg/kg, maximum=3.0 mg per dose) versus placebo	Children with cerebral palsy (83.3%) and other unspecified mental retardation or neurological disorder	Change in severity of drooling at 8 weeks; patient satisfaction at 8 weeks; discontinuation of medication due to side effects at 8 weeks	

Treatments for sialorrhoea

Table 77: Clinical evidence summary: Botulinum toxin versus placebo in patients with MND

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MND botulinum toxin (95% CI)
Health-related quality of life (SEIQOL-DW; 0–100; higher is better)	20 (1 study) 2 weeks	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean health-related quality of life in the control groups was 59.3	The mean health-related quality of life in the intervention groups was 6 higher (16.35 lower to 28.35 higher)
Patient assessment of severity of sialorrhoea (0–100; higher is worse)	20 (1 study) 2 weeks	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean patient assessment of severity of sialorrhoea in the control groups was 75	The mean patient assessment of severity of sialorrhoea in the intervention groups was 26 lower (44.01 to 7.99 lower)
Patient assessment of saliva thickness (0–100; higher is better)	20 (1 study) 2 weeks	LOW[a] due to risk of bias	–	The mean patient assessment of severity of sialorrhoea in the control groups was 79	The mean patient assessment of saliva thickness in the intervention groups was 11 higher (4.59 lower to 26.59 higher)
Caregiver assessment of severity of sialorrhoea (0–100; higher is worse)	20 (1 study) 2 weeks	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean caregiver assessment of severity of sialorrhoea (0–100) in the control groups was 70	The mean caregiver assessment of severity of sialorrhoea in the intervention groups was 18 lower (42.23 lower to 6.23 higher)
Caregiver assessment of saliva thickness (0–100; higher is better)	20 (1 study) 2 weeks	VERY LOW[a,b] due to risk of bias, imprecision	–	The mean caregiver assessment of saliva thickness (0–100) in the control groups was 64	The mean caregiver assessment of saliva thickness in the intervention groups was 2 higher (19.07 lower to 23.07 higher)
Function (ALSFRS 0–48; higher is better)	20 (1 study)	VERY LOW[a,b] due to risk of	–	The mean function rating in the control groups was 28.8	The mean function rating in the intervention groups was 0.9

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MND botulinum toxin (95% CI)
	2 weeks	bias, imprecision			lower (9.29 lower to 7.49 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 78: Clinical evidence summary: Botulinum toxin versus placebo in patients from indirect populations

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with botulinum toxin injections (95% CI)
Change in impact of drooling on daily activities (10–40; higher is worse)	27 (1 study) 4 weeks	LOW[b,c] due to risk of bias, indirectness	–	The mean change in impact of drooling on daily activities in the control groups was -1.9	The mean change in impact of drooling on daily activities in the intervention groups was 5.3 lower (8.18 to 2.42 lower)
Patient assessment of severity of sialorrhoea severity	84 (3 studies) 1 months	MODERATE[c] due to indirectness	–	The mean patient-reported sialorrhoea severity in the control groups was 5	The standardised mean patient-reported sialorrhoea severity in the intervention groups was 1.39 lower (1.87 to 0.90 lower)
Patient reported change in sialorrhoea severity (Drooling Frequency and Severity Scale 2–9, higher is better)	27 (1 study) 4 weeks	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	–	The mean patient-reported change in sialorrhoea severity in the control groups was -0.81	The mean patient-reported change in sialorrhoea severity in the intervention groups was 0.92 lower (2.03 lower to 0.19 higher)
Change in drooling score (carer reported severity and frequency of saliva problem; 2–9)	24 (1 study) 1 month	LOW[b,c] due to risk of bias, indirectness	–	The median change in drooling score in the control group was 0	The median change in drooling score in the intervention group was -2
Frequency and severity of drooling score	13	VERY LOW[c]	–	The mean reported frequency	The mean reported frequency and

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with botulinum toxin injections (95% CI)
(assessor unclear, 1–9)	(1 study) 2 weeks	due to risk of bias, indirectness, imprecision		and severity of drooling in the control groups was -0.81	severity of drooling in the intervention groups was 0.96 lower (1.82 to 0.10 lower)
Patient satisfaction	68 (2 studies) 1 month	MODERATE[c] due to indirectness	RR 2.6 (1.65 to 4.09)	Moderate	
				351 per 1000	562 more per 1000 (from 228 more to 1000 more)
Dysphagia (0–4; higher is worse)	75 (3 studies)	MODERATE[c] due to indirectness	–	The mean dysphagia in the control groups was 1	The mean dysphagia in the intervention groups was 0.15 lower (0.7 lower to 0.39 higher)
Dysphagia (present/not present)	14 (1 study) 1 month	VERY LOW[b,c] due to risk of bias, indirectness	–	Moderate	
				0 per 1000	See comment[e]
Aspiration pneumonia	27 (1 study) 20 weeks	LOW[b,c] due to risk of bias, indirectness	–	Moderate	
				0 per 1000	See comment[e]
Discontinuation of medication due to side effects	27 (1 study) 20 weeks	VERY LOW[b,c,d] due to risk of bias, indirectness, imprecision	Peto OR 0.17 (0 to 8.54)	Moderate	
				67 per 1000	67 fewer per 1000 (from 244 fewer to 110 more)[a]

[a] Absolute effect calculated as analysis used Peto Odds Ratio
[b] 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
[c] Downgraded by 1 increment as the evidence included an indirect population
[d] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[e] Absolute effect could not be calculated as zero events in both arms

Table 79: Clinical evidence summary: Botulinum toxin versus no treatment in patients from indirect populations

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with botulinum toxin (95% CI)
Caregiver assessment of severity of sialorrhoea (2–9; higher is worse)	14 (1 study) 4 weeks	VERY LOW[a,b] due to risk of bias, indirectness	–	The mean carer-reported severity and frequency of sialorrhoea in the control groups was -1.9	The mean carer-reported severity and frequency of sialorrhoea in the intervention groups was 5.2 lower (6.03 to 4.37 lower)
Muscle weakness	14 (1 study) 4 weeks	VERY LOW[a,b] due to risk of bias, indirectness	–	Moderate	
				0 per 1000	See comment[c]

[a] 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
[b] Indirect population: children with cerebral palsy
[c] Absolute effect could not be calculated as zero events in both arms

Table 80: Clinical evidence summary: Glycopyrrolate versus placebo in patients from indirect populations

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with glycopyrrolate (95% CI)
Caregiver assessment of severity of sialorrhoea (1–9; higher is worse)	136 (3 studies) 4 days–8 weeks	LOW [b,c] due to indirectness, inconsistency	–	The median carer-reported severity of sialorrhoea in the control groups was 4.6	The mean carer-reported severity of sialorrhoea in the intervention groups was 2.28 lower (4.45 to 0.11 lower)[e]
Caregiver satisfaction with medication	37 (1 study) 8 weeks	VERY LOW[a,c,d] due to risk of bias, indirectness,	RR 1.76 (1.17 to 2.66)	Moderate	
				556 per 1000	423 more per 1000 (from 95 more to 923 more)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with glycopyrrolate (95% CI)
		imprecision			
Change in motor symptoms	46 (1 study) 4–7 days	VERY LOW[c,d] due to indirectness, imprecision	RR 0.75 (0.19 to 2.98)	Moderate	
				174 per 1000	43 fewer per 1000 (from 141 fewer to 345 more)
Discontinuation of medication due to side effects	104 (2 studies) 8 weeks	VERY LOW[a,b,c,d] due to risk of bias, inconsistency, indirectness, imprecision	RR 3.41 (0.75 to 15.56)	Moderate	
				44 per 1000	106 more per 1000 (from 11 fewer to 641 more)

[a] 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
[b] Downgraded by 1 increment because the point estimates varied widely across studies
[c] Downgraded by 1 increment if the evidence included an indirect population or by 2 increments if the evidence included a very indirect population
[d] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[e] Analysis conducted using random effects

Table 81: Clinical evidence summary: Benztropine versus placebo in patients from indirect populations

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with benztropine (95% CI)
Caregiver assessment of severity of sialorrhoea (Teacher drooling scale 1–9; higher is worse)	40 (1 study) 1–2 weeks	VERY LOW[a,b] due to risk of bias, indirectness	–	The mean drooling severity in the control groups was 3.53	The mean drooling severity in the intervention groups was 1.15 lower (1.68 to 0.62 lower)
Discontinuation of medication due to side effects	54 (1 study) <2 weeks	VERY LOW[a,b] due to risk of bias, indirectness,	Peto OR 7.99 (0.8 to	Moderate	
				0 per 1000	111 more per 1000 (from 21 fewer to 243

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with benztropine (95% CI)
		imprecision	80.28)		more)[c]

[a] 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
[b] The evidence included evidence from indirect populations
[c] Absolute effect calculated as data analysed using Peto OR

14.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 82: Unit cost of interventions for management of sialorrhoea

Intervention type	Intervention	Pharmaceutical form	Dose/quantity	Annual cost (£)	Source
Anticholinergic	Atropine (non-proprietary)	Tablet	0.6 mg per day	£310	NHS eDrug Tariff (accessed 10/7/14)
	Hyoscine butylbromide (branded)	Tablet (Buscopan)	40 mg per day	£44	NHS eDrug Tariff (accessed 10/7/14)
	Hyoscine hydrobromide (branded)	Transdermal patch (Scopoderm)	0.165 mg per day (equivalent to 0.5 mg over 72 hours)	£124	
	Glycopyrrolate (non-proprietary)	Powder for solution	3 mg (divided)	£97	BNF67
		Solution for injection	Two 0.2 mg injection per day	£37	DH CMU eMIT (accessed 10/7/14)
	Benztropine mesylate	–	–	–	No source of unit cost could be found
Tricyclic antidepressant (TCA)	Amitriptyline (non-proprietary)	Tablet	25 mg per day	£10	NHS eDrug Tariff (accessed 10/7/14)
		Oral solution	25 mg per day	£111	
Anti-hypertensive	Clonidine	Injection, tablet or patch or via gastrostomy	100 mg per day	£19	NHS eDrug Tariff (accessed 10/7/14)
Chemical neurolysis	Botulinum toxin (Type A)	Injection to gland	1 injection of 100 units every 12 weeks	£561	NHS eDrug Tariff (accessed 10/7/14)
	Botulinum toxin (Type B)	Injection to gland	1 injection of 2500 units every 12 weeks	£451	BNF67
Destruction of salivary glands	Radiotherapy	Simple radiotherapy	One-off	£330	NHS Reference costs database 2012–13
Surgical modification of salivary glands	Ligation of ducts, re-routing of ducts	Simple general surgery for MND with comorbidity	One-off	£293	NHS Reference costs database 2012–13

Intervention type	Intervention	Pharmaceutical form	Dose/quantity	Annual cost (£)	Source
		score 0–1			
Dietary modification	Avoid dairy, alcohol. Recommend fruit juice (red grape, pineapple), caffeine, high cocoa chocolate, papase/papaya.	Speech and language therapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013
Behavioural approaches	Advice on swallowing	Speech and language therapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013
Device	Portable suction pump		1 unit	£96	Supplier: Beaucare Medical
Postural advice	Patient/carer training	Community physiotherapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013
Oral care	Patient/carer training	Speech and language therapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013

Table 83: Unit cost of interventions for management of thick tenacious saliva

Intervention type	Intervention	Pharmaceutical form	Dose/quantity	Annual cost (£)	Source
Beta-blockers	Propranolol (non-proprietary)	Tablet	80 mg per day	£7	NHS eDrug Tariff (accessed 10/7/14)
	Metoprolol (non-proprietary)	Tablet	100 mg per day	£15	
Mucolytic	Carbocisteine (Branded)	Capsules	1500 mg per day	£231	NHS eDrug Tariff (accessed 10/7/14)
		Oral liquid	1500 mg per day	£241	
Protease enzyme	Bromelaine (non-prescription)	Tablet	500 mg per day	£53	Healthspan (Supplier)
Dry mouth spray	Bioxtra	Spray gel	5 mg per day	£254	ChemistDirect (Supplier)
Dietary modification	Avoid dairy. Recommend pineapple juice, caffeine, papase.	Speech and language therapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013

Intervention type	Intervention	Pharmaceutical form	Dose/quantity	Annual cost (£)	Source
Device	Humidification and nebuliser		1 unit	£5–£300	NHS Supply Chain catalogue, April 2014
	Portable suction pump		1 unit	£96	Supplier: Beaucare Medical
Postural advice	Patient/carer training	Community physiotherapist	1 hour per month	£659	PSSRU Unit costs of health and social care 2013

14.5 Evidence statements

Clinical

Botulinum toxin versus placebo

- One study compared botulinum toxin versus placebo in patients with MND. The evidence showed that there was a clinical benefit of botulinum toxin for patient and caregiver assessment of severity of drooling. There was no clinical difference between botulinum toxin and placebo for health-related quality of life, patient and caregiver assessment of saliva thickness, or patient function. The evidence was of Low or Very Low quality.
- Seven studies compared botulinum toxin versus placebo in patients from indirect populations. The evidence showed that there was a clinical benefit of botulinum toxin for impact of drooling on daily activities, patient perceived change in severity of drooling, patient satisfaction, and discontinuation of medication due to side effects. There was no clinical difference between botulinum toxin and placebo for patient assessment of severity of drooling, severity of dysphagia, and aspiration pneumonia. The evidence was of Moderate, Low or Very Low quality.

Botulinum toxin versus no treatment

- One study compared botulinum toxin versus no treatment in patients from indirect populations. The evidence showed that there was a clinical benefit of botulinum toxin for caregiver assessment of severity of drooling, and no clinical difference between botulinum toxin and no treatment for muscle weakness. The evidence was of Very Low quality.

Glycopyrrolate versus placebo

- Three studies compared glycopyrrolate versus placebo in patients from indirect populations. The evidence showed that there was a clinical benefit of glycopyrrolate for caregiver assessment of severity of drooling and caregiver satisfaction with medication. The evidence showed a clinical harm of glycopyrrolate for discontinuation of medication due to side effects. There was no clinical difference between glycopyrrolate and placebo for change in motor symptoms. The evidence was of Moderate or Very Low quality.

Benztropine versus placebo

- One study compared benztropine versus placebo in patients from indirect populations. The evidence showed that there was a clinical benefit of benztropine for caregiver assessment of severity of drooling, and a clinical harm of benztropine for discontinuation of medication due to side effects. The study was of Very Low quality.

Economic

- No relevant economic evaluations were identified.

