Motor neurone disease

The use of non-invasive ventilation in the management of motor neurone disease
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Introduction

Motor neurone disease (MND) is a fatal neurodegenerative disease. It is characterised by the onset of symptoms and signs of degeneration of primarily the upper and lower motor neurones. This leads to progressive weakness of the bulbar, limb, thoracic and abdominal muscles. Respiratory muscle weakness resulting in respiratory impairment is a major feature of MND, and is a strong predictor of quality of life and survival. Non-invasive ventilation can improve symptoms and signs related to respiratory impairment and hence survival.

There is currently no evidence-based guideline for use in England, Wales and Northern Ireland that addresses the use of non-invasive ventilation in patients with MND. This guideline considers the signs and symptoms that can be used for predicting respiratory impairment in patients with MND, the diagnostic accuracy of investigations for detecting and monitoring respiratory impairment, the clinical and cost effectiveness of non-invasive ventilation for treating respiratory impairment and the information and support needs of patients and their families and carers relating to the use of non-invasive ventilation.
Patient-centred care

This guideline offers best practice advice on the use of non-invasive ventilation in the care of adults (aged 18 and over) with a diagnosis of motor neurone disease (MND).

Treatment and care should take into account patients’ needs and preferences. People with MND should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health’s advice on consent (available from [www.dh.gov.uk/consent](http://www.dh.gov.uk/consent)) and the code of practice that accompanies the Mental Capacity Act (summary available from [www.publicguardian.gov.uk](http://www.publicguardian.gov.uk)). In Wales, healthcare professionals should follow advice on consent from the Welsh Assembly Government (available from [www.wales.nhs.uk/consent](http://www.wales.nhs.uk/consent)).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient’s needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.
1 Summary

1.1 List of all recommendations

Multidisciplinary team

1.1.1 A multidisciplinary team should coordinate and provide ongoing management and treatment for a patient with MND, including regular respiratory assessment and provision of non-invasive ventilation.

- The team should be led by a healthcare professional with a specific interest in MND. The leader should ensure that the patient’s multidisciplinary care plan (see recommendation 1.1.19) is coordinated and is communicated to relevant healthcare and social care professionals, including the patient’s primary care team, as well as to the patient and (where appropriate) their family and carers.

- The team should include a neurologist, a respiratory physician, an MND specialist nurse, a respiratory specialist nurse, a specialist respiratory physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist (team members do not have to be at the same location).

- Access to other healthcare professionals should be provided as needed.

- Team members who provide non-invasive ventilation should have appropriate competencies.
Information and support needs of patients with MND and their families and carers

1.1.2 Offer to discuss the possible use of non-invasive ventilation with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times:

- soon after MND is first diagnosed
- when monitoring respiratory function
- when respiratory function deteriorates
- if the patient asks for information.

1.1.3 Discussions should be appropriate to the stage of the patient’s illness, carried out in a sensitive manner and include information on:

- the possible symptoms and signs of respiratory impairment (see table 1 in recommendation 1.1.7)
- the natural progression of MND and what to expect in the future
- the purpose, nature and timing of respiratory function tests, and explanations of the test results
- available interventions for managing respiratory impairment, including the benefits and limitations of each intervention
- accessing and using respiratory equipment, including that for non-invasive ventilation
- how non-invasive ventilation (as a treatment option) can improve symptoms associated with respiratory impairment and can be life prolonging, but does not stop progression of the underlying disease
- how non-invasive ventilation can be withdrawn
- palliative strategies as an alternative to non-invasive ventilation.

1.1.4 Inform all relevant healthcare professionals about key decisions reached with the patient and their family and carers.
1.5 Provide the patient and their family and carers with support and assistance to manage non-invasive ventilation. This should include:

- training on using non-invasive ventilation and ventilator interfaces, for example:
  - emergency procedures
  - night-time assistance if the patient is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)
  - how to use the equipment with a wheelchair or other mobility aids if required
  - what to do if the equipment fails
- assistance with secretion management
- information on general palliative strategies
- an offer of ongoing emotional and psychological support\(^1\) for the patient and their family and carers.