14.6 Recommendations and link to evidence

Recommendations	**Saliva problems** **54. If a person with MND has problems with saliva, assess the volume and viscosity of the saliva and the person's respiratory function, swallowing, diet, posture and oral care. [new 2016]** **55. If a person with MND has problems with drooling of saliva (sialorrhoea), provide advice on swallowing, diet, posture, positioning, oral care and suctioning. [new 2016]** **56. Consider a trial of antimuscarinic medicine[b] as the first-line treatment for sialorrhoea in people with MND. [new 2016]** **57. Consider glycopyrrolate[b] as the first-line treatment for sialorrhoea in people with MND who have cognitive impairment, because it has fewer central nervous system side effects. [new 2016]** **58. If first-line treatment for sialorrhoea is not effective, not tolerated or contraindicated, consider referral to a specialist service for Botulinum toxin A[c]. [new 2016]** **59. If a person with MND has thick, tenacious saliva:** • **review all current medicines, especially any treatments for sialorrhoea** • **provide advice on swallowing, diet, posture, positioning, oral care, suctioning and hydration** • **consider treatment with humidification, nebulisers and carbocisteine. [new 2016]**
Research recommendation	**4. How is excessive drooling of saliva (sialorrhoea) managed in people with MND?**
Relative values of different outcomes	The GDG identified health-related quality of life, patient and carer reported outcomes (pain, symptoms, satisfaction) and aspiration pneumonia (in people with tenacious saliva) as critical outcomes in evaluating the clinical effectiveness of interventions for saliva control. Patient function, hospital admissions, and adverse effects of treatment (increased muscle weakness and side effects resulting in the discontinuation of the intervention) were identified as important outcomes. Patient- and carer-reported saliva thickness was reported by several of the studies included in the review, and decisions on clinical benefit or harm of this outcome were made on a case-by-case basis. For evaluating the effectiveness of interventions for tenacious saliva, a reduction in saliva thickness was considered to be a clinical benefit. The primary outcome for assessing interventions for sialorrhoea (drooling of saliva) was a

[b], [c] At the time of publication (February 2016), these medicines did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

	reduction in volume. Therefore in this population, no change in saliva thickness, or change that did not produce tenacious saliva or sialorrhoea, was considered to be of clinical benefit.
Trade-off between clinical benefits and harms	Evidence from indirect populations was included due to the scarcity of evidence available in people with MND. The GDG identified people with Parkinson's disease, cerebral palsy, spinal muscular atrophy and multiple system atrophy as indirect populations for evaluating treatments for sialorrhoea. The GDG considered that these populations experienced problems with saliva management due to a similar mechanism as people with MND (that is, due to dysphagia). **Sialorrhoea** The only direct evidence in an MND population was 1 trial of botulinum toxin versus placebo. The results were mixed, with one outcome favouring botulinum toxin and others showing no clinical difference between the two. There was more evidence in indirect populations and 15 studies were included in the review. These studies covered 4 comparisons: botulinum toxin versus placebo, botulinum toxin versus no treatment, glycopyrrolate versus placebo, benztropine versus placebo. Seven studies evaluated botulinum toxin versus placebo and the results were more positive than the direct evidence with a clinical benefit of botulinum toxin for 4 outcomes including impact of drooling on daily activities. However, there were still 4 outcomes where there was no difference between the two treatments. The other evidence around botulinum toxin was in 1 study where it was compared to no treatment. The results were more positive again, showing botulinum toxin improves caregiver assessment of drooling while not causing muscle weakness. However, this study should be treated with caution because it uses a "no treatment" group and this does not account for the placebo effect. Three studies that compared glycopyrrolate versus placebo and 1 study of benztropine versus placebo found both drugs to be effective for caregiver assessment of severity of drooling. However, a clinically significant number of patients discontinued the treatments due to side effects. **Tenacious saliva** No studies were identified on the management of tenacious saliva in direct or indirect populations.
Trade-off between net health effects and costs	No economic evidence was identified for sialorrhoea or tenacious saliva. Unit costs of interventions were considered by the GDG. The costs of included interventions were generally low. As the number of individuals requiring these interventions is small, the economic impact of selecting an intervention for tenacious saliva or sialorrhoea is likely to be minimal. Although there is clinical experience of side effects of anticholinergic drugs, these do have a lower cost compared to botulinum toxin for which clinical evidence was available. The GDG decided to recommend anticholinergic medication as the treatment of first choice. Where the first choice treatment has not worked, botulinum toxin was considered to be a possible option; health benefits shown by the clinical review were thought to justify its acquisition and administration cost.
Quality of evidence	The quality of the evidence varied from Moderate to Very Low. All outcomes from the direct evidence (1 trial comparing botulinum toxin versus

	placebo), were graded Low or Very Low. This was due to risk of bias and imprecision. The GDG expressed concerns over the quality of the study and therefore chose to also consider evidence on the use of botulinum toxin in other relevant indirect populations. The rest of the evidence was in indirect populations and all of the outcomes were downgraded by 1 increment accordingly. The outcomes for the indirect evidence of botulinum toxin versus placebo ranged from Moderate to Very Low. In addition to indirectness, some outcomes were downgraded for risk of bias and/or imprecision. All other outcomes for the other 3 comparisons (botulinum toxin versus no treatment, glycopyrrolate versus placebo and benztropine versus placebo) were consistently graded Low (1 outcome) or Very Low (7 outcomes). In addition to indirectness, some outcomes were downgraded for risk of bias and/or imprecision and/or inconsistency. No evidence was identified on the management of tenacious saliva in a direct or indirect population.
Other considerations	The GDG recognised that problems related to saliva can be significant and distressing for people with MND. The GDG highlighted that the relationship between saliva management, swallowing difficulties and respiratory impairment is complex and requires careful assessment by an appropriately trained MDT. It is important to assess and manage saliva, especially sialorrhoea, because over-management of sialorrhoea may result in the development of tenacious saliva. The GDG considered that assessment of volume, colour and viscosity of saliva, and respiratory function, swallowing, diet, posture and oral care were important for all people with saliva problems. In addition to the pharmacological treatment, the GDG agreed that advice should be given on swallowing, diet, posture, positioning, oral care and suctioning to people with sialorrhoea**.** **Tenacious saliva** No studies were identified on the management of tenacious saliva. The GDG therefore developed a recommendation for people with MND who have tenacious saliva using informal consensus. Dietary modifications, such as avoiding dairy and consuming pineapple juice, caffeine and papase, have been reported as being beneficial for some people who have MND and tenacious saliva. Some people will have tenacious saliva as an adverse effect of drug treatments, including treatment for sialorrhoea, and assessment of whether current medications are contributing to the problem is a first step. Advice on suctioning and hydration may be helpful. Given the lack of available evidence, the GDG were unable to recommend specific pharmacological treatment. As well as advice on swallowing, diet, posture and hydration, the GDG considered that humidification and the use of nebulisers, and carbocisteine, can be helpful. The GDG highlighted that beta blockers are not widely used in current practice for the purposes of tenacious saliva management. **Sialorrhoea** The GDG considered that advice on swallowing, diet, posture, positioning, oral care and suctioning can be helpful for people with sialorrhoea. The GDG recommended a trial of antimuscarinic medication as first-line treatment for the management of sialorrhoea. The GDG noted that antimuscarinic medication is available on prescription and is less invasive than other treatments (for example, botulinum toxin), making it preferable as a first-line treatment. However, whilst no evidence was identified to suggest that the use of antimuscarinic medication causes the development of side effects, these drugs are known to cause side effects and may

	not be effective or well tolerated. The formulation of the medication may need to be considered: liquid preparations or transdermal patch would be more appropriate if there are swallowing difficulties. The GDG noted that other medications are widely used within current clinical practice and may be beneficial for the needs of specific individuals, for example amitriptyline because of its sedative properties. The GDG noted that confusion may be a side effect of hyoscine, and recommended that centrally acting antimuscarinic medication is not used in patients with cognitive impairment. Glycopyrrolate should be considered instead in this situation. The evidence review included studies evaluating botulinum toxin. Whilst this intervention is a possibility, the GDG did not consider it usual practice. They did think however that assessment by a specialist who can perform this may be appropriate for some people with MND and sialorrhoea. No evidence was identified for the destruction of salivary glands by radiotherapy and the GDG considered this to be a radical therapeutic option suitable only in rare individual cases. **Research recommendation** The GDG developed a high-priority research recommendation for saliva management in people with MND. They considered that an initial study collecting information on current practice was essential as a baseline from which to develop comparative studies. For further details please see Appendix N: Research recommendations.

15 Equipment and adaptations to aid activities of daily living and mobility

15.1 Introduction

People with MND have multiple functional problems and may therefore have complex equipment needs. Since MND is a progressive disorder the need for aids and adaptations will change over time. This chapter presents the qualitative evidence found in the provision of equipment for people with MND. The aim of the review was to explore people's experience of equipment, and the recommendations are based on this and on the experience of the GDG. There is overlap between this Section of the guideline and the evidence reviews and recommendations for social care (Section 11.6) and communication (Section 18.6).

15.2 Review question: What are the equipment needs of people with MND for improving mobility and fulfilling activities of daily living due to muscle weakness?

For full details see the review protocol in Appendix C.

Table 84: PICO characteristics of review question

Population	Adults (aged 18 and over) with MND
Intervention(s)	Interventions: • 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 • Braces or splints • Walking aid (stick or frame) • Assistive technology devises including environmental controls, personal alarms, telecare/ health systems • Home adaptations including wheelchair access, access to all facilities
Comparison(s)	N/A
Outcomes	• These would emerge from the qualitative review • Patient-reported requirements
Study design	Order of preference for study designs for each intervention: • Systematic reviews of qualitative studies • Interviews or surveys of people with MND 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.

We looked for qualitative evidence to establish what equipment MND patients feel they require to improve their mobility and to fulfil activities of daily living, which may be impaired due to muscle weakness.

15.3 Clinical evidence

Two studies were included in the review;[52,104] these are summarised in Table 85 below. Themes identified from the studies are summarised in Table 86. Key findings from these studies are summarised in the modified clinical evidence summary table (Table 87). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 85: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Surveys				
Gruis 2011[51,52]	Surveys	People with MND; USA study	To understand patients' self-reported satisfaction with various types of assistive technology.	
Peters 2009[104,104]	Surveys	People with MND – primary lateral sclerosis; USA study	To establish the needs for support services for people with primary lateral sclerosis.	

Evidence

Table 86: Themes and sub-themes

Main theme	Sub-themes
Devices	Frequency of use of devices
	How well devices worked/satisfaction with devices
	Assistance with activities of daily living

Table 87: Theme 1 – Devices

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
Sub-theme 1: Frequency of use of devices					
(Gruis 2011)[52];Peters (2009)[104]	Survey	Devices used most often by 20–55% of respondents were: 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 (Gruis 2011)[52]. Peters (2009)[104] found all people with primary lateral sclerosis (PLS) in their study used some form of gait assistance device (cane, walker or wheelchair).	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 2: How well devices worked/satisfaction with devices					
(Gruis 2011)[52]	Survey	The ankle brace, transfer board, all bathroom devices, slip-on shoes, speaker phone and electronic seating controls were used frequently and had a high or very	Applicability of evidence	Applicable[a]	Adequate
			Theme	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		high median rating for how well they worked or the satisfaction people had with the devices. Walkers, motorised wheelchairs, personal digital assistants (PDAs), laptop computers had high median ratings for how well the devices worked but low satisfaction scores with them. Motorised scooters, letter, work or picture boards, electronic bed controls and sound or voice-activated environmental controls were used less often but had a very high rating for how they worked and satisfaction. Button hook, dressing stick with hook, and long-handled reaching tool had low or very low median ratings of usefulness and satisfaction.	saturation/sufficiency		
Sub-theme 3: Assistance with activities of daily living					
Peters (2009)[104]	Survey	Looked at how many people required assistance: 76% required mobility assistance, 40% household help with chores such as cleaning, 36% help with cooking, 32% help with dressing/personal hygiene, 12% speech assistance, 4% ventilator assistance. However the type of equipment they required was not investigated.	Applicability of evidence	Applicable[a]	Adequate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

15.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

In the absence of recent UK cost-effectiveness analysis, examples of the relevant typical unit costs are provided to aid consideration of cost-effectiveness.

Costs of wheelchairs and training to use them

Wheelchairs may have multiple users over their reported 5 years of useful life. All wheelchairs should be maintained on a regular basis.

A physiotherapist or occupational therapist is required to assess the chair and train the patient/carer. Staff may typically be Agenda for Change Band 6 or 7, may require 1 hour for assessment, and provide up to 4 one-hour sessions of training.

The annualised cost of wheelchair provision is shown in Table 88.

Table 88: Unit costs of equipment

Type	Estimated unit cost[a] (range)	Annual maintenance cost	One-off cost of training[c]	Annualised total cost for a single patient
Manual (self or attendant propelled)	£270 (£100–£650)	£60	£238 (£215–£260)	£89
Active user[b]	£673	£149	£238 (£215–£260)	£178
Powered	£1,345 (£700–£3,000)	£298	£238 (£215–£260)	£412

Source: PSSRU Handbook 2013.[25,26]

(a) Represents capital cost of wheelchair; the expected life of a new chair is 5 years

(b) Active users require a lighter type of chair designed for individuals who are permanently restricted to a wheelchair but are otherwise well and have high mobility needs

(c) Training costs are based on 5 hours of per patient from an AfC band 6 hospital based physiotherapist or occupational therapist (lower end of range), or an AfC Band 7 community-based physiotherapist or occupational therapist (higher end of range). Hourly cost of staff is from the PSSRU Handbook 2013. [25,26]

Simple aids of daily living (SADL)

The unit costs of simple aids of daily living used are given in Table 89.

Table 89: The unit costs of simple aids of daily living (SADL)

SADL item	Typical range in cost
Walker[a]	£26–£147
Ankle brace[a]	£9–£188
Sliding transfer board[a]	£14–£538
Modified eating utensils (kettle tipper, plate guard, non-spill	£2–£28

SADL item	Typical range in cost
mug)[a]	
Wrist brace[a]	£28–£37
Head support/rest[b]	£48–£71
Toilet frame and seat[a]	£30
Adjustable shower chairs[c]	£14–£148
Mobile shower chair[c]	£55
Speaker phone[c]	£19
Variety of indoor and outdoor grab rails[c]	£3–£91
Walking sticks[c]	£22–£54

Source:
(a) Gruis et al.[52]
(b) NHS Supply chain catalogue 2013 [1]
(c) PSSRU Handbook 2013 [25,26]

Complex aids of daily living (CADL)

The unit costs of simple aids of daily living used are given in Table 90. Costs of installation and regular servicing are not included in these estimates.

Table 90: Unit costs of CADLs

CADL item	Typical range in cost
Mobile seat hoists (powered)	£2,505–£5,821
Variable posture beds	£626–£8,541
Lifting cushions	£1,019–£1,646
Backrests with pressure relieving features	£351–£650

Source: PSSRU Handbook 2013[25,26]

Home adaptations

Example costs of commonly used NHS-provided home adaptations were obtained from a GDG member. These costs (Table 91) are for the equipment or work carried out and do not include ongoing maintenance, insurance for equipment or cost of occupational therapist case services.

Table 91: Unit costs home adaptations

Adaptation	Typical cost
Lift	£12,000–£32,500
Internal door widening	£250
External door widening	£1,000
Threshold lowering	£850
Remote control of environment (depending on extent)	£900–£6,850
Infrared remote dimmer switch	£42
Infrared automatic door opener	£1,595

Source: Costs were supplied by a member of the GDG

15.5 Evidence statements

Clinical

- One study found that devices used most often were walker, motorised wheelchair, ankle brace, sliding transfer board, writing on paper to communicate, laptop computer, 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.
- One study found ankle brace, transfer board, all bathroom devices, slip-on shoes and speakerphone were used frequently and had high or very high ratings for how well they worked and satisfaction. Walkers, motorised wheelchairs, PDAs, laptop computers had high ratings for how well they worked but low satisfaction scores. Button hooks, dressing stick with hook and long-handled reaching tool had low or very low ratings for how well they worked and satisfaction.
- One study found that almost all patients with PLS required gait assistive devices (a cane, walker or wheelchair) over a long period of time. 76% required mobility assistance and others required help with household tasks (40%), cooking (36%), dressing/personal hygiene (32%), speech assistance (12%), ventilator assistance (4%).

Economic

- No relevant economic evaluations were identified.

15.6 Recommendations and link to evidence

Recommendations	**Equipment and adaptations to aid activities of daily living and mobility** **60. Healthcare professionals and social care practitioners, which will include physiotherapists and occupational therapists, should assess and anticipate changes in the person's daily living needs, taking into account the following:** • **Activities of daily living, including personal care, dressing and bathing, housework, shopping, food preparation, eating and drinking, and ability to continue with current work and usual activities.** • **Mobility and avoiding falls and problems from loss of dexterity.** • **The home environment and the need for adaptations.** • **The need for assistive technology, such as environmental control systems. [new 2016]** **61. Provide equipment and adaptations that meet the person's needs without delay, so that people can participate in activities of daily living and maintain their quality of life as much as possible. [new 2016]** **62. Refer people to specialist services without delay if assistive technology such as environmental control systems is needed. People should be assessed and assistive technology provided without delay. [new 2016]** **63. Refer people to wheelchair services without delay if needed. Wheelchair needs should be assessed and a manual and/or powered wheelchair that meets the person's needs should be provided without delay. [new 2016]**