1.6 Ensure that families and carers:

- have an initial assessment if the patient they care for decides to use non-invasive ventilation, which should include:
  - their ability and willingness to assist in providing non-invasive ventilation
  - their training needs
- have the opportunity to discuss any concerns they may have with members of the multidisciplinary team and/or other healthcare professionals.
Identification and assessment of respiratory impairment in patients with MND

Symptoms and signs

1.1.7 Monitor the symptoms and signs listed in Table 1 routinely to detect potential respiratory impairment.

Table 1 Symptoms and signs of potential respiratory impairment

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Breathlessness</td>
<td>Increased respiratory rate</td>
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<tr>
<td>Orthopnoea</td>
<td>Shallow breathing</td>
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<tr>
<td>Recurrent chest infections</td>
<td>Weak cough²</td>
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<tr>
<td>Disturbed sleep</td>
<td>Weak sniff</td>
</tr>
<tr>
<td>Non-refreshing sleep</td>
<td>Abdominal paradox (inward movement of the abdomen during inspiration)</td>
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<tr>
<td>Nightmares</td>
<td>Use of accessory muscles of respiration</td>
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<tr>
<td>Daytime sleepiness</td>
<td>Reduced chest expansion on maximal inspiration</td>
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<tr>
<td>Poor concentration and/or memory</td>
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<tr>
<td>Confusion</td>
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<td>Hallucinations</td>
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<td>Morning headaches</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Poor appetite</td>
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</table>
Respiratory function tests

1.1.8 As part of the initial assessment to diagnose MND, or soon after diagnosis, a healthcare professional from the multidisciplinary team who has appropriate competencies should perform the following tests (or arrange for them to be performed) to establish the patient’s baseline respiratory function:

- oxygen saturation measured by pulse oximetry (SpO₂):
  - this should be a single measurement of SpO₂ with the patient at rest and breathing room air
  - if it is not possible to perform pulse oximetry locally, refer the patient to a specialist respiratory service

then one or both of the following:

- forced vital capacity (FVC) or vital capacity (VC)
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)

1.1.9 If the patient has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment:

- ensure that SpO₂ is measured (at rest and breathing room air)
- do not perform the other respiratory function tests (FVC, VC, SNIP and MIP) if interfaces are not suitable for the patient.

1.1.10 A healthcare professional with appropriate competencies should perform the respiratory function tests every 3 months, although tests may be performed more or less often depending on:

- whether there are any symptoms and signs of respiratory impairment (see recommendation 1.1.7)
- the rate of progression of MND
- the patient’s preference and circumstances.
1.1.11 Perform arterial or capillary blood gas analysis if the patient’s SpO₂ (measured at rest and breathing room air):

- is less than or equal to 92% if they have known lung disease
- is less than or equal to 94% if they do not have lung disease.

If it is not possible to perform arterial or capillary blood gas analysis locally, refer the patient to a specialist respiratory service.

1.1.12 If the patient’s SpO₂ (measured at rest and breathing room air) is greater than 94%, or 92% for those with lung disease, but they have sleep-related respiratory symptoms:

- consider referring them to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study and
- discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.

1.1.13 If the patient’s arterial partial pressure of carbon dioxide (PaCO₂) is greater than 6 kPa:

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

1.1.14 If the patient’s PaCO₂ is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnoea (see recommendation 1.1.7):

- refer them to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study and
- discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.
1.1.15 If any of the results listed in table 2 is obtained, discuss with the patient and (if the patient agrees) their family and carers:

- the impact of respiratory impairment
- treatment options
- possible referral to a specialist respiratory service for further assessment.

Table 2 Results of respiratory function tests

<table>
<thead>
<tr>
<th>Forced vital capacity (FVC) or vital capacity (VC)</th>
<th>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)</th>
</tr>
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<tbody>
<tr>
<td>• FVC or VC less than 50% of predicted value</td>
<td>• SNIP or MIP less than 40 cmH2O</td>
</tr>
<tr>
<td>• FVC or VC less than 80% of predicted value plus any symptoms or signs of respiratory impairment (see recommendation 1.1.7), particularly orthopnoea</td>
<td>• SNIP or MIP less than 65 cmH2O for men or 55 cmH2O for women plus any symptoms or signs of respiratory impairment (see recommendation 1.1.7), particularly orthopnoea</td>
</tr>
<tr>
<td>• Repeated regular tests show a rate of decrease of SNIP or MIP of more than 10 cmH2O per 3 months</td>
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Patients with a diagnosis of dementia

1.1.16 Base decisions on respiratory function tests for a patient with a diagnosis of dementia on considerations specific to their needs and circumstances, such as:

- their ability to give consent
- 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.
Non-invasive ventilation for treatment of respiratory impairment in patients with MND

1.1.17 Offer a trial of non-invasive ventilation if the patient's symptoms and signs and the results of the respiratory function tests indicate that the patient is likely to benefit from the treatment.

- Discuss both the benefits and limitations of the intervention with the patient and their family and carers.
- Only consider a trial of non-invasive ventilation for a patient who has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment if they may benefit from an improvement in sleep-related symptoms or correction of hypoventilation.

1.1.18 Before starting non-invasive ventilation, the multidisciplinary team should carry out and coordinate a patient-centred risk assessment, after discussion with the patient and their family and carers. This should consider:

- the most appropriate type of non-invasive ventilator and interfaces, based on the patient’s needs and lifestyle factors
- the patient’s tolerance of the treatment
- the risk, and possible consequences, of ventilator failure
- the power supply required, including battery back-up
- how easily the patient can get to hospital
- risks associated with travelling away from home (especially abroad)
- whether a humidifier is required
- issues relating to secretion management
- the availability of carers.
1.1.19 Before starting non-invasive ventilation, the multidisciplinary team should prepare a comprehensive care plan, after discussion with the patient and their family and carers (who should be offered a copy of the plan). This should cover:

- long-term support provided by the multidisciplinary team
- the initial frequency of respiratory function tests and monitoring of respiratory impairment
- the frequency of clinical reviews of symptomatic and physiological changes
- the provision of carers
- arrangements for device maintenance and 24-hour emergency clinical and technical support
- secretion management and respiratory physiotherapy assessment, including cough-assist therapy (if required)
- training in and support for the use of non-invasive ventilation for the patient and their family and carers
- regular opportunities to discuss the patient’s wishes in relation to continuing or withdrawing non-invasive ventilation, and other end-of-life considerations (see also recommendations 1.1.24 and 1.1.25).

1.1.20 When starting non-invasive ventilation:

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

1.1.21 Continue non-invasive ventilation if the clinical reviews show:

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

1.1.22 Discuss all decisions to continue or withdraw non-invasive ventilation with the patient and (if the patient agrees) their family and carers.

Patients with a diagnosis of dementia

1.1.23 Before a decision is made on the use of non-invasive ventilation for a patient with a diagnosis of dementia, the neurologist from the multidisciplinary team should carry out an assessment that includes:

• the patient’s capacity to make decisions and to give consent
• the severity of dementia and cognitive problems
• whether the patient is likely to accept treatment
• whether the patient is likely to achieve improvements in sleep-related symptoms and/or behavioural improvements
• a discussion with the patient’s family and/or carers (with the patient’s consent if they have the capacity to give it).

Planning end-of-life care

1.1.24 Offer to discuss end-of-life care with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times:

• around the time that MND is first diagnosed (but only if requested by the patient explicitly, or if the patient’s clinical condition indicates that ventilator support will be needed in the immediate future)
• when non-invasive ventilation is accepted or declined

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• when the patient is becoming increasingly dependent on non-invasive ventilation
• if the patient asks for information.

1.1.25 Discussions about end-of-life care should include:

• planning of end-of-life care
• considering advance decisions to refuse treatment
• considering what to do if non-invasive ventilation fails because of either:
  – an acute, but potentially reversible, deterioration in health or
  – irreversible disease progression
• strategies to withdraw non-invasive ventilation if the patient wishes
• the involvement of family and carers in decision making (with the patient’s consent if they have the capacity to give it).

1.2 Care pathways

Care pathways for the assessment of respiratory function and for non-invasive ventilation (see the next two pages) are reproduced from the quick reference guide for the guideline, which is available at

www.nice.org.uk/guidance/CG105/QuickRefGuide
Assessment pathway

Measure SpO₂ (single measurement, with patient at rest and breathing room air)\(^a\)

Then measure one or both of:
- FVC or VC\(^b\)
- SNIP and/or MIP

Do not perform these tests if interfaces are not suitable because the patient has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment

Is SpO₂ less than or equal to:
- 92% if patient has known lung disease
- 94% if no lung disease?

Yes

Perform arterial or capillary blood gas analysis\(^a\)

Is PaCO₂ greater than 6 kPa?