	64. Ensure that equipment, adaptations, daily living aids, assistive technology and wheelchairs meet the changing needs of the person and their family and/or carers (as appropriate) to maximise mobility and participation in activities of daily living. [new 2016] **65. Ensure regular, ongoing monitoring of the person with MND's mobility and daily life needs and abilities as their disease progresses. Regularly review their ability to use equipment and to adapt equipment as necessary. [new 2016]** **66. Healthcare professionals, social care practitioners and other services providing equipment should liaise to ensure that all equipment provided can be integrated, for example, integrating AAC aids and devices and environmental control systems with wheelchairs. [new 2016]** **67. Enable prompt access and assessment for funding for home adaptation. If the person is not eligible for funding, continue to offer information and support in arranging home environment adaptations. [new 2016]**
Relative values of different outcomes	The equipment required by people with MND in order to aid their mobility and activities of daily living was noted as an important outcome. This was explored through a qualitative analysis.
Trade-off between clinical benefits and harms	One study found that ankle brace, transfer board, all bathroom devices, slip-on shoes and speakerphone were used frequently and had high or very high ratings for how well they worked and for satisfaction. Walkers, motorised wheelchairs, PDAs and laptop computers had high ratings for how well they worked but low satisfaction scores. Button hooks, dressing stick with hook and long-handled reaching tool had low or very low ratings for how well they worked and for satisfaction. A second study found that almost all patients with PLS required gait assistive devices (a cane, walker or wheelchair) over a long period of time.
Trade-off between net health effects and costs	No cost-effectiveness evidence was identified for this question. The GDG considered the unit costs of equipment. It was concluded however that people have different needs and it was not possible to establish the cost-effectiveness of individual interventions for the general population with MND as cost-effectiveness would differ significantly on a per-person basis. The GDG considered that the provision of appropriate equipment resultant from a timely assessment would reduce overall costs as it is likely to minimise risk of adverse events, such as falls and equipment wastage. Equipment wastage can result from poor assessment leading to the ordering of unsuitable equipment, or a delay in provision such that by the time the equipment is available the disease has progressed and the equipment is no longer suitable or required. Therefore, the timing of the needs assessment was considered to be crucial for providing equipment in a cost-effective manner. It was also felt important to ensure that equipment is flexible and can be adapted as the person's abilities progress, without the need for multiple provision of equipment. The GDG noted that providing equipment was also associated with the additional cost of training and support for patients and carers by appropriate health and social care professionals. Finally, the GDG felt that the provision of equipment would have substantial health benefits for both the individual with MND and also the carer. These health benefits,

	along with the potential cost-savings, would make suitable equipment provision cost-effective. The GDG felt the crucial aspect was the appropriate monitoring and timely access to equipment that would maximise health benefits and increase cost-savings.
Quality of evidence	No directly relevant evidence was found. The GDG considered 2 qualitative studies: 1 study at high risk of bias and 1 study at very high risk of bias. One study included patients with PLS (Peters, 2009)[104,104] and the other study (Gruis, 2011)[51,52] included patients with ALS. These studies explored what equipment was used most often, how well the equipment worked and the individual's satisfaction with the equipment. The methodological quality of each study was assessed using NCGC-modified NICE checklists and the quality of the evidence was assessed by a modified GRADE approach for each outcome.
Other considerations	The recommendations were developed using the evidence and the experience of the GDG. There is overlap with the evidence and recommendations in Section 11.6 on social care. The therapists involved in the assessment and provision of equipment, such as physiotherapists and occupational therapists, may be employed by health or social care, and work in hospital and/or community settings. Both the assessment for and provision of equipment may involve the coordination of various health and social care professionals across these divisions. Although the assessment and provision of equipment will be individual to each person, the GDG considered that there are some types of equipment that specifically benefit people with MND. These include: mobile arm supports to aid feeding (and in some instances to assist with accessing communication aids), riser recliner arm chairs to support posture and improve mobility (for example sitting to standing), ankle foot orthosis (AFO) to help with walking, collars (for head support), and specialist manual and/or powered wheelchairs. It was acknowledged that the provision of equipment in a timely manner maximises the impact of the device on the person's quality of life, allowing them to continue with work or usual activities and could reduce adverse events, such as falls and hospital admission. The GDG considered that there are particular issues relevant to the provision of aids and equipment for people with MND. The disease is progressive over a short period of time and can affect all muscle groups. This is in contrast to deficits such as after a stroke, where the deficit is not expected to change. This means that assessment for and provision of equipment should take into consideration the needs of the person as they are likely to develop, that equipment is needed without delay, and that people will be using multiple aids that need to be integrated. Both people with MND and their carers should be trained in the use of any equipment. Monitoring should assess changing needs and the need to alter or adapt equipment. The GDG recognised that cognitive changes in people with MND may not always be known during the assessment for equipment. This possibility is an additional pointer to the need for continual assessment to ensure that people with MND have the right equipment for them and for the stage of progression of the disease. In addition, the GDG highlighted that there is a need (where possible) to ensure that equipment can be adapted to cope with progression in the person's needs. Home adaptation may be necessary and people should be provided with information and support for speedy assessment and access to available funding streams. People with MND may deteriorate rapidly and any adaptations need to be done without delay. Not all those who require household adaptations will be eligible for public funding, but are likely to require continuing advice from health and social care practitioners. The GDG noted that social care practitioners have a particular role in assessing the person's home environment and providing appropriate aids and home

	environment adaptations. An example of the need for coordination between professionals and services is the use of a wheelchair. For the most effective use of a wheelchair, wheelchair ramps for access to the home, and other home adaptions such as bathroom modifications and the installation of environmental controls, are necessary. The wheelchair is of less use if communication aids cannot be mounted on it, because the person's independence and quality of life is limited despite the provision of the wheelchair.

16 Nutrition

16.1 Introduction

People with MND can develop difficulties in feeding and swallowing. These develop because of the effect of MND on muscle function and can result in people with MND suffering from lack of adequate nutrition. This may be indicated by weight loss. Some weight loss is however characteristic of MND because of muscle wasting and this will not be prevented by dietary intervention. This chapter focusses on interventions other than gastrostomy. NICE has developed a clinical guideline on Nutrition support in adults (CG32) which covers the care of patients with malnutrition or at risk of malnutrition, whether they are in hospital or at home.

16.2 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?

For full details see the review protocol in Appendix C.

Table 92: PICO characteristics of review question

Population	• Adults (aged 18 and over) with MND Strata: • 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 Strata: • People with cognitive impairment including frontotemporal dementia
Intervention(s)	• 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(s)	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 (EQ-5D, SF-36, SF-12) • Patient/carer reported outcomes (functioning[for example ALSFRS], satisfaction) • Survival • Change in nutritional status (Malnutrition Universal Screening Tool [MUST]; change in BMI and % weight loss; skin fold thickness, including tricep skin fold thickness [TSFT], bio-impedance, mid-upper arm circumference [MUAC]) Important:

	• Hospital admissions
Study design	RCTs or systematic reviews of RCTs Abstract of RCTs or cohort studies (sample size=20) MND populations only will be considered given the metabolic change which would affect our ability to extrapolate from other populations.

16.3 Clinical evidence

Two studies were included in the review;[36,115] these are summarised in Table 93 below. Evidence from these studies is summarised in the GRADE clinical evidence summary tables below (Table 94 and Table 95). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 93: Summary of studies included in the review

Study	Intervention /comparison	Population	Outcomes	Comments
Dorst 2013[36]	High fat content versus high carbohydrate content supplements	ALS patients who had previously lost body weight; BMI at start was median 24.2 (19.4–33.9) in the high fat content group and median 28.1 (17.6–38.5) in the high carbohydrate group. Overall median 25.5 (17.6–38.5). The study aimed to stabilise the weight of those who had previously lost weight.	Change in body weight; change in BMI; diarrhoea.	More patients had bulbar onset in the high carbohydrate group; BMI was lower in the high fat group at baseline and there was longer disease duration in the high fat content group. No details as to whether these were significant.
Silva 2010[116,115]	Milk whey proteins supplementation versus maltodextrin	ALS patients with mean BMI 21.7 (+/- 0.4), (range 18.12–27.03) in the intervention group and mean BMI 22.9 (+/-0.4) (range 17.2–26.9) in the control group.	Change in body weight; change in BMI; change in tricipital skinfold thickness (TSFT); change in mid-arm muscle circumference; change in ALSFRS-R.	Higher fat content in the supplement group but no details as to whether these were significant.

Table 94: Clinical evidence summary: High fat content versus high carbohydrate content

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with high fat content versus high carbohydrate content (95% CI)
Weight gain (kg/month)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	0.28	The mean weight gain in the intervention groups was 0.24 higher (0.08 to 0.4 higher)
Change in BMI	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	0.18	The mean change in BMI in the intervention groups was 0.42 higher (0.62 lower to 1.46 higher)
Diarrhoea	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.39 (0.15 to 372.38)	Moderate	
				0 per 1000	130 more per 1000 (from 160 fewer to 410 more)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 95: Clinical evidence summary: Milk whey protein supplement versus maltodextrin (control group)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with milk whey protein supplementation versus maltodextrin (95% CI)
Change in weight (at 4 months)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[2]	–	Median 1.1 kg increase in intervention group and 1.5kg decrease in control group
Change in BMI (at 4 months)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[2]	–	Median 0.2 kg/m^2 increase in intervention group and 0.7kg/m^2 decrease in control group

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with milk whey protein supplementation versus maltodextrin (95% CI)
Change in TSFT (mm) (at 4 months)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[2]	–	Median 0.9 mm increase in intervention group and 1.5 mm increase in control group
Change in mid-arm muscle circumference MAMC (cm) (at 4 months)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[2]	–	Median 0.7 cm decrease in intervention group and 1.4 cm decrease in control group
Change in ALSFRS-R (at 4 months)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	Not estimable[2]	–	Median 2.1 decrease in ALSFRS-R scale in the intervention group and 3.4 decrease in ALSFRS-R scale in the control group

[a] 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
[b] Could not calculate imprecision as results given as medians

16.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

16.5 Evidence statements

Clinical

- Very Low quality evidence from 1 RCT comprising 16 participants found no clinical benefit of high fat content compared to high carbohydrate for weight gain (kg/month) and change in BMI. The evidence was at very serious risk of bias and serious imprecision.
- Very Low quality evidence from 1 RCT comprising 16 participants found a clinical harm of high fat content compared to high carbohydrate content for diarrhoea. The evidence was at very serious risk of bias and very serious imprecision.
- Very Low quality evidence from 1 RCT comprising 16 participants found a clinical benefit of milk whey protein compared to maltodextrin for change in weight and BMI at 4 months. The evidence was at very serious risk of bias and very serious imprecision.
- Very Low quality evidence from 1 RCT comprising 16 participants found no clinical difference for milk whey protein compared to maltodextrin for change in TSFT, change in MAMC, change in ALSFRS-r at 4 months. The evidence was at very serious risk of bias and very serious imprecision.

Economic

- No relevant economic evaluations were identified.

16.6 Recommendations and link to evidence

Recommendations	**Nutrition** **Please also refer to the recommendations in NICE's guideline on nutrition support in adults.** **68. At diagnosis and at multidisciplinary team assessments, or if there are any concerns about weight, nutrition or swallowing, assess the person's weight, diet, nutritional intake, fluid intake, hydration, oral health, feeding, drinking and swallowing, and offer support, advice and interventions as needed. [new 2016]** **69. Assess the person's diet, hydration, nutritional intake and fluid intake by taking into account:** • **fluids and food intake versus nutritional and hydration needs** • **nutritional supplements, if needed** • **appetite and thirst** • **gastrointestinal symptoms, such as nausea or constipation** • **causes of reduced oral intake (for example, swallowing difficulties,**

	limb weakness or the possibility of low mood or depression causing loss of appetite). [new 2016] **70. Assess the person's ability to eat and drink by taking into account:** • **the need for eating and drinking aids and altered utensils to help them take food from the plate to their mouth** • **the need for help with food and drink preparation** • **advice and aids for positioning, seating and posture while eating and drinking** • **dealing with social situations (for example, eating out). [new 2016]** **71. Arrange for a clinical swallowing assessment if swallowing problems are suspected. [new 2016]** **72. Assess and manage factors that may contribute to problems with swallowing, such as:** • **positioning** • **seating** • **the need to modify food and drink consistency and palatability** • **respiratory symptoms and risk of aspiration and/or choking** • **fear of choking and psychological considerations (for example, wanting to eat and drink without assistance in social situations). [new 2016]**
Research recommendation	**5. Does a high calorific diet prolong survival of people with MND if initiated following diagnosis or following initiation of feeding using a gastrostomy?**
Relative values of different outcomes	Health-related quality of life; patient/carer reported outcomes (functioning [for example ALS-FRS], satisfaction); survival; and change in nutritional status, including Malnutrition Universal Screening tool, change in BMI and % weight loss, skin fold thickness (including triceps skin fold thickness [TSFT], bio-impedance, mid-upper arm circumference [MUAC]), were identified as critical outcomes. Hospital admissions were an important outcome.
Trade-off between clinical benefits and harms	One Very Low quality RCT showed no clinical benefit of high fat supplements compared to high carbohydrate supplements for weight gain or increase in BMI. The study demonstrated clinical harm of high fat supplements for diarrhoea compared to high carbohydrate supplements. One Very Low quality RCT demonstrated no clinical benefit of milk whey protein supplement versus maltodextrin (control group) for increase in weight and BMI. The study also demonstrated no clinical benefit of maltodextrin versus milk whey protein for change in triceps skin fold thickness (TSF), mid-arm muscle circumference (MAMC), and the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).
Trade-off between net health effects and costs	No relevant economic evaluations were identified. The GDG recognised there would be an additional cost involved in providing a nutritional assessment as part of the MDT assessment. Providing this assessment ensures that the individual's nutritional management is appropriate and tailored to them, thus improving the efficacy of any intervention provided. The cost of this assessment is therefore justified by improving

	health outcomes and preventing unsuitable interventions from being prescribed.
Quality of evidence	Two RCT studies were included in the review. One study compared high fat content versus high carbohydrate content supplements and was graded as Very Low quality. The other study compared milk whey protein supplementation versus maltodextrin (placebo), and was also graded as Very Low quality.
Other considerations	The GDG used their expertise to develop consensus recommendations. On the basis of clinical experience and evidence that weight loss is a poor prognostic sign, the GDG commented that the maintenance of a person's weight may prolong survival. The GDG wished to highlight that MND is a disease which changes rapidly, and as such it is important to assess hydration, feeding ability, swallowing and nutritional factors, including intake, at every possible opportunity to prevent weight loss. The GDG developed a recommendation to highlight the need for regular assessment of an individual's weight to ensure that weight is maintained and weight loss prevented. The GDG agreed that the ability to feed and swallow should be considered at diagnosis and at each subsequent review. The GDG did not wish to include the use of BMI within the recommendations. They considered that measurements of weight and height can be difficult in people with MND and therefore preferred to mention weight only, rather than mandating measurement of height for BMI calculation. When considering diet, the GDG recognised that although the available evidence showed no benefit of supplements, food supplementation may be useful for some people and should be considered on an individual basis following a nutritional assessment. The GDG identified that it was preferable to increase calorie intake by enriching food, for example adding butter to mashed potato, instead of providing food supplements. They acknowledged that there is a particular difficulty with this when a person is reliant on a care package, as this is not the way in which food is provided. The GDG acknowledged the quality of life issues associated with fluids and nutritional intake for people with MND, and emphasised the importance of considering a wide variety of factors when conducting a nutritional and fluid assessment, in particular the palatability of food, appetite, thirst and psychological issues. People with MND can have difficulty in feeding and drinking due to muscle weakness and may require feeding and aids, altered utensils and adaptations to help positioning. The GDG noted that poor oral care may contribute to difficulties in feeding, and suggested that oral health should be included in overall assessments. Swallowing problems are common in MND and formal assessment from a speech and language therapist is required to assess this. However, swallowing may also be affected by positioning, the consistency of food and resultant palatability, breathing problems and fear of choking. The GDG recognised that there are particular nutrition management issues for people with MND and frontotemporal dementia. One of the problems can be the tendency to gorge on food. People with cognitive problems may also not understand the potential risk of choking with certain foods and carers may have significant difficulty in controlling these behaviours. The GDG were cognisant of the fact that gastrostomy may be part of a person's

	disease management, and that where appropriate, clinicians should consider referral for gastrostomy within the risk assessment aspect of a nutritional and hydration assessment. See Section 17.6 for discussion and recommendations about gastrostomy. The NICE Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition guideline (CG32) provides general details on the provision of care for those who require nutritional support. This guidance should be taken into consideration when adhering to the recommendation for people with MND. **Research recommendation** The GDG agreed that there is little specific guidance on the optimal calorie intake for people with MND and decided to make a high-priority research recommendation to assess whether a high calorific diet prolongs survival. The research would be stratified into 2 key time points where nutrition can be modified to most effect: the period following diagnosis and the period following initiation of feeding using a gastrostomy. In the future this research will inform and modify these consensus-based recommendations. For further details please see Appendix N: Research recommendations.

17 Gastrostomy

17.1 Introduction

A gastrostomy is a surgical opening through the abdomen into the stomach. A feeding device is inserted through this opening whereby artificial feeds are directly inserted into the stomach, bypassing the mouth and throat. During the progression of their disease, people with MND may face nutritional deficiency due to swallowing difficulties and increasing difficulty in feeding themselves. As a result, gastrostomy is commonly considered as an intervention to support the person with MND to meet their nutritional requirements. This chapter examines the appropriate timing of gastrostomy in people with MND. The NICE guideline (CG32) on Nutrition support in adults includes recommendations on other aspects of enteral feeding.

17.2 Review question: What is the clinically appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND?

For full details see the review protocol in Appendix C.