Yes

- Refer the patient urgently to a specialist respiratory service (to be seen within 1 week) and explain the reasons for and implications of the urgent referral to them and (if they agree) their family and carers

If the patient has no symptoms or signs of respiratory impairment, particularly orthopnoea:
- refer them to a specialist respiratory service for overnight oximetry and/or a limited sleep study
- discuss both the impact of respiratory impairment and treatment options with them and (if they agree) their family and carers

If the patient has sleep-related respiratory symptoms:
- consider referring them to a specialist respiratory service for overnight oximetry and/or a limited sleep study
- discuss both the impact of respiratory impairment and treatment options with them and (if they agree) their family and carers

Discuss with the patient and (if the patient agrees) their family and carers:
- the impact of respiratory impairment
- treatment options
- possible referral to a specialist respiratory service for further assessment

No

FVC or VC:
- less than 50% of predicted or
- less than 80% of predicted plus any symptoms or signs of respiratory impairment, particularly orthopnoea or
- SNIP and/or MIP (if both tests are performed; base assessment on the better respiratory function reading):
  - less than 40 cmH₂O or
  - less than 65 cmH₂O for men or 55 cmH₂O for women plus any symptoms or signs of respiratory impairment, particularly orthopnoea or
  - rate of decrease of more than 10 cmH₂O per 3 months in repeated regular tests
Non-invasive ventilation

If patient's symptoms and signs and the results of the respiratory function tests indicate that non-invasive ventilation is likely to be of benefit

Does the patient have:
- severe bulbar impairment or
- severe cognitive problems that may be related to respiratory impairment?

No

- Offer a trial of non-invasive ventilation
- Discuss benefits and limitations with the patient and their family and carers

Yes

- Only consider a trial of non-invasive ventilation if the patient may benefit from an improvement in sleep-related symptoms or correction of hypoventilation
- Discuss benefits and limitations with the patient and their family and carers

Before starting non-invasive ventilation, carry out and coordinate a patient-centred risk assessment and prepare a comprehensive care plan, after discussion with the patient and their family and carers (who should be offered a copy of the plan)

- When starting non-invasive ventilation:
  - perform initial acclimatisation during the day when the patient is awake
  - usually start regular treatment at night, before and during sleep
  - gradually build up hours of use as necessary

Continue if the clinical reviews show symptomatic and/or physiological improvements
- Discuss all decisions to continue or withdraw non-invasive ventilation with the patient and (if the patient agrees) their family and carers

Continue if the clinical reviews show an improvement in sleep-related symptoms
- Discuss all decisions to continue or withdraw non-invasive ventilation with the patient and (if the patient agrees) their family and carers
1.3 Overview

1.3.1 The use of non-invasive ventilation in the management of motor neurone disease

Motor neurone disease (MND) is an incurable and progressive neurodegenerative condition (Eng 2006). It can be defined as a neurodegenerative disorder that is characterised by progressive muscular paralysis and wastage, reflecting degeneration of motor neurones in the primary motor cortex, brainstem and spinal cord (Wijesekera and Leigh 2009). This results clinically in weakness of the bulbar, limb, thoracic and respiratory muscles (Andrews 2009). MND is also commonly known as amyotrophic lateral sclerosis (ALS) (especially in North America) or Lou Gehrig’s disease. Although the cause of MND is unknown, many potential causes have been proposed, including exposure to neurotoxic agents, genetic or autoimmune disease, deficiencies of nerve growth factors, and viral infection (Benditt and Boitano 2008). Although most cases of MND are sporadic, about 5% of patients have a family history of MND (familial MND) (Wijesekera and Leigh 2009).

The annual incidence of MND in England and Wales is approximately 2.9 per 100,000 population (Bourke et al. 2002), and men are slightly more commonly affected than women (ratio of 1.7 to 1). The incidence increases with age, with a mean age of onset of 63 years. It is estimated by the MND Association (www.mndassociation.org) that there might be up to 5000 people with MND in the UK.

The clinical features of MND are the result of the degeneration of both the upper and lower motor neurones. Features resulting from upper motor neurone degeneration include spasticity, hyperactive reflexes, extensor plantar responses, snout reflex, gag reflex and emotional liability. Degeneration of the lower motor neurones can result in atrophy, weakness, fasciculations, hyporeflexia and muscle cramps (spinal symptoms).

Note that some of the included studies in the evidence profiles and evidence tables used the term ‘amyotrophic lateral sclerosis’ rather than motor neurone disease, as they were US-based studies.
Dysarthria, dysphagia, fatigability and respiratory insufficiency are usually caused by a combination of lower and upper motor neurone degeneration (Jackson and Bryan 1998; Andrews 2009).

The disease is progressive, and about 50% of patients survive for around 30 months after the onset of symptoms (Andrews 2009). Fewer than 10% survive beyond 10 years.