Table 96: PICO characteristics of review question

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 • Patient/carer reported outcomes (symptoms, satisfaction) • Hospital readmissions 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
Study design	Cohort studies
Key confounders	Time since symptom onset

The purpose of this review was to identify the clinically appropriate timing of performing a gastrostomy for patients with MND with respect to 3 key clinical prognostic markers: severity of dysphagia, weight loss, and respiratory function. Previous research has demonstrated that these 3 factors predict patient outcome following gastrostomy, with a poorer clinical outcome associated with poorer respiratory function, dysphagia, and greater weight loss prior to the procedure. However in practice, there is still uncertainty about when gastrostomy should be performed to optimise patient outcomes. To address this question, this prognostic review sought to identify existing research that has examined the relationship between each risk factor and outcomes specified in the protocol following gastrostomy. Rather than investigating whether or not a risk factor was associated with the outcome (that is, the presence of a statistically significant relationship between a risk factor and the outcome), this review sought to identify a threshold for each risk factor at which point

outcomes following gastrostomy become unacceptably poor. Accordingly, where studies assessed risk factors as a continuous measure, we sought to extract regression coefficients to calculate the risk of a poor outcome associated with increasing severity of the risk factor. Where studies assessed risk factors as a dichotomous measure, we sought to calculate the relative risk for each comparison, and compare these qualitatively across studies with more/less severe cut-off values for each risk factor. While there may be some correlation between the 3 risk factors specified in the protocol, the presence or absence of these symptoms will vary widely across this patient group, and clinicians may need to consider all 3 risk factors when making a decision about the appropriate timing of gastrostomy. As a consequence, the review sought to include studies that included 1 or more of the risk factors in their analysis. However, as a strong negative correlation was expected between the time since symptom onset and several of the outcomes in the review (time to death and health-related quality of life), studies were excluded if they did not include the time since symptom onset as a covariate in their analysis, or if this factor was not balanced across groups where a dichotomous cut-off for the risk factor was used.

17.3 Clinical evidence

No clinical evidence was identified.

17.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

17.5 Evidence statements

Clinical

- No relevant clinical studies were identified.

Economic

- No relevant economic evaluations were identified.

17.6 Recommendations and link to evidence

Recommendations	**73. Discuss gastrostomy at an early stage, and at regular intervals as MND progresses, taking into account the person's preferences and issues, such as ability to swallow, weight loss, respiratory function, effort of feeding and drinking and risk of choking. Be aware that some people will not want to have a gastrostomy. [new 2016]** **74. Explain the benefits of early placement of a gastrostomy, and the possible risks of a late gastrostomy (for example, low critical body mass, respiratory complications, risk of dehydration, different methods of insertion, and a higher risk of mortality and procedural complications). [new 2016]** **75. If a person is referred for a gastrostomy, it should take place without**

	unnecessary delay. [new 2016] **76. Pay particular attention to the nutritional and hydration needs of people with MND who have frontotemporal dementia and who lack mental capacity. The multidisciplinary team assessment should include the support they need from carers, and their ability to understand the risks of swallowing difficulties. [new 2016]** **77. Before a decision is made on the use of gastrostomy for a person with MND who has frontotemporal dementia, the neurologist from the multidisciplinary team should assess the following:** • **The person's ability to make decisions and to give consent[d].** • **The severity of frontotemporal dementia and cognitive problems.** • **Whether the person is likely to accept and cope with treatment.** **Discuss with the person's family members and/or carers (as appropriate; with the person's consent if they have the ability to give it). [new 2016]**
Relative values of different outcomes	The GDG identified health-related quality of life, patient/carer reported outcomes (symptoms, satisfaction), hospital readmissions and unplanned admissions, time to death, and mortality related to procedure as critical outcomes. Nutritional status (Malnutrition Universal Screening Tool, % change in weight loss, change in BMI) and hospital length of stay were identified as important outcomes.
Trade-off between clinical benefits and harms	Placing a gastrostomy could potentially benefit the patient by improving hydration and nutrition and lowering the risk of aspiration. Performing the procedure when a patient is malnourished is more difficult. A gastrostomy can however be psychologically difficult for people to cope with.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. The GDG recognised that the earlier a gastrostomy is placed, the lower the risks of complications and death, and the shorter the length of hospital stay. Therefore, if it is felt that a gastrostomy is an appropriate intervention to consider then an earlier referral will improve health outcomes and may result in lower costs associated with complications.
Quality of evidence	No evidence was identified on the clinically appropriate timing of placement of a gastrostomy tube for nutrition management in people with MND.
Other considerations	The GDG used informal consensus to develop their recommendations. The GDG considered that the early placement of a gastrostomy can help to ease a person's discomfort during the progression of MND by preventing malnutrition through enteral administration of fluids, food and medication. This may prolong survival. However, the GDG noted that some people with MND prefer to delay the procedure. No clinical evidence was identified on the clinically appropriate timing of placement of a gastrostomy tube for nutrition management. Given the complexity of the considerations surrounding the placement of a gastrostomy, and the absence of relevant clinical evidence, the GDG did not consider it appropriate to recommend a time for placement of gastrostomy. The GDG did recommend regular assessments by the MDT to review breathing,

[d] See Mental Capacity Act 2005

	weight, nutritional intake, feeding, eating and swallowing. These assessments should trigger discussions on gastrostomy. For example, the GDG noted that a loss of 5–10% of total body weight is a commonly used clinical marker for risk of malnutrition. The GDG agreed that gastrostomy placement should only be considered with the presence of symptoms including weight loss, dysphagia and compromised respiratory function, and following discussion with the person with MND. The GDG also highlighted that on occasions whereby a person chooses to decline a gastrostomy, the healthcare professional should discuss with them the possible clinical harms and risks of a late gastrostomy or no gastrostomy: for example, low critical body mass, respiratory complications, risk of dehydration, different methods of insertion, and a higher risk of mortality and procedural complications. The GDG were clear that it is the person's decision, where cognitive capacity allows, as to whether a gastrostomy is appropriate for them. The decision to place a gastrostomy, therefore, should be made in collaboration with the person following discussion of their wishes and the relative risks and benefits of the procedure. The GDG were concerned that some people can feel pressurised into having a gastrostomy and that healthcare professionals should be aware that not everyone will want this procedure. The GDG agreed that people with frontotemporal dementia require particular consideration in terms of their nutritional assessment and also in terms of whether they should be offered gastrostomy. The GDG stated that people with frontotemporal dementia can be less likely to accept and cope with a gastrostomy and as such should be thoroughly assessed before treatment is offered to establish its likely effectiveness and their acceptance. Recommendations on the provision of nutrition support in adults can be found in NICE clinical guideline 32 Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition.

18 Communication

18.1 Introduction

Speech problems are a common symptom of MND. People with MND can experience a range of difficulties, particularly with articulation and voice quality. Changes can be very severe resulting in a total inability to use natural speech for communication. Difficulties with upper limb function can also result in an inability to access technology for non-face-to-face communication such as email. The effects of speech deterioration can be profound, affecting social relationships as well as engagement with health and social care.

The term AAC (augmentative and alternative communication) covers a wide range of techniques that support or replace spoken and/or text-based communication. These include gesture, symbols, communication boards and books, as well as voice output communication aids. AAC systems may be computer-based (high-technology) or non-electronic (low- or light-technology). AAC needs are highly individualised, requiring an appropriate professional assessment as well as ongoing and timely support and review, particularly as abilities and needs may change quickly. Many people with MND require more than one AAC system during the progression of their disease.

18.2 Review question: What is the clinical- and cost-effectiveness of augmentative and alternative communication (AAC) systems for supporting communication in people with MND?

For full details see the review protocol in Appendix C.

Table 97: PICO characteristics of review question

Population	• Adults (aged 18 and over) with MND. Strata: • People with cognitive impairment including frontotemporal dementia • People with functional upper limbs • People with immobile upper limbs
Intervention(s)	• 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
Comparison(s)	Compared to 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
Study design	Randomised controlled trials and systematic reviews of RCTs If no randomised controlled trials are available we will look for abstracts of RCTs and cohort studies (sample size=20)

18.3 Clinical evidence

No relevant clinical studies were identified.

18.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 98: Unit cost of high-tech AAC systems and their access devices

Technology level	Device function	Unit cost range (£) [a,b]
High, including high-tech access devices	Manual symbol selection to produce synthesised voice	£204–£408
	Voice pens to synthesise voice from symbol	£350–£1,200
	QWERTY keyboard to produce synthesised voice	£999–£3,500
	Enhanced tablet to produce synthesised voice	£895–£1,105
	Unenhanced tablet	£320–£660
	Bespoke tablet to produce synthesised voice	£1,450–£7,990
	Specialised switch for simple decision input	£138–£249
	Eye blink communicator aid	£714
	Eye gaze interface for user input	£1,735–£4,395
	Tablet enhancement package for specialised usability	£3,650
Software	AAC app for voice synthesis	£0–£110
	Allows bespoke creation of 'talking paper' for voice pen	£425
	Software that adds sounds and images to words	£499
Light/low	Simple keyboard for spelling of words	£65
	Velcro symbols with board	£24–£42
	Symbol communication book	£16
	Flip chart and symbols	£36

(a) Unit costs sourced from manufacturers and suppliers listed at www.communicationmatters.org.uk

(b) There are also costs associated with the training of the patients and their carers in using these systems, which should be provided by a trained healthcare professional. The appropriate training will ensure that the systems are used efficiently and the benefits of the equipment are maximised. These systems may have a lifespan of 3–5 years but they could be re-used by other patients. Therefore the cost per person will be lower depending on the number of the times the equipment can be re-used.

Economic considerations

- No studies on the effect of AAC devices on health-related quality of life which met the study design criteria were included in the clinical evidence review. The use of a device for AAC might improve the usual activities and anxiety/depression dimensions of the EQ-5D assessment HR-QoL tool, and therefore improve health-related quality of life.
- No evidence was identified to indicate a reduction in the utilisation of NHS or personal social service resources associated with the use of AAC systems which might offset any additional cost of the system itself.

18.5 Evidence statements

18.5.1 Clinical

- No relevant clinical evidence was identified.

18.5.2 Economic

- No relevant economic evaluations were identified.

18.6 Recommendations and link to evidence

Recommendations	**Communication** **78. When assessing speech and communication needs during multidisciplinary team assessments and other appointments, discuss face-to-face and remote communication, for example, using the telephone, email, the Internet and social media. Ensure that the assessment and review is carried out by a speech and language therapist without delay. [new 2016]** **79. Provide AAC equipment that meets the needs of the person without delay to maximise participation in activities of daily living and maintain quality of life. The use of both low-level technologies, for example, alphabet, word or picture boards and high-level technologies, for example, PC or tablet-based voice output communication aids may be helpful. Review the person's communication needs during multidisciplinary team assessments. [new 2016]** **80. Liaise with, or refer the person with MND to, a specialised NHS AAC hub if complex high technology AAC equipment (for example, eye gaze access) is needed or is likely to be needed. [new 2016]** **81. Involve other healthcare professionals, such as occupational therapists, to ensure that AAC equipment is integrated with other assistive technologies, such as environmental control systems and personal computers or tablets. [new 2016]** **82. Ensure regular, ongoing monitoring of the person's communication needs and abilities as MND progresses, and review their ability to use AAC equipment. Reassess and liaise with a specialised NHS AAC hub if needed. [new 2016]**

	83. Provide ongoing support and training for the person with MND, and their family members and/or carers (as appropriate), in using AAC equipment and other communication strategies. [new 2016]
Research recommendation	**6. What is the current pattern of provision and use of augmentative and alternative communication (AAC) by people with MND in England?**
Relative values of different outcomes	Health-related quality of life (EQ5D, SF-36, SF-12) and patient/carer reported outcomes (for example symptoms, pain, satisfaction) were considered to be critical outcomes. Function measured by disability scores, and speech and language scales, were important outcomes.
Trade-off between clinical benefits and harms	The ability to communicate can be a vital element for maintaining quality of life and interaction with family, friends and general activities. It also enables communication with professionals which enhances the quality of health and social care provided. Harms may be caused by the provision of inappropriate equipment and delay in provision of equipment.
Trade-off between net health effects and costs	As there was no economic evidence identified for this review question, the GDG considered the unit costs of different communication systems and devices. The GDG highlighted that improved communication may avert instances of health risk, which may lead to a reduction in healthcare professional engagement, hospitalisations, and risk of death. It was also felt that effective improvement in communication would improve quality of life, for example by reducing anxiety and/or depression as well as improving the individual's ability to perform usual activities. It was noted that the provision of equipment would need to be appropriate to the individual, regularly re-assessed, and utilised to its full functionality for it to be cost-effective. The GDG also considered the cost of the support required for individual and carer training in using the communication systems and devices. For these reasons, the GDG felt it was important that equipment is targeted to the individual according to need and by means of a timely and comprehensive assessment in order to maximise cost-effectiveness. The GDG also acknowledged that more than one communication system may be needed for some patients since communication is important in most settings, and that in their selection consideration should be given to access of electronic social media. The selection of high-tech communication devices should be made with consideration of acquisition cost, since a range of devices provide a similar core function. People with MND may not necessarily benefit more from more expensive equipment. It is also important that peripheral devices, for example device wheelchair mounts, are provided to allow for the most suitable level of functionality and adaptation for the person's needs.
Quality of evidence	No evidence was identified on the clinical effectiveness of communication aids for people with MND.
Other considerations	The GDG therefore used informal consensus to develop recommendations. The GDG considered that communication should be understood as multi-faceted, which encompasses many different forms and means. In this regard, these recommendations take into account communication via email, internet, and social networking, as well as high- and low-technologies. The GDG noted that the ability to communicate is a high priority for people with MND and has a significant impact on their quality of life. The GDG highlighted that the ability to communicate needs, for example being able to call for assistance, also has a potentially significant impact on survival.

The GDG recognised the importance of speech and language therapy in the overall management of communication and alternative and augmentative communication in people with MND and considered it important that a speech and language therapist is involved in assessment and ongoing review as soon as possible. There is a danger that without the appropriate involvement of a speech and language therapist the emphasis can shift to technology rather than the person's needs.

The GDG agreed that effective communication would help the individual maintain their role in society and the workforce and agreed that healthcare professionals should consider providing communication aids to all people with communication difficulties. As different modes of communication are used, this should include remote as well as face-to-face communication. The GDG discussed that timely provision of suitable equipment should be made from the range of low- and high-level technology available, as individual needs dictate that high-tech devices may not always be clinically appropriate; in some instances a low-tech device, such as an alphabet board, may be more effective and preferred. From experience, the GDG agreed that a combination of high- and low-tech devices are commonly used in order to meet the needs of the individual following assessment. The capability of devices to adapt to suit people's needs as their disease progresses was considered an important factor by the GDG. The GDG were cognisant of the ever-changing field of technological developments and the broader range of devices that may become available.

Given the rapid progression of MND, requirements for devices may change quickly and the GDG noted that the timely provision of suitable equipment will maximise the impact these devices have on people's quality of life. The GDG therefore chose to develop a recommendation highlighting that the full range of suitable equipment should be considered, on the basis of individual needs and costs, and may involve low- and high-tech devices, or a combination of the two.

The GDG identified the importance of working collaboratively with the person with MND when assessing and making provision for their communication needs. They also recognised the need for healthcare professionals to manage patient expectations during this process, and to provide information specific to the individual's requirements. Inclusion of other healthcare professionals in the assessment will ensure that provision of AAC and other technological systems are complementary. Healthcare professionals should also consider cognitive abilities and cognitive change when making their assessments. The GDG noted that this assessment should be repeated during the course of the disease, as communication difficulties and people's needs for support will change. Liaison with a specialist NHS AAC hub will help provide for those with more complex needs. 'Complex needs' in this context was defined as in addition to impairment of the voice, where the person also loses hand function (and therefore cannot use more basic text-to-speech communication aids). In non-complex cases, assuming no anticipatory referral, local speech and language therapy services should meet the person's needs, not an AAC hub.

As well as the provision of appropriate equipment, the GDG acknowledged that health and social care professionals and carers should understand how to use the equipment being provided. The GDG highlighted that this should include the provision of training and ongoing support for the use of equipment for the person with MND, families, and carers.

Research recommendation

The GDG did not consider that the provision and use of AAC devices across England was well understood. They also agreed that establishing the current baseline provision and needs of this population is crucial to understanding how to best utilise AAC equipment. The GDG developed a research recommendation for this purpose. For

	further details please see Appendix N: Research recommendations.

19 Respiratory function and respiratory symptoms

19.1 Introduction

Respiratory muscle weakness resulting in respiratory impairment is a major feature of MND. This chapter includes recommendations on the overall approach to respiratory impairment in MND and recommendations on pharmacological management of breathing difficulties. Recommendations relating specifically to the use of NIV are covered in Chapter 21.

19.2 Recommendations and link to evidence

Recommendations	**Respiratory function and respiratory symptoms** **84. Assess and monitor the person's respiratory function and symptoms. Treat people with MND and worsening respiratory impairment for reversible causes (for example, respiratory tract infections or secretion problems) before considering other treatments. [new 2016]** **85. Offer non-invasive ventilation as treatment for people with respiratory impairment (see Chapter 21). Decisions to offer non-invasive ventilation should be made by the multidisciplinary team in conjunction with the respiratory ventilation service, and the person (see recommendations 19–23). [new 2016]** **86. Consider urgent introduction of non-invasive ventilation for people with MND who develop worsening respiratory impairment and are not already using non-invasive ventilation. [new 2016]**
Other considerations	These recommendations are informed by (1) informal consensus of the GDG (2) the evidence reviews on pharmacological treatments for breathing problems (Section 19.3), (3) the evidence reviews examining withdrawal of NIV (Sections 21.4 and 21.12) and (4) the existing recommendations in NICE guideline CG105[86] (Section 21.3). No recommendations are worded identically to any in CG105 and as such are considered new for the 2016 guideline. The GDG developed these recommendations to establish a hierarchy in treatments for people with MND and respiratory impairment. They recognised that people with MND are prone to respiratory tract infections and secretion problems and that they should be assessed, monitored and treated for these potentially reversible causes before other treatments are considered. CG105 includes a recommendation offering NIV following assessment. The GDG wished to emphasise that NIV should be considered as the treatment of choice for respiratory impairment. The GDG noted that it improves quality of life in people with respiratory impairment and may extend survival in some people with MND. The GDG therefore included a new recommendation to indicate the place of NIV in the hierarchy of treatments for breathing problems.

	The GDG agreed that NIV should be considered for people who present urgently with worsening respiratory impairment. The GDG discussed that NIV is ideally initiated in a planned way following assessments and discussion. However, people do present with respiratory failure as their first presentation of MND or with very rapid progression of respiratory symptoms when this type of planning has not been possible. The GDG wished to emphasise the importance of ensuring these people are also considered for NIV and that procedures are in place to arrange urgent initiation if necessary. There may be circumstances where NIV is inappropriate but the GDG expected that in most cases NIV was appropriate in this scenario. This guideline recommends the use of an MDT for delivery of care for people with MND (Chapter 9). CG105 made recommendations for a specific respiratory-related MDT to be involved in decisions to deliver NIV. That recommendation is replaced by recommendations for MDT based on clinical- and cost-effectiveness evidence.

19.3 Pharmacological management of breathing difficulties

19.4 Introduction

Weakness of the respiratory muscles affects most people with MND as their disease progresses. This can cause compensatory increase in respiratory rate and use of accessory muscles. People can feel short of breath as well as having symptoms as a result of reduced respiratory function. Feeling breathless can cause anxiety which may exacerbate the feeling of breathlessness. NICE developed a clinical guideline 'Care of dying adults in the last days of life' (NICE guideline NG31) which advises on treatment and use of anticipatory medication in the last days of life.

19.5 Review question: What is the clinical- and cost-effectiveness of pharmacological treatments for managing breathing difficulties in people with MND?

For full details see the review protocol in Appendix C.

Table 99: PICO characteristics of review question

Population	Adults (aged ≥18 years) with MND
Intervention(s)	• 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(s)	Compared with the above Placebo 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
Study design	RCTs and systematic reviews of RCTs If no RCTs are available we will look for abstracts of RCTs and cohort studies (sample size limit =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.

The GDG did not expect evidence to be found in an MND population but agreed that there were indirect populations from which recommendations could be drawn. The GDG identified the following indirect populations, in whom breathing difficulties are caused by a similar mechanism to that of MND: multiple system atrophy, Parkinson's disease, progressive supranuclear palsy and spinal muscular atrophy. If no direct evidence from an MND population is found then RCTs in these populations will be considered.

19.6 Clinical evidence

No studies identified.

19.7 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

Relevant unit costs are provided in Table 100 below to aid consideration of cost-effectiveness. These are monthly drug acquisition costs and do not include the cost of drug administration. Note that dosage information has been drawn from the British National Formulary. Unit prices have been sourced from the NHS electronic drug tariff (NHS Business Services Authority), which provides an average cost of medicines when prescribed in a primary care setting. Exceptions are indicated.

Table 100: Unit cost of pharmacotherapies for breathing difficulty

Drug class	Drug name	Preparation	Dose (mg/day)	Drug acquisition cost for 1 month
Benzodiazepine	Midazolam	10 mg ampoule	5	£19[a]
		10 mg oromucosal solution, pre-filled syringe	0.3 [10 x 10 mg syringes per year]	£19
	Lorazepam	Tablets	4	£15
		Ampoule		£11[b]
	Diazepam	Tablets	10	£1
		Oral solution		£145
		Solution for injection		£14
		Rectal solution		£42

Drug class	Drug name	Preparation	Dose (mg/day)	Drug acquisition cost for 1 month
	Clonazepam	Tablets	4	£3
		Oral solution		£183
Opioid analgesic	Morphine	Tablets	60	£17
		MR tablets		£16
		MR capsules		£11
		Oral solution		£15
		Suppository		£90
		Solution for injection		£171
	Diamorphine	Tablets	30	£21
		Powder for injection		£466
	Oxycodone	MR tablets	60	£82
		Oral solution		£71
		Solution for injection		£292
	Fentanyl	Transdermal patch (50 ug per hour)	0.6	£68

Unit costs are sourced from the NHS electronic drug tariff (NHS Business Services Authority), except:

(a) Sourced from CMU eMIT June 2014

(b) Sourced from MIMs online June 2014

Abbreviations: BNF=British National Formulary; DH CMU=Department of Health Commercial Medicines Unit; MR=modified (slow) release; SL=sublingual

Economic considerations

- No relevant economic evaluations were identified.

19.8 Evidence statements

Clinical

- No relevant clinical evidence was identified.

Economic

- No relevant economic evaluations were identified.

19.9 Recommendations and link to evidence

Recommendations	**87. Consider opioids[e] as an option to relieve symptoms of breathlessness. Take into account the route of administration and acquisition cost of medicines. [new 2016]** **88. Consider benzodiazepines[e] to manage breathlessness that is exacerbated by anxiety. Take into account the route of administration and acquisition cost of medicines. [new 2016]**
Relative values of	The GDG identified health-related quality of life (EQ-5D, SF-36, SF-12) and patient

[e] At the time of publication (February 2016), these medicines did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

different outcomes	reported outcomes (tolerance, improvement in breathing difficulties, improvement in cough, improvement in mobility, anxiety, pain [VAS]) as critical outcomes for the evaluation of pharmacological interventions for breathing difficulties. Hospital admissions (including unplanned admissions), adverse events of treatment (sleepiness, nausea and vomiting) and mortality were also identified as important outcomes.
Trade-off between clinical benefits and harms	Symptoms of breathing problems can be extremely distressing and treatments which alleviate these would be beneficial for those affected.
Trade-off between net health effects and costs	No economic evaluations were identified. The GDG agreed that both opioids and benzodiazepines are likely to be cost-effective versus placebo, since their acquisition and administration costs are low and the consensus was of superior effectiveness versus placebo. It is not expected that cost-effectiveness between drug classes would be significantly different, and in any case the economic impact would be low.
Quality of evidence	No clinical evidence was identified.
Other considerations	No evidence was identified in direct or indirect populations of people with MND and the GDG developed consensus-based recommendations. The GDG discussed the use of opioids as a treatment for breathlessness in the MND population. There was no consensus to recommend one opioid over another. The GDG noted that the use of morphine should be accompanied by careful discussion with the person and their carer to explain the purpose of treatment. As breathlessness may be exacerbated by symptoms of anxiety, benzodiazepines may be useful for some patients. Opioids and benzodiazepines are recognised as treatments for breathlessness in palliative care. The BNF, in a section on symptom control in palliative care, suggests that breathlessness at rest may be relieved by regular oral morphine in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam is suggested at 5–10 mg daily for dyspnoea associated with anxiety.[63] The GDG considered that the treatment of people with cognitive impairment should be the same as those without cognitive impairment. It was decided that a separate recommendation would not be developed for this population. Recommendations on the care of adults in the last 2–3 days of life are provided by 'Care of dying adults in the last days of life' (NICE guideline NG31).

20 Cough effectiveness

20.1 Introduction

An effective cough is essential for secretion clearance and protection against pulmonary complications. Individuals with MND may have weak inspiratory and expiratory muscles resulting in reduced chest wall compliance, poor lung volume and cough impairment contributing to respiratory tract infections. Respiratory tract infections have been identified as a major cause of morbidity and mortality in this patient group. Cough augmentation techniques is an umbrella term for non-invasive techniques that are used to enhance cough strength, facilitating secretion clearance in MND patients when conventional secretion management techniques are no longer effective.

A simple, generally accepted means of assessing cough strength is peak cough flow (PCF). A PCF of 160 litres per minute is required to generate sufficient cough flow to clear airway debris. A PCF of 270 litres per minute has been accepted as the threshold for individuals to be taught cough augmentation techniques, as their PCF is likely to fall below the critical threshold of 160 litres per minute during respiratory infections. The choice of the most appropriate regime to augment effective secretion clearance requires careful consideration, taking into account factors including PCF, presence of infection, bulbar function, fatigue and patient/carer education in the technique(s).

20.2 Review question: What is the clinical- and cost-effectiveness of cough augmentation techniques for people with MND who have an ineffective cough?

For full details see the review protocol in Appendix C.

Table 101: PICO characteristics of review question

Population	Adults (aged 18 and over) with MND who have reduced ability to cough Strata: • People with cognitive impairment including frontotemporal dementia • People with significant respiratory dysfunction • People who are at the end of life
Intervention(s)	Basic cough augmentation techniques: • Active cycle of breathing techniques (ACBT) for example thoracic expansion exercises (TEE), breathing control, huffing (breathing technique) • Postural drainage and manual techniques (shaking/percussion/vibration(s), gravity assisted positioning (GAP) • Manual assisted coughing techniques (quad coughing, assisted coughing) • Maximal insufflation capacity techniques (MIC) for example unassisted/assisted breath stacking, thoracic range of movement exercises, glossopharyngeal breathing (GPB), respiratory muscle training (RMT) 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

	Devices will be reviewed individually or in combination.
Comparison(s)	• Compared with each other, or with nothing
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 (PCF) • Reduction of chest infection (community- or hospital-acquired pneumonia 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]
Study design	Order of preference for study designs for each group of interventions: • Systematic reviews of RCTs which meet our PICOs • Randomised controlled trials • If no randomised controlled trials are available we will look for abstracts of RCTs and cohort studies (sample size >20) • Non-blinded, single and double-blinded trials will be included 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.

20.3 Clinical evidence

One Cochrane review was found[80] which included 2 studies that met our protocol and have been included in the review. One further study was found from our search, therefore 3 studies were included;[82,114,109] these are summarised in Table 102 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 103, Table 104, Table 105, Table 106, Table 107, Table 108, Table 109, Table 110, Table 111, Table 112, Table 113, Table 114, Table 115, Table 116, Table 117, Table 118 and Table 119). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K. There were 3 additional studies in the Cochrane review that were conducted in populations other than MND.

In both studies all the patients received all the interventions, in a random order.

Table 102: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Comments
Mustfa 2003[82,82]	1. Maximal unaided coughs 2. Manually assisted cough using abdominal pressure 3. Manually initiated exsufflation using the mechanical in-exsufflator device (the negative pressure was gradually titrated to the maximum tolerated exsufflation), initiated just	People with ALS	Peak cough flow (PCF)	All patients received all interventions

Study	Intervention/comparison	Population	Outcomes	Comments
	prior to coughing 4. Insufflation with the in-exsufflator incrementally increased to the maximum tolerated pressure prior to a maximal cough 5. MI-E coordinated with the patients' cough efforts, using a mechanical in-exsufflator (MI-E interface was a face mask). In-exsufflation pressures and times were not reported.			
Rafiq 2014[108,109]	Mechanical in-exsufflator (MI-E) versus a breath-stacking technique	Patients with ALS	Survival; number of patients with at least 1 chest infection; total number of chest infections; number of patients with any hospitalisation; total number of hospitalisations; quality of life (MCS and SAQLI sym); PCF	This was a preliminary RCT and was therefore not powered to detect differences in survival and QoL. There were a lot of non-compliant participants , further reducing numbers within the study.
Senent 2011[114,114]	1. Expiratory abdominal thrust after air stacking on spontaneous deep breath, using an Ambu Silicone Resuscitator (LVR) 2. Expiratory abdominal thrust from end-inspiratory volume using bi-level pressure ventilator with normal settings (BI-PAP) 3. Expiratory abdominal thrust from end-inspiratory volume obtained by increasing inspiratory positive airway pressure, iPAP, to +30 cm H**2**O (IPAP) 4. MI-E assisted cough using a face mask interface. Maximum insufflation and exsufflation pressure were gradually increased to 40 cm H_2O and -40 cm H_2O. Four to six in-exsufflation cycles were given with a 1 to 3 seconds inter-cycle pause. Insufflation and exsufflation times were	Stable patients with ALS, who had been on home mechanical ventilation for >2 months	Peak cough flow (PCF); efficacy VAS; comfort VAS	One hour after 3 manual cough techniques, the techniques were applied in random order at 10 to 15 minute intervals.

Study	Intervention/comparison	Population	Outcomes	Comments
	not reported. The cough assist mechanical in-exsufflator was used. (MI-E)			

Table 103: Clinical evidence summary: MI-E versus exsufflation

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus exsufflation (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	252 (81.5)	The mean PCF in the intervention groups was 14.05 lower (45.6 lower to 17.51 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 104: Clinical evidence summary: MI-E versus insufflation

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus insufflation (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	207 (75)	The mean PCF in the intervention groups was 30.81 higher (0.57 to 61.04 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 105: Clinical evidence summary: MI-E versus manual

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus manual (95% CI)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus manual (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	220 (73)	The mean PCF in the intervention groups was 17.46 higher (12.37 lower to 47.3 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 106: Clinical evidence summary: MI-E versus unassisted

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus unassisted (95% CI)
Change in PCF (litres/min ute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	197 (72.5)	The mean PCF in the intervention groups was 40.28 higher (10.55 to 70.01 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 107: Clinical evidence summary: Exsufflation versus insufflation

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with exsufflation versus insufflation (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	207 (75)	The mean PCF in the intervention groups was 44.19 higher (12.67 to 75.72 higher)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with exsufflation versus insufflation (95% CI)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 108: Clinical evidence summary: Exsufflation versus manual

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with exsufflation versus manual (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	220.5 (68)	The mean PCF in the intervention groups was 31.18 higher (0.01 to 62.36 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 109: Clinical evidence summary: Exsufflation versus unassisted

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with exsufflation versus unassisted (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	197.5 (72.5)	The mean PCF in the intervention groups was 53.69 higher (22.65 to 84.72 higher)

[a] 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

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with exsufflation versus unassisted (95% CI)
risk of bias [b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 110: Clinical evidence summary: Insufflation versus manual

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with insufflation versus manual (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	220.5 (73)	The mean PCF in the intervention groups was 12.7 lower (42.17 lower to 16.76 higher)
[a] 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 [b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 111: Clinical evidence summary: Insufflation versus unassisted

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with insufflation versus unassisted (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	197.5 (72.5)	The mean PCF in the intervention groups was 9.6 higher (19.67 lower to 38.86 higher)
[a] 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 [b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 112: Clinical evidence summary: Manual versus unassisted

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with manual versus unassisted (95% CI)
Change in PCF (litres/minute)	47 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	220.5 (72.5)	The mean PCF in the intervention groups was 22.06 higher (6.01 lower to 50.13 higher)

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 113: Clinical evidence summary: MI-E versus bilevel positive airway pressure (BIPAP)

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with MI-E and BIPAP – median (IQR)
Change in PCF (litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 488 (243–605) and the median PCF in the BiPAP group was 212 (99–595)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 8 (6–8) and the median PCF in the BiPAP group was 7 (6–8)
Comfort (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 7 (3-8) and the median PCF in the BiPAP group was 8 (7-8)

[a] 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
[b] Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 114: Clinical evidence summary: MI-E versus IPAP

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with MI-E and IPAP – median (IQR)
Change in PCF (litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 488 (243–605) and the median PCF in the IPAP group was 233 (100–389)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 8 (6–8) and the median PCF in the IPAP group was 6 (5–7)
Comfort (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 7 (3–8) and the median PCF in the IPAP group was 6 (5–7)

[a] 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
[b] Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 115: Clinical evidence summary: MI-E versus LVR

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with MI-E and LVR – median (IQR)
Change in PCF (litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 488 (243–605) and the median PCF in the LVR group was 284 (146–353)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the MI-E groups was 8 (6–8) and the median PCF in the LVR group was 7 (5–8)
Comfort (VAS)	16	VERY LOW[a,b]	–	–	The median PCF in the MI-E groups was

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with MI-E and LVR – median (IQR)
	(1 study)	due to risk of bias, imprecision			7 (3–8) and the median PCF in the LVR group was 6 (5–8)

[a] 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
[b] Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 116: Clinical evidence summary: BIPAP versus IPAP

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with BiPAP and IPAP – median (IQR)
Change in PCF (litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 212 (99–595) and the median PCF in the IPAP group was 233 (100–389)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 7 (6–8) and the median PCF in the IPAP group was 6 (5–7)
Comfort (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 8 (7–8) and the median PCF in the IPAP group was 6 (5–7)