The treatment of people with MND is complex for both patients and healthcare professionals because it requires the management of medical problems, severe disability and psychosocial issues. Consequently, expert opinion and some evidence suggest that a multidisciplinary approach is preferable (Radunovic et al. 2007). Pharmacological options for the treatment of MND are limited (Phukan and Hardiman 2009). Although MND is considered incurable, many of the symptoms that arise during the course of the disease are treatable, and all efforts should be made to improve quality of life and help maintain the person’s autonomy for as long as possible (Wijesekera and Leigh 2009).

Respiratory problems are the main cause of death in people with MND. Respiratory weakness causes dyspnoea, either during exertion or at rest, and orthopnoea, but patients can also present with symptoms of nocturnal hypoventilation and sleep disruption (Radunovic et al. 2007). Laboratory assessments that are used to check respiratory function may include measurement of sniff nasal inspiratory pressure (SNIP), forced vital capacity (FVC), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). Other investigations may also be carried out, such as oxygen saturation measured by pulse oximetry (SpO₂) and analysis of arterial or capillary blood gases (to check for hypoxia and hypercapnia respectively) (Corcia and Meininger 2008). No single test of respiratory function or of respiratory muscle weakness can be used to reliably predict the onset of respiratory failure or to identify the most appropriate timing for starting non-invasive ventilation (Miller et al. 1999; Lyall et al. 2001a). Measures of respiratory muscle weakness are poor predictors of respiratory failure in
patients with bulbar symptoms (Lyall et al. 2001a) such as dysarthria and dysphagia.

The management of respiratory impairment in patients with MND comprises ventilatory support, which can be invasive or non-invasive, and pharmacological treatment (Radunovic et al. 2007). A number of reports and studies have demonstrated improved survival and quality of life for patients on non-invasive ventilation. However, there are no clear guidelines on when non-invasive ventilation should be started (Andrews 2009).

Non-invasive ventilation is usually used initially for intermittent support to relieve symptoms of hypoventilation at night. As respiratory muscle strength declines, daytime non-invasive ventilation may become an option. Non-invasive ventilation can be delivered through nasal masks, oronasal masks or mouthpieces, and can be controlled by a pressure-cycled ventilator (bilevel positive airway pressure ventilator) or a volume-cycled ventilator. Bilevel positive airway pressure ventilator devices are commonly used by people with MND in the UK.

The use of non-invasive ventilation by people with MND varies greatly across North America and Europe (Bradley et al. 2001; Borasio and Miller 2001; Cedarbaum and Stambler 2001; Chio et al. 2001; Bourke 2003. Evidence from several retrospective and some prospective studies indicates that non-invasive ventilation may be associated with a gain in survival (Ponto et al. 1995; Aboussouan et al. 1997; Kleopa et al. 1999; Bach 2002), improved quality of life (Aboussouan et al. 2001; Lyall et al. 2001b; Bourke et al. 2003) and improved cognitive function (Newsom-Davis et al. 2001). People with MND who have significant bulbar involvement may have lower tolerance of non-invasive ventilation compared with people with little or no bulbar muscle weakness (Cazzolli and Oppenheimer 1996; Aboussouan et al. 1997).

This short clinical guideline aims to improve the care and quality of life of people with MND by making evidence-based recommendations on the use of non-invasive ventilation in the management of MND.
1.3.2  Who this guideline is for

This document is intended to be relevant to healthcare professionals who care for people with MND. The target population is adults (aged 18 and over) with a diagnosis of MND.

2  How this guideline was developed

‘Motor neurone disease: the use of non-invasive ventilation in the management of motor neurone disease’ (NICE clinical guideline 105) is a NICE short clinical guideline. For a full explanation of how this type of guideline is developed, see 'The guidelines manual' (2009) at www.nice.org.uk/GuidelinesManual

2.1  The identification and assessment of respiratory impairment in patients with motor neurone disease: clinical symptoms and signs

2.1.1  Evidence review

A total of 1009 studies were retrieved by the systematic searches. Of these, only one study met the inclusion and exclusion criteria (for review protocol and inclusion/exclusion criteria, see appendix 9.2). The one included study was appraised and presented using GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles (for the methodology of GRADE, see appendix 9.2) adapted for diagnostic tests or strategies (Schunemann et al. 2008), and evidence statements were drawn to further summarise the evidence. In this adaptation of GRADE for diagnostic tests or strategies, the GRADE Working Group (Schunemann et al. 2008) suggested that cohort studies and case–control studies are considered as high quality, but can be downgraded to moderate, low or very low quality depending on other GRADE criteria. The one included study is summarised in table 3.
Table 3 Characteristics of the included study