[a] 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
[b] Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 117: Clinical evidence summary: BIPAP versus LVR

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with control	Risk with BiPAP and LVR – median (IQR)
Change in PCF(litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 212 (99–595) and the median PCF in the LVR group was 284 (146–353)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 7 (6–8) and the median PCF in the LVR group was 7 (5–8)
Comfort (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the BiPAP groups was 8 (7–8) and the median PCF in the LVR group was 6 (5–8)

[a] 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
[b] Downgraded by 2 increments as the data were given in medians and interquartile ranges

Table 118: Clinical evidence summary: IPAP versus LVR

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with IPAP and LVR – median (IQR)
Change in PCF (litres/minute)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the IPAP groups was 233 (100–389) and the median PCF in the LVR group was 284 (146353)
Efficacy (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the IPAP groups was 6 (5–7) and the median PCF in the LVR group was 7 (5–8)
Comfort (VAS)	16 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	–	–	The median PCF in the IPAP groups was 6 (5–7) and the median PCF in the LVR group was 6 (5–8)

[a] 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

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk with IPAP and LVR – median (IQR)
risk of bias [b] Downgraded by 2 increments as the data were given in medians and interquartile ranges					

Table 119: Clinical evidence summary: MI-E versus breath-stacking technique

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus breath-stacking technique (95% CI)
Survival	40 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	HR 1.94 (0.87 to 4.33)	Moderate	
				–	Median survival in the MI-E group was 266 days and the median survival in the breath-stacking group was 535 days
Chest infection – number of patients with at least 1 chest infection	40 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	OR 0.78 (0.16 to 3.8)	Moderate	
				See comment[e]	See comment[e]
Chest infection – total number of chest infections	40 (1 study)	VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	RR 1.06 (0.31 to 3.62)	Moderate	
				See comment[e]	See comment[e]
Hospitalisation – number of patients with any hospitalisation	40 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	OR 0.87 (0.16 to 4.73)	Moderate	
				See comment[e]	See comment[e]
Hospitalisation – total number of hospitalisations	40 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.45 (0.3 to 7.01)	Moderate	
				See comment[e]	See comment[e]
PCF	40 (1 study)	VERY LOW[a,f] due to risk of bias,	–	–	PCF increased by 0.9 litres/minute/month in the MI-E group and declined by 5.77 litres/minute/month in

Outcomes	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with MI-E versus breath-stacking technique (95% CI)
		imprecision			the breath-stacking group, p=0.43. Baseline values differed significantly (p<0.001): 120 litres/minute for MI-E and 215 litres/minute for breath stacking.
Quality of life (MCS)	40 (1 study)	VERY LOW[a,f] due to risk of bias, imprecision	–	–	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)
Quality of life (SAQLI sym)	40 (1 study)	VERY LOW[a,f] due to risk of bias, imprecision	–	–	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).

[a] 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
[b] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[c] Number of patients with chest infection, not reduction in chest infection
[d] Total number of chest infections, not reduction in chest infections
[e] Adjusted figures reported so absolute number could not be analysed
[f] Imprecision could not be calculated as data could not be analysed

20.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

Unit costs

The following costs are those associated with managing non-effective cough in a non-acute setting.

Table 120: Equipment costs associated with mechanical cough assist device

Item	Cost	Units	Unit cost	Per patient per use cost	Source
Cough assist machine	£4,646	1	£4,646	£2.55[a]	NHS supply chain[1] GDG opinion
Cough assist consumables (for example filter, hose, mask, mouth piece)	£130	16	£8.16	£1.16[b]	NHS supply chain[1] GDG opinion
			TOTAL	£3.71[c]	

(a) Assuming the machine is used once per day for 5 years before it is replaced (£4,646/[365x5]=£2.55)
(b) Assuming the kit is replaced once a week and used once per day ([£8.16x52]/365=£1.16)
(c) This cost is incurred every time the equipment is used, therefore if it was used once a day for a year the cost would be (£3.71x365=£1354)
(d) The GDG noted that local agreements with manufacturers may mean a lower cost, however the per-patient cost will not change dramatically

20.5 Evidence statements

20.5.1 Clinical

- Very Low quality evidence from 1 RCT comprising 47 participants found a clinical benefit of MI-E compared to insufflation; MI-E compared to unassisted; exsufflation compared to insufflation; exsufflation compared to manual; exsufflation compared to unassisted for PCF (litres/minute). No clinical difference was found between MI-E and exsufflation; MI-E compared to manual; insufflation and manual; insufflation and unassisted; manual and unassisted for PCF (litres/minute).
- Very Low quality evidence from 1 RCT comprising 16 participants found a clinical benefit of MI-E compared to BIPAP for PCF (litres/minute); MI-E compared to IPAP for median PCF (litres/minute); MI-E compared to LVR for median PCF (litres/minute) and found no clinical difference between: MI-E and BIPAP for efficacy (VAS) and comfort (VAS); MI-E and IPAP for efficacy (VAS) and comfort (VAS); MI-E and LVR for efficacy (VAS) and comfort (VAS); BIPAP and IPAP for PCF (litres/minute), efficacy (VAS) and comfort (VAS); BIPAP and LVR for PCF (litres/minute), efficacy (VAS) and comfort (VAS); IPAP and LVR for PCF (litres/minute), efficacy (VAS) and comfort (VAS).
- Very Low quality evidence for 1 RCT comprising 40 participants found: a clinical benefit of breath-stacking compared to MI-E for survival, total number of hospitalisations and quality of life; of MI-E compared to breath stacking for number of patients with chest infection and number of patients hospitalised; no clinical difference for total number of chest infections and PCF.

20.5.2 Economic

- No relevant economic evaluations were identified.

20.6 Recommendations and link to evidence

Recommendations	**Cough effectiveness** **89. Offer cough augmentation techniques such as manual assisted cough to people with MND who cannot cough effectively. [new 2016]** **90. Consider unassisted breath stacking and/or manual assisted cough as the first-line treatment for people with MND who have an ineffective cough. [new 2016]** **91. For patients with bulbar dysfunction, or whose cough is ineffective with unassisted breath stacking, consider assisted breath stacking (for example, using a lung volume recruitment bag). [new 2016]** **92. Consider a mechanical cough assist device if assisted breath stacking is not effective, and/or during a respiratory tract infection. [new 2016]**
Research recommendation	**7. How does peak cough flow and the use of cough augmentation techniques to enhance cough efficacy correlate with respiratory outcomes and quality of life in people with MND?**
Relative values of different outcomes	Survival, health-related quality of life (for example, EQ5D, SF-36, SF-12, SRQ) and patient/carer reported outcomes (ability to cough, ability to clear secretions, concordance, breathlessness [SOBAR/SOBOE], fatigue) were critical clinical outcomes for the assessment of cough augmentation techniques. Change in peak cough flow, reduction of chest infection (community- or hospital-acquired pneumonia and aspiration), hospital admissions (and unplanned admissions) and length of hospital stay were important clinical outcomes.
Trade-off between clinical benefits and harms	The evidence on cough augmentation devices for peak cough flow showed a clinical benefit of mechanical insufflator-exsufflator (MI-E) when compared to BiPAP, iPAP, lung volume recruitment (LVR), insufflation, and unassisted breath-stacking. There was no clinical difference between the other cough augmentation devices for change in peak cough flow, except for a clinical benefit of exsufflation compared to insufflation, manual breath-stacking and unassisted breath-stacking. The GDG, however, acknowledged that the true benefit of change in peak cough flow is difficult to establish as it may not equate to cough clearance. There was no clinical difference for efficacy or comfort for any of the devices. There was a clinical benefit of breath-stacking compared to MI-E for survival, total number of hospitalisations and quality of life. There was a clinical benefit of MI-E compared to breath-stacking for number of patients with at least one chest infection and any hospitalisations.
Trade-off between net health effects and costs	No economic evidence was found for this question. For people without infection, the clinical evidence showed that mechanical cough assist was no more effective than breath stacking. Since breath stacking is of a lower cost than mechanical cough assist it is likely to be the more cost-effective intervention, given that mechanical cough assist offers no additional clinical benefit. The up-front cost of the mechanical cough assist machine was found to be between £4,000–£5,000 and additional costs of replaceable consumables were found to be £424–£890 per year. Although there are consumables used for assisted breath stacking, such as lung volume recruitment (LVR) bags, these are of a significantly

	lower cost and there is no upfront cost of a machine. The GDG noted that training to use the mechanical cough assist machine would have to be reviewed on a regular 6 week to 3 month basis, whereas training for breath staking would not require such thorough review. Therefore the NHS would incur further costs associated with physiotherapist's time to perform the training. No evidence was identified for the use of these interventions in patients during an episode of infection, when the risk of hospitalisation and respiratory failure may be increased due to excessive mucus production. The GDG considered that under these circumstances the additional cost of mechanical cough assist for insufflation-exsufflation therapy may be offset by a combination of a reduction in the risk of hospital admission and an increased effectiveness of mechanical assistance in the presence of excess mucus, compared to breath stacking. The GDG also noted that the cost-effectiveness of mechanical assist strategy increases if the device is used on more people and thus the initial capital cost of the machine is offset by the more frequent use.
Quality of evidence	The evidence was limited to 3 small studies with Very Low quality GRADE ratings. The GDG also expressed concern that the Senent[114,114] study applied cough assist techniques at 10–15 minutes which would lead to fatigue of the participants. Change in PCF was the main outcome within the studies to show benefit and the GDG felt this was problematic as a measure of cough augmentation, and in practice poor cough to good cough would be a better measure. The GDG noted that other outcomes were provided as median values rather than mean values, suggesting that the data were skewed.
Other considerations	The GDG used their experience to augment the available evidence to make recommendations. The GDG noted that people with bulbar symptoms are recognised as being less able to take a breath and hold the air and were therefore often separated in the studies. However for the purpose of this review, all data were combined as the GDG felt that the recommendations applied to all people with MND needing cough assist. From a clinical perspective it is important to establish whether or not the patient has an infection as the presence of infection has an effect on cough but may also require different intervention. The GDG stated that in current practice, regular breath stacking is used for ineffective cough. The GDG highlighted the importance of differentiating between breath stacking and assisted breath stacking. The GDG noted that the evidence did not support the use of one cough augmentation technique over another. There was no evidence for unassisted breath stacking compared to assisted breath stacking and no clear clinical difference between breath stacking and cough augmentation devices. The GDG concluded that the evidence indicated that doing something to aid cough augmentation was better than doing nothing. Therefore, the GDG used informal consensus to recommend that cough augmentation techniques should be attempted first. The GDG considered that these are easier to deliver, are readily available and are associated with reduced staff time and cost. The GDG felt that where cough augmentation techniques are inappropriate or ineffective, manual breath stacking, then assisted breath stacking, and finally mechanical cough assistance devices, should be considered. Carers require training in how to perform manual cough assist. **Research recommendation**

	There is consensus that secretion encumbrance resulting from an ineffective cough is a contributor to morbidity and mortality in MND. However this has not been formally established in a clinical study. In order to confirm this link, the GDG developed a research recommendation to investigate the association between cough and respiratory and patient outcomes. This research would be important for interpretation of current research and design of future clinical trials. For further details please see Appendix N: Research recommendations.

21 Non-invasive ventilation

21.1 Introduction

This guideline replaces NICE clinical guideline CG105 Motor neurone disease: The use of non-invasive ventilation in the management of motor neurone disease, and the recommendations from that guideline are amalgamated in this guideline. CG105 considered the identification and assessment of respiratory impairment, the clinical- and cost-effectiveness of NIV, key elements in the management of the use of NIV, and information and support needs of patients, families and carers. These questions were not reviewed again for this guideline. The scope for this guideline included managing discontinuation of non-invasive ventilation and preparation for, and anticipation of, end of life. It has also reviewed wider aspects of care such as MDTs. Tracheostomy and ventilation were outside of the scope and were therefore not included. Oxygen therapy was not included in CG105 or the current guideline. The British Thoracic Society have guidelines on home oxygen use.

There is inevitable overlap between some of the areas reviewed for this guideline and the recommendations in CG105, and some CG105 recommendations have therefore been amended for consistency and to avoid repetition. The recommendations are presented in the order that the GDG considered made most clinical sense. The overall order of the recommendations is reflected in this chapter and organised as follows:

1) Recommendations from CG105 on information and support for non-invasive ventilation (Section 21.2).
2) Evidence review on patient experience of discontinuation of NIV (Section 21.4).
3) New recommendations on information and support for non-invasive ventilation informed by evidence review (Section 21.10).
4) Recommendations from CG105 on the processes of assessment of respiratory function (Section 21.11).
5) Evidence review on the management of discontinuation of NIV (Section 21.12).
6) New recommendations on the management of discontinuation of NIV (Section 21.18).

Details of the development of CG105 recommendations are not repeated here and can be found in Appendix R.

21.2 Information and support for non-invasive ventilation

21.3 Recommendations from CG105

Recommendations	**93. Offer to discuss the possible use of non-invasive ventilation with the person and (if the person 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** • **if the person asks for information. [2010]** **94. 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 box 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]**

21.4 Experience of discontinuation of NIV

21.5 Introduction

It is established in law that if a patient who has capacity declines a treatment this instruction should be followed, and this applies to the discontinuation of NIV. Many patients with MND who discontinue NIV will die shortly afterwards. The proximity of the withdrawal of NIV and the death of the patient might be expected to produce emotional responses in relatives and carers both lay and professional who witness the withdrawal or are instrumental in it. This chapter examines the evidence relating the experiences of these people at this time.

21.6 Review question: What factors influenced the experience of discontinuation, at a patient's request, of NIV for relatives/carers/healthcare/social care professionals?

For full details see the review protocol in Appendix C.

Table 121: PICO characteristics of review question

Population and setting	• Families or carers of people with MND • Health and social care professionals • Strata – dependent
Topic of interest	To establish how the discontinuation of NIV was managed from the point of view of the relatives/carers/health and social care professionals
Context (specific aspects of interest – for example the themes hoping to get opinions on: pain, criteria relevant)	• 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
Review strategy	Population size and directness: • Studies with indirect populations will not be considered, for example patients with other neuromuscular disorders 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 • Thematic analysis of the data will be conducted and findings presented. • 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.
Study design	• Qualitative studies (for example interviews, focus groups) • Surveys if no qualitative studies are retrieved

21.7 Clinical evidence

Two studies were included in the review;[10,42] these are summarised in Table 122 below. Themes identified from the studies are summarised in Table 123. Key findings from these studies are summarised in the modified clinical evidence summary table (Table 124). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J, GRADE tables in Appendix I and excluded studies list in Appendix K.