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical variables</th>
<th>Outcome of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lo Coco et al. (2006)</td>
<td>ALS (amyotrophic lateral sclerosis) - Functional Rating Scale (ALS-FRS) score</td>
<td>Chronic hypoventilation</td>
</tr>
<tr>
<td></td>
<td>Appel ALS Rating Scale (AARS) score</td>
<td></td>
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<tr>
<td></td>
<td>Forced vital capacity (FVC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body mass index</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALS onset (bulbar or spinal)</td>
<td></td>
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<tr>
<td></td>
<td>Duration of disease</td>
<td></td>
</tr>
</tbody>
</table>

2.1.2 Evidence statements

2.1.2.1 There was mixed-quality evidence that gender, age, ALS onset, body mass index, ALS-Functional Rating Scale score, Appel ALS Rating Scale score, duration of disease and FVC were not significant predictors of chronic hypoventilation in people with MND/ALS [defined as the presence of dyspnoea, morning headache, daytime hypsomnolence and/or one of the following:(i) FVC < 50% of predicted value; (ii) PaCO₂ ≥ 45 mmHg; (iii) arterial oxygen saturation (SaO₂) < 88% for 5 consecutive minutes]. (Statement linked to GRADE profile 1.)

2.1.2.2 There was low-quality evidence that Appel ALS rating subgroup (rapid group: slope of total score > 4 points per month) was a significant predictor of chronic hypoventilation in people with MND/ALS [defined as the presence of dyspnoea, morning headache, daytime hypsomnolence and/or one of the following:(i) FVC < 50% of predicted value; (ii) PaCO₂ ≥ 45 mmHg; (iii) SaO₂ < 88% for 5 consecutive minutes]. (Statement linked to GRADE profile 1.)
### GRADE profile 1 Predicting chronic hypoventilation

**Outcome:** Chronic hypoventilation
(defined as the presence of dyspnoea, morning headache, daytime hypersomnolence; and/or one of the following: (i) FVC < 50% of predicted value; (ii) \( \text{PaCO}_2 \geq 45 \text{ mmHg} \); (iii) nocturnal desaturation (\( \text{SaO}_2 < 88% \) for 5 consecutive minutes).

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>No. of patients</th>
<th>Relative risk (RR) (95% CI)</th>
<th>p value</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictor/variable: Gender</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>0.89 (0.37, 2.17)</td>
<td>0.8058</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S&lt;sup&gt;b&lt;/sup&gt;</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: Age</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>1.05 (1.00, 1.09)</td>
<td>0.8126</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: ALS onset (bulbar or spinal)</strong></td>
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<td></td>
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<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>0.95 (0.29, 3.12)</td>
<td>0.9356</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: BMI</strong></td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>1.00 (0.90, 1.11)</td>
<td>0.0902</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: ALS-Functional Rating Scale (ALS-FRS) score</strong></td>
<td></td>
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<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>1.16 (0.98, 1.37)</td>
<td>0.9826</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: Appel ALS Rating Scale (AARS) score</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>1.05 (0.99, 1.11)</td>
<td>0.0825</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: Appel ALS Rating Scale (AARS) subgroups&lt;sup&gt;a&lt;/sup&gt; – Rapid group</strong></td>
<td></td>
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</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>12.71 (3.51, 46.07)</td>
<td>0.0001</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S&lt;sup&gt;c&lt;/sup&gt;</td>
<td>S&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Predictor/variable: Duration of disease</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>0.98 (0.96, 1.02)</td>
<td>0.0652</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Predictor/variable: FVC</strong></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>0.99 (0.93, 1.09)</td>
<td>0.0595</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Mean duration of disease at entry (months – median, IQR) = 15 (10-36)
All patients were followed up to 26 months and the occurrence of chronic hypoventilation was recorded as the study endpoint.

BMI, body mass index; CI, confidence interval; FVC, forced vital capacity; IQR, interquartile range.
N = no serious; S = serious.

<sup>a</sup> The total scores ranged from 30 (normal) to 164 (maximal dysfunction). There are three subgroups of disease progression: Rapid, slope of total score > 4 points per month; Intermediate, slope of total score between 2 and 4 points per month; Slow, slope of total score < 2 points per month (after an initial evaluation period of 3 months).

<sup>b</sup> The 95% CI around the estimate of effect includes both (1) no effect and (2) appreciable benefit; downgraded 1 level.

<sup>c</sup> Imprecise estimate of effect as wide CI; downgraded 1 level.

<sup>d</sup> Disease progression categories for the AARS were not validated (only through unpublished observations); downgraded 1 level.

[LC] = Lo Coco et al. (2006a).
2.1.3 Evidence to recommendations

The Guideline Development Group (GDG) agreed that there was very limited evidence on the clinical symptoms and signs that can be used to predict or identify respiratory impairment in patients with MND. The only significant predictor of respiratory impairment in the study by Lo Coco et al. (2006a) was Appel ALS rating subgroup. However, the GDG agreed that the evidence was of low quality because of imprecision, and also noted that the Appel ALS Rating Scale was not validated and that in any case the scale is not used in current clinical practice in the UK. Therefore the GDG agreed that this evidence should not be used as the basis for recommendations.

In the absence of good-quality evidence, the GDG used the EFNS task force guideline (Andersen et al. 2005) and the Motor Neurone Disease Association (MNDA) review (www.mndassociation.org) on the management of respiratory insufficiency in patients with MND/ALS as a starting point to facilitate discussion. Based on the knowledge, experience and expertise of GDG members, a list of clinical symptoms and signs that should be routinely monitored to detect potential respiratory impairment in patients with MND was developed through GDG informal consensus.
2.1.4 Recommendations

Recommendation 1.1.7
Monitor the symptoms and signs listed in table 1 routinely to detect potential respiratory impairment.

Table 1 Symptoms and signs of potential respiratory impairment

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

2.2 The identification and assessment of respiratory impairment in patients with motor neurone disease: respiratory function tests

2.2.1 Evidence review

A total of 1009 studies were retrieved by the systematic searches. Of these, only five studies met the inclusion and exclusion criteria (for the review protocol and inclusion/exclusion criteria, see appendix 9.2). The five included studies used different reference standards to define respiratory impairment. One of the included studies reported subgroup analyses on patients with bulbar symptoms and patients with spinal symptoms. No study was identified that addressed the identification and assessment of respiratory impairment in patients with MND with cognitive impairment and/or a diagnosis of dementia.

7 Weak cough could be assessed by measuring cough peak flow.
The five included studies were appraised and presented using GRADE profiles adapted for diagnostic tests or strategies (Schunemann et al. 2008), and evidence statements were drawn to further summarise the evidence. In this adaptation of GRADE for diagnostic tests or strategies, the GRADE Working Group (Schunemann et al. 2008) suggested that cohort studies and case–control studies are considered as high quality, but can be downgraded to moderate, low or very low quality depending on other GRADE criteria. The five included studies are summarised in table 4.

[Note: both MIP and PImax are abbreviations for maximal inspiratory pressure, and both MEP and PEmax are abbreviations for maximal expiratory pressure. The abbreviations that were used in the actual studies are quoted in the evidence statements. The abbreviation MIP is used in the guideline recommendations. Similarly, both Sniff Pdi and Pdi-sniff are abbreviations for maximal sniff transdiaphragmatic pressure; the abbreviations that were used in the actual studies are quoted in the evidence statements.]
### Table 4 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Index tests</th>
<th>Reference standard in GRADE profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaudri et al. (2000)</td>
<td>SNIP, VC (sitting), MIP, MEP</td>
<td>Hypercapnia (defined as PaCO$_2$ $\geq$ 6 kPa)</td>
</tr>
<tr>
<td>Pinto et al. (2009)</td>
<td>FVC (sitting), PImax (sitting), PEmax (sitting), MOP at 100 ms (P0.1), PNampl</td>
<td>Hypercapnia (defined as pCO$_2$ $&gt;$ 45 mmHg)</td>
</tr>
<tr>
<td>Lyall et al. (2001b)</td>
<td>VC (sitting), FEV$_1$, MIP, Sniff Pdi, Sniff Poes, SNP, Cough Pgas, CMS Pdi</td>
<td>Hypercapnia (defined as ELBG CO$_2$ tension $&gt;$ 6 kPa)</td>
</tr>
<tr>
<td>Lechtzin et al. (2002)</td>
<td>Supine and upright FVC, MIP, PaCO$_2$, Accessory muscle use: Abdominal paradox</td>
<td>Abnormal diaphragmatic strength, defined as Pdi-sniff &lt; 70 cmH$_2$O</td>
</tr>
<tr>
<td>Pinto et al. (1999)</td>
<td>MOP</td>
<td>Nocturnal O$_2$ saturation $&lt; 90%$</td>
</tr>
</tbody>
</table>