Table 122: Summary of studies included in the review

Study	Design	Population	Research aim	Comments
Qualitative studies (1:1 interviews, focus groups, partner interviews, semi-structured interviews etc.)				
Baxter 2013C[10]	Qualitative interviews	Family, carers and healthcare professionals	To describe carer and healthcare professional experiences of end of life care for MND patients using NIV	
Faull 2014[42]	Survey	Palliative medicine doctors	To identify issues and challenges that palliative medicine doctors encounter in relation to the withdrawal of NIV in MND patients	6.2% had not cared for an MND patient who used NIV, 35.4% had not been involved in the actual withdrawal of NIV at the request of the patient

Evidence

21.7.1.1 Themes and sub-themes derived from the evidence

Table 123: Themes and sub-themes

Main theme	Sub-themes
Factors affecting experience of discontinuation of NIV	Planning and timing
	Avoidance of hospitalisation
	Attempts to resuscitate
	Decision-making regarding the withdrawal of NIV
	Peaceful final moments
	Turning off the machine
	Professional uncertainty regarding the withdrawal of NIV
	Concerns regarding NIV use at end of life
	Emotional burden
	Team involvement

Table 124: Summary of evidence: Factors affecting experience of discontinuation of NIV

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	Design		Criteria	Rating	Overall
Sub-theme 1: Planning and timing					
2	Qualitative	Deterioration towards end of life occurred more rapidly than	Applicability of evidence	Applicable[a]	High

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
	interviews and survey	expected and adversely impacted on the plan for end of life care, such as not being able to guide the family through in a controlled way, although rapidity was also easier for some families **(healthcare professionals and carers)**. There was huge time and planning burden inherent in the process and there were difficulties in discussions with patients in the absence of any prior advance decisions or planning **(healthcare professionals)**. Healthcare professionals said that it may be down to timing that patients were not able to die at home, such as bank holidays or paperwork not being in place. They felt that advance care plans required careful timing and staff with knowledge of the care plan needed to be available at critical points of rapid deterioration.	Theme saturation/sufficiency	Saturated[b]	
Sub-theme 2: Avoidance of hospital					
1	Qualitative interviews	Patients wished to die at home but a few had not been able to. They did not want to attend hospital at all in case they were admitted **(healthcare professionals and carers)**. Patients who were admitted were usually via emergency calls to the ambulance service; it could be a difficult decision for carers and healthcare professionals whether to telephone an ambulance or not because of this.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Saturated[b]	
Sub-theme 3: Attempts to resuscitate					
1	Qualitative interviews	Some patients were subjected to attempts to resuscitate, which was distressing for families **(healthcare professionals and carers)**. Some patients had advance directives, but some did not and it was a difficult subject for healthcare professionals to broach, particularly as the disease progressed so quickly **(healthcare professionals)**.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 4: Decision-making regarding the withdrawal of NIV					
2	Qualitative interviews	Difficult decisions about whether and how NIV should be	Applicability of evidence	Applicable[a]	Moderate

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
	and survey	discontinued did not arise in the patients within the qualitative review. Healthcare professionals' prior experience was that those who discussed it usually decided to keep the NIV in place **(healthcare professionals)**. In the survey, healthcare professionals had concerns as to whether or not to wean ventilation, how to manage distressing symptoms and the use of sedative drugs (what and how), and who should remove the mask. In the qualitative review weaning was considered for 2 patients, but did not occur. However, **healthcare professionals** recalled 2 experiences of weaning for patients outside this study, with one describing it as a 'natural thing to just turn the machine down'.	Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 5: Peaceful final moments					
1	Qualitative interviews	Little difference in the final days and hours of those who died with mask in situ and those who did not. Descriptions tended to be of a peaceful end, no reports of choking or struggling for breath in final moments **(carers)**.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 6: Turning off the machine					
1	Qualitative interviews	The machine continued to operate after death, which made it look to carers like the person was still breathing **(carers)**. Healthcare professionals highlighted the need for families to understand that the machine does this **(healthcare professionals)**.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 7: Professional uncertainty regarding the withdrawal of NIV					
2	Qualitative interviews and survey	Healthcare professionals described some uncertainty regarding how best to manage NIV in the final stage, and whether usage should be withdrawn. Uncertainty on whether to remove NIV seemed partially influenced by the perception that NIV was being used as a ventilator, rather than as providing support **(healthcare professionals)**. There was a need for intentions to be made clear to	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

Study design and sample		Descriptors of themes	Quality assessment		
Number of studies	**Design**		**Criteria**	**Rating**	**Overall**
		everyone, and for time to be taken to discuss ethical issues and issues related to capacity and ADRTs with staff. Some construed the process as causing the death and potentially open to external criticism. It was not clear that allowing death to occur, rather than causing death, was fully appreciated by all involved **(healthcare professionals).** Some healthcare professionals feel that withdrawal of NIV is different to withdrawal of other treatments.			
Sub-theme 8: Concerns regarding NIV use at end of life					
1	Qualitative interviews	The majority described positive experiences of NIV usage at end of life **(carers);** 3 professionals mentioned concerns. Two healthcare professionals recalled that the mask could muffle the patient trying to communicate. One healthcare professional found that the patient's dependency on the mask meant that their mouth care deteriorated in the final phase.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 9: Emotional burden					
1	Survey	The healthcare professionals managed the emotions of others (patient, family and staff) throughout the process, including through supporting others and conflict resolution. Concerns about causing harm or distress to the patient were common, and about death related to an action, albeit not the intention of the action.	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	
Sub-theme 10: Team involvement					
2	Qualitative interviews and survey	Many carers found that medical professionals had limited involvement in the final phase; decisions regarding end-of-life NIV were made by professionals in community teams. A recurrent theme in the survey was for NIV withdrawal to be a multidisciplinary team decision **(healthcare professionals).**	Applicability of evidence	Applicable[a]	Moderate
			Theme saturation/sufficiency	Not saturated[b]	

a Applicable if evidence was directly applicable to the question, partially applicable if it was related but not sufficiently
b Theme saturated if the findings for a theme were based on a broad range of views, including quotes and experience from a range of people and authors followed up enough people to have sufficient saturation of data

21.8 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

21.9 Evidence statements

21.9.1 Clinical

Planning and timing

- Deterioration at the end of life occurred more rapidly than expected so patients were not as prepared as they had hoped, which had good and bad points (healthcare professionals and carers). A great deal of time and planning was involved in discussing advance care decisions or planning, but there was the need for staff with knowledge of the care plan to be available at critical points (healthcare professionals).

Avoidance of hospital

- Patients wished to die at home but a few had not been able to. They avoided going to hospital in case they were admitted, this leading to difficult decisions about whether to call an ambulance or not (healthcare professionals and carers).

Attempts to resuscitate

- Some patients were subjected to attempts at cardiopulmonary resuscitation, which was distressing for families (healthcare professionals and carers). Some patients had advance directives, but some did not and it was a difficult subject for healthcare professionals to broach, particularly as the disease progressed so quickly (healthcare professionals).

Decision-making regarding the withdrawal of NIV

- Decisions about whether and how NIV should be discontinued did not arise in the patients within the qualitative review but it was part of healthcare professionals' prior experience that those who discussed it usually decided to keep the NIV in place (healthcare professionals). Healthcare professionals had concerns as to whether or not to wean ventilation, how to manage distressing symptoms and the use of sedative drugs (what and how), and who should remove the mask. Weaning was considered for 2 patients, but did not occur. Healthcare professionals recalled 2 experiences of weaning for patients outside this study, with one describing it as a 'natural thing to just turn the machine down'.

Peaceful final moments

- There was little difference in the final days and hours of those who died with mask in situ and those who did not. Descriptions tended to be of a peaceful end, with no reports of choking or struggling for breath in the final moments (carers).

Turning off the machine

- The machine continued to operate after death, which made it look to carers like the person was still breathing (carers). Healthcare professionals thought there was a need to let families know that the machine does this.
- Healthcare professionals described some uncertainty regarding how best to manage NIV in the final stages, and whether usage should be withdrawn. This was partially influenced by the

perception that NIV was being used as a ventilator, rather than as providing support (healthcare professionals).

Professional uncertainty regarding the withdrawal of NIV

- There was a need for intentions to be made clear to everyone, and for time to be taken to discuss ethical issues and issues related to capacity and ADRTs with staff. Some construed the process as causing the death and felt potentially open to external criticism. It was not clear that allowing death to occur, rather than causing death, was fully appreciated by all involved (healthcare professionals). It was viewed as very different compared to withdrawal of other treatments.

Concerns regarding NIV use at end of life

- The majority described positive experiences of NIV usage at end of life (carers); 3 healthcare professionals mentioned concerns such as the mask muffling the patient's communication. One healthcare professional found that the patient's dependency on the mask meant their mouth care deteriorated in the final phase.

Emotional burden

- Healthcare professionals managed the emotions of others (patient, family and staff) throughout the process, including supporting others and conflict resolution. Concerns about causing harm or distress to the patient were common, and about death related to an action, albeit not the intention of the action.

Team involvement

- Many carers found medical professionals had limited involvement in the final phase; decisions regarding end-of-life NIV were made by professionals in community teams.
- A recurrent theme was for NIV withdrawal to be a multidisciplinary team decision (healthcare professionals).

21.9.2 Economic

- No relevant economic evaluations were identified.

21.10 Recommendations and link to evidence

Recommendations	**95. When discussing non-invasive ventilation, explain 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 medication for breathing problems** • **psychological techniques and support. [new 2016]** **96. Check that the person thinking about non-invasive ventilation:** • **understands what non-invasive ventilation is and 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.** • **understands possible problems with compatibility with other equipment, for example, eye gaze access systems.[new 2016]** **97. 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. Inform people that medicines can be used to alleviate symptoms (see recommendation 121). [new 2016]**
Relative values of different outcomes	This qualitative review aimed to analyse the experiences of families, carers and health professionals of discontinuation of NIV. Information from interviews and focus groups was synthesised into themes and sub-themes through thematic analysis.
Trade-off between clinical benefits and harms	The review outlined the type of information and support that people with MND, their families and carers required in coping with NIV and withdrawing it. The evidence indicated that having these discussions early in the process was helpful in how people coped with NIV.
Trade-off between net health effects and costs	No relevant economic evaluations were identified. Informal discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations.
Quality of evidence	All the evidence was adequate as it was applicable to the review question. The themes were not saturated, apart from 'planning and timing'. The studies were graded as Moderate or High quality.
Other considerations	The GDG agreed that a person's experience of discontinuation of NIV was heavily influenced by conversations with healthcare professionals before initiation. The GDG discussed what should be included in the conversations and recommended items that should be included in all such discussions. The GDG emphasised that NIV is one of a number of treatments for breathlessness and as such people should be made aware of other ways of managing breathlessness. NIV has advantages and disadvantages and these should be communicated to the potential recipient in the initial discussions. The GDG stated that these conversations should be repeated at different points over the course of a person's illness and should include common concerns such as problems with dependency on NIV, how to treat infection, and how to recognise and cope with a distressing situation. The GDG felt it was important that people with MND and their family members and/or carers have a realistic understanding of what NIV is and what it can achieve. They agreed that its use should be reviewed regularly and that people with MND should be provided with enough information to make decisions about how and when to use it. The GDG were aware that many people with MND use NIV in ways that suit their needs and considered that people should be empowered to do this. The GDG also discussed how important it was for people with MND and their family and/or carers to understand how the NIV machine works. In one study, carers and families spoke of the emotional distress when the NIV machine continued to operate after death, making it look like the person was still breathing. The GDG considered that a more comprehensive understanding of NIV might help conversations about stopping NIV and alleviate some of the distress reported by carers. The GDG stated that NIV can be discontinued at any time and healthcare professionals can offer help and

	advice if required. For those people who are dependent on NIV, healthcare professionals can offer help and support. The available evidence indicated that stopping NIV is a situation that many palliative care doctors had not had experience of and which they had concerns about.

21.11 Recommendations from CG105 unchanged

Recommendations

98. Ensure that families and carers:

- **have an initial assessment if the person they care for decides to use non-invasive ventilation, which should include:**
  - **i. their ability and willingness to assist in providing non-invasive ventilation**
  - **ii. their training needs**
- **have the opportunity to discuss any concerns they may have with members of the multidisciplinary team, the respiratory ventilation service and/or other healthcare professionals. [2010]**

Identification and assessment of respiratory impairment

Symptoms and signs

99. Monitor the symptoms and signs listed in box 1 to detect potential respiratory impairment. [2010, amended 2016]

Box 1 Symptoms and signs of potential respiratory impairment

Symptoms	Signs
Breathlessness	Increased respiratory rate
Orthopnoea	Shallow breathing
Recurrent chest infections	Weak cough[1]
Disturbed sleep	Weak sniff
Non-refreshing sleep	Abdominal paradox (inward movement of the abdomen during inspiration)
Nightmares	Use of accessory muscles of respiration
Daytime sleepiness	Reduced chest expansion on maximal inspiration
Poor concentration and/or memory	

Confusion	
Hallucinations	
Morning headaches	
Fatigue	
Poor appetite	

[1] Weak cough could be assessed by measuring peak cough flow.

Respiratory function tests

100. 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 person's baseline respiratory function:

- **oxygen saturation measured by pulse oximetry (SpO_2):**

i. **this should be a single measurement of SpO_2 with the person at rest and breathing room air**

ii. **if it is not possible to perform pulse oximetry locally, refer the person to a respiratory ventilation service.**

Then one or both of the following:

- **forced vital capacity (FVC) or vital capacity (VC)[f]**
- **sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP). [2010]**

101. If the person has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment:

- **ensure that SpO_2 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 person. [2010]**

102. 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 box 1)**
- **the rate of progression of MND**
- **the person's preference and circumstances. [2010, amended 2016]**

103. Perform arterial or capillary blood gas analysis if the person's SpO_2

[f] The difference between the measurement of vital capacity and forced vital capacity is very subtle and so either can be used.

(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 person to a respiratory ventilation service. [2010]

104. If the person's SpO_2 (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 respiratory ventilation service for continuous 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 person agrees) their family and carers. [2010]**

105. If the person's arterial partial pressure of carbon dioxide ($PaCO_2$) is greater than 6 kPa:

- **refer them urgently to a respiratory ventilation service (to be seen within 1 week) and**
- **explain the reasons for and implications of the urgent referral to the person and (if the person agrees) their family and carers. [2010]**

106. If the person's $PaCO_2$ is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnoea (see recommendation 107):

- **refer them to a respiratory ventilation service for nocturnal (overnight) oximetry and/or a limited sleep study and**
- **discuss both the impact of respiratory impairment and treatment options with the person and (if the person agrees) their family and/or carers (as appropriate). [2010]**

107. If any of the results listed in box 2 is obtained, discuss with the person and (if appropriate) their family and carers:

- **their respiratory impairment**
- **their treatment options**
- **possible referral to a respiratory ventilation service for further assessment based on discussion with the person, and their wishes. [2010, amended 2016]**

Box 2 Results of respiratory function tests

Forced vital capacity (FVC) or vital capacity (VC)	**Sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)** **(if both tests are performed,**

	base the assessment on the better respiratory function reading)
FVC or VC less than 50% of predicted value **FVC or VC less than 80% of predicted value plus any symptoms or signs of respiratory impairment (see recommendation 99), particularly orthopnoea**	**SNIP or MIP less than 40 cmH_2O** **SNIP or MIP less than 65 cmH_2O for men or 55 cmH_2O for women plus any symptoms or signs of respiratory impairment (see recommendation 99), particularly orthopnoea** **Repeated regular tests show a rate of decrease of SNIP or MIP of more than 10 cm H_2O per 3 months**

People with a diagnosis of frontotemporal dementia

108. 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[g]**
- **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. [2010, amended 2016]**

Non-invasive ventilation for treatment of respiratory impairment in people with MND

109. 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]

110. 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]

111. Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should carry out and coordinate a patient-centred risk assessment, after discussion with the

[g] See Mental Capacity Act 2005.

person and their family and carers. This should consider:

- **the most appropriate type of non-invasive ventilator and interfaces, based on the person's needs and lifestyle factors and safety**
- **the person's tolerance of the treatment**
- **the risk, and possible consequences, of ventilator failure**
- **the power supply required, including battery back-up**
- **how easily the person 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. [2010]**

112. Before starting non-invasive ventilation, the multidisciplinary team together with the respiratory ventilation service should prepare a comprehensive care plan, after discussion with the person and their family and carers (who should be offered a 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 augmentation (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]**

113. When starting non-invasive ventilation:

- **perform initial acclimatisation during the day when the person is awake**
- **usually start regular treatment at night, before and during sleep**
- **gradually build up the person's hours of use as necessary. [2010]**

114. Continue non-invasive ventilation if the clinical reviews show:

- **symptomatic and/or physiological improvements for a person without severe bulbar impairment and without severe cognitive problems**
- **an improvement in sleep-related symptoms for a person with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment. [2010]**

	115. 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:** i. **emergency procedures** ii. **night-time assistance if the person is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)** iii. **how to use the equipment with a wheelchair or other mobility aids if required** iv. **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 the person and their family and carers. [2010, amended 2016]** **116. Discuss all decisions to continue or withdraw non-invasive ventilation with the person and (if the person agrees) their family and carers. [2010]** **117. Before a decision is made on the use of non-invasive ventilation for a person with a diagnosis of frontotemporal dementia, the multidisciplinary team together with the respiratory ventilation service should carry out an assessment that includes:** • **the person's capacity to make decisions and to give consent[h]** • **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]**

21.12 Management of discontinuation of NIV

21.13 Introduction

NICE clinical guideline 105 (2010) addressed the initiation of NIV to manage ventilatory insufficiency for people with MND. This has facilitated increased awareness about and uptake of NIV with attendant improvements in quality of life and length of survival for many people with MND. However, NIV does not affect the progression of disability due to weakness in non-respiratory muscles. In this context, at some point in the progression of their condition, some patients may wish to discontinue NIV and seek non-life-sustaining ways to palliate respiratory symptoms. This will include patients who are regular NIV users but not dependent as well as those who can only breath

[h] See Mental Capacity Act 2005

for a few minutes or not at all without mechanical support. This chapter examines the evidence base for the different ways of stopping NIV treatment.

21.14 Review question: What is the most appropriate management of discontinuation, at a patient's request, of NIV?

For full details see the review protocol in Appendix C.

Table 125: PICO characteristics of review question

Population	Adults (aged 18 and over) with MND
Interventions	• Immediate discontinuation • Gradual discontinuation
Comparison	To each other
Outcomes	Critical: • Pain • Distress of the person with MND • Respiratory symptoms including rapid breathing • Time to death
Study design	Cohort studies (prospective or retrospective)

21.15 Clinical evidence

No relevant clinical studies comparing immediate discontinuation with gradual discontinuation were identified.

21.16 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

21.17 Evidence statements

21.17.1 Clinical

No relevant clinical evidence was identified.

21.17.2 Economic

- No relevant economic evaluations were identified.

21.18 Recommendations and link to evidence

Recommendations	**118. Consider prescribing medicines to help ease breathlessness that people using non-invasive ventilation can take on an 'as-needed' basis at home, for example, opioids[i] or benzodiazepines. [new 2016]** **119. Inform services that may see the person in crisis situations, such as their GP and services that provide emergency or urgent care, that the person is using non-invasive ventilation. [new 2016]** **Stopping non-invasive ventilation** **120. The healthcare professionals responsible for starting non-invasive ventilation treatment in people with MND should ensure that support is available for other healthcare professionals who may be involved if there is a plan to stop non-invasive ventilation, including the legal and ethical implications. [new 2016]** **121. If a person on continuous non-invasive ventilation wishes to stop treatment, ensure that they have support from healthcare professionals with knowledge and expertise of:** • **stopping non-invasive ventilation** • **the ventilator machine** • **palliative medicines (see the NICE guideline on care of the dying adult)** • **supporting the person, family members and/or carers (as appropriate)** • **supporting other healthcare professionals involved with the person's care** • **legal and ethical frameworks and responsibilities. [new 2016]** **122. If a person on continuous non-invasive ventilation wishes to stop treatment, seek advice from healthcare professionals who have knowledge and experience of stopping non-invasive ventilation. [new 2016]** **123. Healthcare professionals involved in stopping non-invasive ventilation should have up-to-date knowledge of the law regarding the Mental Capacity Act, DNACPR, ADRT orders and Lasting Power of Attorney. [new 2016]**
Relative values of different outcomes	The critical outcomes for this evidence review were pain, distress of the person with MND, respiratory symptoms including rapid breathing, and time to death.
Trade-off between clinical benefits and harms	No relevant clinical studies were identified.

[i] At the time of publication (February 2016), these medicines did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information

Trade-off between net health effects and costs	No relevant economic evaluations were identified. Informal discussion by the GDG of cost-effectiveness highlighted that there were no additional costs to current practice to be incurred as a result of the recommendations.
Quality of evidence	No relevant clinical studies were identified.
Other considerations	The recommendations were informed by the qualitative review on experience of stopping of NIV and the experience of GDG members. The GDG were aware that people use NIV in a variety of ways. The GDG considered it important that people who are using NIV be offered medicines such as opiates and benzodiazepines to have at home to help them manage their breathing difficulties. The GDG acknowledged that not all people will want these medicines at home. Communication about the use of NIV also needs to be circulated appropriately to services such as out-of-hours services. The GDG were aware that many people stop using NIV without advice from healthcare professionals, but it is not known whether people suffer distress. People who become distressed or anxious when they stop NIV are likely to be those who will particularly benefit from increased support. A person with MND who is on NIV may request for it to be withdrawn. Withdrawal of NIV can be accomplished either abruptly (immediate discontinuation) or through a gradual process of turning the ventilator down (weaning). The GDG agreed that there was insufficient evidence and consensus to recommend either immediate discontinuation or gradual discontinuation above the other. The GDG emphasised that management of withdrawal of NIV by healthcare professionals is an uncommon situation in a rare disease. For this reason, direct expertise of management of withdrawal is rare and there is little published evidence in the area. However, the GDG did feel that a number of consensus recommendations could be made that would promote better experiences of withdrawal from NIV for both the person with MND and their family and/or carers and healthcare professionals. The GDG agreed that discussions about whether to discontinue NIV and the management of discontinuation should be ongoing from the time when NIV is initiated. It was highlighted that the use of pharmacological treatments for breathlessness should be explored with the person with MND. Discontinuation of NIV may lead to end of life and discussion about discontinuation could also involve revisiting advance directives, Advance Decision to Refuse Treatment (ADRTs) and No Not Attempt Resuscitation (DNAR) orders. The GDG stated that misinformation about the ethical and legal issues surrounding discontinuation of NIV can be a barrier for healthcare professionals. The GDG were aware of cases where healthcare professionals have refused to be involved in the process due to the perception of discontinuation as euthanasia. The GDG agreed that a comprehensive underpinning of the legal and ethical issues involved in discontinuation among those leading the process would lead to better outcomes. It was also felt that ADRTs and DNARs should be attached to the letter from the respiratory physician involved in initiation or review of NIV, and this would improve community practitioner's knowledge about issues involved in withdrawing treatment. The rarity of withdrawal means that many professionals will not have had experience of it. When people are at the end of life they may be at home under the care of community professionals rather than specialists at an MDT centre. If NIV withdrawal is planned, people who have the relevant skills and expertise should be identified to assist in a number of areas: practical expertise and knowledge of the ventilator

	machine, the use of palliative medication, people to support the person with MND, family members and/or carers (as appropriate). Appropriate support within the healthcare professional community must also be available to support other healthcare professionals both emotionally and in understanding the legal and ethical frameworks. Prior to discontinuation, there should be discussion with the carer about the process of death. Additionally, key decisions should be made within the healthcare team: for example, who will remove the mask for immediate discontinuation. The GDG were aware of consensus guidelines on withdrawal of NIV developed in different areas that healthcare professionals can consult in addition to or in the absence of their own local guidelines. Leicester, Leicestershire and Rutland: http://www.loros.co.uk/healthcare-professionals/clinical-guidelines/ Dorset: http://www.mndassociation.org/Resources/MNDA/Professionals/Documents/Pathways%20and%20guidelines/Withdrawing%20NIV%20Draft%20Guidelines%20-%20Dorset%20feb%2011.doc North Staffordshire: http://palliativedrugs.com/download/120517_Guidelines%20for%20withdrawing%20NIV.pdf Association of Palliative Medicine position statement on withdrawal of ventilatory support at the request of an adult patient[121]

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23 Acronyms and abbreviations

Acronym or abbreviation	Description
AAC	Augmentative and alternative communication
ACBT	Active cycle of breathing techniques
ADRT	Advanced Decisions to Refuse Treatment
ALS	Amyotrophic lateral sclerosis
ALSFRS	Amyotrophic lateral sclerosis functional rating scale
ALSFRS-R	Amyotrophic lateral sclerosis functional rating scale revised
BIPAP	Bilevel positive airway pressure
BMI	Body mass index
BNF	British National Formulary
CADL	Complex aids of daily living
CI	Confidence intervals
CSI	Caregiver Strain Index
DNACPR	Do Not Attempt Cardiopulmonary Resuscitation
EQ-5D	EuroQol-5 dimension
ENT	Ear, nose and throat
FES	Functional electrical stimulation
FSS	Fatigue severity scale
FTD	Frontotemporal dementia
FVC	Forced vital capacity
GAP	Gravity assisted positioning
GPB	Glossopharyngeal breathing
ICER	Incremental cost-effectiveness ratio
IMNDA	Irish Motor Neurone Disease Association
IMT	Inspiratory muscle training
IPA	Interpretative phenomenological analysis
IPAP	Inspiratory positive airway pressure
LPA	Lasting Power of Attorney
LVR	Lung volume recruitment
MAMC	Mid-arm muscle circumference
MCS	Mental component summary of the SF-36 (short form health summary questionnaire)
MDT	Multidisciplinary team
MIC	Maximal insufflation capacity
MI-E	Mechanical in-exsufflator
MND	Motor neurone disease
MRC scale	Medical Research Council scale
MUAC	Mid-upper arm circumference
MUST	Malnutrition universal screening tool
MVC	Maximal voluntary contraction
MVIC	Maximum voluntary isometric contraction
NIV	Non-invasive ventilation

Acronym or abbreviation	Description
NPV	Negative predictive value
PCF	Peak cough flow
PDA	Personal digital assistant
PEG	Percutaneous endoscopic gastrostomy
PIG	Per-oral image guided gastrostomy
PLS	Primary lateral sclerosis
PPC	Preferred priorities for care
PPV	Positive predictive value
QALYs	Quality-adjusted life-years
QOL	Quality of life
RIG	Radiologically inserted gastrostomy
RMT	Respiratory muscle training
ROM	Range of motion
SADL	Simple aids of daily living
SAQLI sym	Sleep apnoea quality of life index symptom domain
SD	Standard deviation
SEIQOL	Schedule for the Evaluation of Individual Quality of Life
SEIQOL-DW	Schedule for the Evaluation of Individual Quality of Life - Direct Weighting
SF	Short form
SNIP	Sniff nasal inspiratory pressure
SOBAR	Shortness of breath at resting
SOBOE	Shortness of breath on exertion
SRQ	St Georges Respiratory Questionnaire
TCA	Tricyclic antidepressant
TEE	Thoracic expansion exercises
TENS	Transcutaneous electrical nerve stimulation
TMS	Transcranial magnetic stimulation
TSFT	Triceps skin fold thickness
UCL	Utrecht Coping List
VAS	Visual analogue scale

24 Glossary

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

General terms used in this guideline

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the

Term	Definition
	condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.

Term	Definition
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is

Term	Definition
	that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
EQ-5D (EuroQol-5 dimension)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of

Term	Definition
	whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Term	Definition
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See ‘Health-related quality of life’.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Term	Definition
	QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive

Term	Definition
	result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term ‘Sensitivity’. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.

Term	Definition
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

Guideline-specific terms used

Term	Definition
Active cycle of breathing techniques	A set of breathing exercises that loosens and moves the sputum from the airways.
Advance care planning	Discussion and recording of a person's wishes relating to their care made while the person is able to do so, and allowing their wishes to be known if they later lose capacity to make decisions.
Amyotrophic lateral sclerosis	The most common form of MND. It affects both upper and lower motor neurones.
Atrophy	The partial or complete wasting away of a part of the body.
Augmentative and alternative communication systems (AAC)	Devices or methods used to replace or supplement speech for people who have impaired speech or who are unable to use verbal speech to communicate.
Bilevel positive airway pressure	Used during mechanically-assisted ventilation. It delivers air at alternating levels of pressure—higher for inspiration and lower for expiration.
Breath stacking	Taking several small breaths in without breathing out in-between. This technique is used to increase the volume of air taken into the lungs, therefore strengthening the cough. It may be conducted with a manual resuscitation bag and is also known as lung volume recruitment (LVR).
Cognitive behavioural therapy	A talking therapy that can help a person to manage their problems by changing the way they think and behave.
Cognitive impairment	A reduction in intellectual functioning, such as a reduced ability to think, reason or remember. It is not necessarily severe enough to interfere with everyday life.
Complex aids of daily living	Examples include mobile seat hoists (powered), variable posture beds, lifting cushions, back rests with pressure relieving features. See also 'Simple aids of daily living'.
Complex needs in AAC assessment criteria	Where a person, in addition to impairment of the voice, loses hand function and therefore cannot use more basic text-to-speech communication aids.
Do Not Attempt Cardiopulmonary Resuscitation	A written statement to not give cardiopulmonary resuscitation if someone has a cardiac arrest.
Dysarthria	A motor speech disorder resulting from neurological injury, characterised by poor articulation.
Dysphagia	Difficulty in swallowing.
Dyspnoea	Difficulty breathing.
Fasciculation	A small, local, involuntary muscle contraction (twitching) visible under the skin arising from the spontaneous discharge of a bundle of skeletal muscle fibres.

Term	Definition
Foot drop (or drop foot)	A muscular weakness or paralysis that makes it difficult to lift the front part of the foot and toes.
Forced expiratory volume	A measure of how much air a person can exhale during a forced breath. The amount of air exhaled may be measured during the first (FEV1), second (FEV2), and/or third seconds (FEV3) of the forced breath.
Forced vital capacity	The total amount of air exhaled during the FEV test (See forced expiratory volume).
Frontotemporal dementia	A type of dementia associated with shrinking of the frontal and temporal anterior lobes of the brain. The symptoms of FTD fall into two clinical patterns that involve either changes in behaviour or problems with language. Spatial skills and memory remain intact. There is a strong genetic component to the disease and it often runs in families.
Functional electrical stimulation	Stimulation of the peripheral nerves that supply the paralysed muscle using electrodes that may be implanted or placed on the surface of the skin. The aim is to restore muscular function.
Gastrostomy	A surgical opening through the abdomen into the stomach. A feeding device is inserted through this opening, which allows the person to be fed directly into their stomach, bypassing the mouth and throat.
Glossopharyngeal breathing	A technique of forcing air into the lungs with the pharynx and tongue muscles. The technique can be taught to patients whose respiratory muscles are weak.
Gravity-assisted positioning	Body positions used to aid the drainage of secretions.
Inspiratory muscle training	A component of respiratory muscle training (see respiratory muscle training).
Inspiratory positive airway pressure	Applied during the inspiratory phase of mechanically-assisted ventilation.
Lung volume recruitment	See ‘breath stacking’.
Manual assisted coughing	Used to significantly increase peak cough flow by a well-timed abdominal thrust or thoracic compression from a carer/relative of the patient during the expiratory phase of a cough.
Maximal expiratory pressure (PEmax)	A measure of the strength of the respiratory muscles, obtained by having the patient exhale as strongly as possible with the mouth against a mouthpiece. The maximum value is near total lung capacity.
Maximal inspiratory pressure (PImax)	A measure of the strength of the respiratory muscles, obtained by having the patient inhale as strongly as possible with the mouth against a mouthpiece. The maximum value is near the residual volume.
Maximal insufflation capacity	The largest amount of air that can be held in the lungs.
Mechanical in-exsufflator	Delivers a positive-pressure insufflation followed by an expulsive exsufflation, thereby simulating a normal cough.
Multidisciplinary team	A team of healthcare professionals all of whom contribute their expertise in providing care independent of each other, with clearly defined roles.
Non-invasive ventilation	Non-invasive ventilation refers to methods of providing ventilatory support to a patient without placing an artificial airway in the main windpipe (trachea). This is usually achieved by fitting a mask covering the nose or mouth and nose, or using nasal tubes or a mouthpiece, which is connected to a ventilator by tubing. The ventilator detects when the patient tries to take a breath in and delivers an extra flow of air to increase the volume of air inhaled.
Palliative care	Treatment to relieve the symptoms of a serious illness. It aims to keep the patient comfortable, improve quality of life and provide support, rather than to treat the disease itself.

Term	Definition
Peak cough flow	Used to assess the strength and speed exerted by expiration in litres per minute by means of a voluntary cough (that is, a maximal inspiration followed by a fast expiration).
Percutaneous endoscopic gastrostomy	A method of inserting a feeding tube used in gastrostomy (see gastrostomy). The tube is inserted directly into the stomach through a small incision in the abdominal wall with the assistance of an instrument known as an endoscope.
Personal digital assistant	A handheld device that combines features including computing, Internet, telephone/fax and networking.
Per-oral image guided gastrostomy	A method of inserting a feeding tube used in gastrostomy (see gastrostomy). The tube is inserted into the mouth and down to the stomach using X-ray guidance.
Preferred priorities for care (PPC) document	A document designed to help people prepare for the future. It gives them an opportunity to think about, talk about and write down their preferences and priorities for care at the end of life. It is useful when recording advance care planning. It should be considered by professionals and family but is not a legal document unlike the ADRT or DNACPR. It was developed by the NHS End of life care programme. It is a tool to be used to fulfil advance care planning.
Primary lateral sclerosis	A rare type of MND that affects the upper motor neurones.
Progressive bulbar palsy	A type of MND that affects both the upper and lower motor neurones, with the lowest motor neurones of the brain stem being most affected.
Progressive muscular atrophy	A form of MND which initially affects the lower motor neurones leading to weakness and wasting of muscles, often of the arms but may be of the legs. It is more common in men and starts at an earlier age, and has a longer prognosis.
Pulse oximetry	A non-invasive method that allows the oxygenation of a patient's haemoglobin to be monitored, which gives a value for oxygen saturation.
Radiologically inserted gastrostomy	A method of inserting a feeding tube used in gastrostomy (see gastrostomy). The tube is inserted through the skin directly into the stomach using X-ray guidance.
Range of motion exercise	Putting the joint through its full range of normal movements, either actively or passively.
Respiratory muscle training	A series of exercises, breathing and other, to increase the strength of the respiratory muscles and therefore improve respiration.
Sialorrhea	Drooling with watery saliva.
Simple aids of daily living	Examples include grab rails, modified eating utensils, sliding transfer board, toilet frame and seat. See also 'Complex aids of daily living'.
Sniff nasal inspiratory pressure	Peak nasal pressure is measured in one nostril during a maximal sniff performed through the other nostril.
Thoracic expansion exercises	A component of active cycle of breathing techniques.
Transcranial magnetic stimulation	Non-invasive method that uses electromagnetic induction to induce weak electric currents using a rapidly changing magnetic field allowing the functioning and interconnections of the brain to be studied.
Transcutaneous electrical nerve stimulation	A method of producing electroanalgesia through electrodes applied to the skin.