CMS Pdi, transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; Cough Pgas, cough gastric pressure; ELBG, earlobe blood gas; (F)V,C, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second; MIP, maximal inspiratory pressure; MIP, maximal expiratory pressure; MOP, mouth occlusion pressure; PaCO$_2$, partial pressure of CO$_2$ in arterial blood; pCO$_2$, partial pressure of CO$_2$; Pdi-sniff, maximal sniff transdiaphragmatic pressure; PEmax, maximal expiratory pressure; Plmax, maximal inspiratory pressure; PNampl, phrenic nerve motor response amplitude; Sniff Pdi, maximal sniff transdiaphragmatic pressure; Sniff Poes, maximal sniff oesophageal pressure; SNIP, sniff nasal inspiratory pressure; SNP, maximal sniff nasal pressure; VC, vital capacity.
2.2.2   Evidence statements

RS = reference standard (throughout the evidence statements).

The definitions of sensitivity, specificity and positive predictive value agreed by the GDG are as follows:

• > 90% = very good
• 70–90% = good
• 60–69% = reasonably good
• < 60% = poor.

The classifications of area under the ROC curve (AUC) are as follows (Cook 2008):

• ≥ 0.900 = excellent discriminative ability
• 0.800–0.899 = good discriminative ability
• 0.700–0.799 = fair discriminative ability
• 0.501–0.699 = poor discriminative ability
• 0.000–0.500 = no discriminative ability.

**Detecting hypercapnia in MND patients overall**
Evidence statements 2.2.2.1 and 2.2.2.2 refer to GRADE profile 2.

PaCO2 ≥ 6 kPa (RS) vs VC + SNIP

2.2.2.1 Vital capacity (VC) at a cut-off of < 49% of predicted together with sniff nasal inspiratory pressure (SNIP) at a cut-off of < 26% of predicted showed good sensitivity and specificity but poor positive predictive value for detecting hypercapnia in patients with MND (high-quality evidence).

PaCO2 ≥ 6 kPa (RS) vs MIP and MEP

2.2.2.2 Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were not significant tests (p > 0.05 in regression analysis) to detect hypercapnia in patients with MND (low-quality evidence).
Evidence statements 2.2.2.3 to 2.2.2.11 refer to GRADE profile 3.

**ELBG CO₂ tension > 6 kPa (RS) vs CMS Pdi**

2.2.2.3 Transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation (CMS Pdi) at a cut-off of 7 cmH₂O showed good sensitivity, good specificity and reasonably good positive predictive value for detecting hypercapnia in patients with MND (high-quality evidence).

**ELBG CO₂ tension > 6 kPa (RS) vs Sniff Pdi**

2.2.2.4 Maximal sniff transdiaphragmatic pressure (Sniff Pdi) at a cut-off of 30 cmH₂O showed good sensitivity, specificity and positive predictive value for detecting hypercapnia in patients with MND with spinal symptoms (high-quality evidence).

2.2.2.5 Maximal sniff transdiaphragmatic pressure (Sniff Pdi) at a cut-off of 40 cmH₂O showed poor sensitivity, specificity and positive predictive value for detecting hypercapnia in patients with MND with bulbar symptoms (low-quality evidence).

**ELBG CO₂ tension > 6 kPa (RS) vs Sniff Poes**

2.2.2.6 Maximal sniff oesophageal pressure (Sniff Poes) at a cut-off of 32 cmH₂O showed good sensitivity, very good specificity and good positive predictive value for detecting hypercapnia in patients with MND (moderate-quality evidence).

**ELBG CO₂ tension > 6 kPa (RS) vs SNP**

2.2.2.7 Maximal sniff nasal pressure (SNP) at a cut-off of 32% of predicted showed good sensitivity, good specificity and reasonably good positive predictive value for detecting hypercapnia in patients with MND (moderate-quality evidence).

**ELBG CO₂ tension > 6 kPa (RS) vs Cough Pgas**

2.2.2.8 Cough gastric pressure (Cough Pgas) at a cut-off of 55 cmH₂O showed good specificity and reasonably good sensitivity but poor
positive predictive value for detecting hypercapnia in patients with MND (moderate-quality evidence).

ELBG CO$_2$ tension > 6 kPa (RS) vs VC
2.2.2.9 Vital capacity (VC) at a cut-off of 50% of predicted showed poor sensitivity, good specificity and reasonably good positive predictive value for detecting hypercapnia in patients with MND (moderate-quality evidence).

ELBG CO$_2$ tension > 6 kPa (RS) vs FEV$_1$
2.2.2.10 Forced expiratory volume in 1 second (FEV$_1$) at a cut-off of 50% of predicted showed poor sensitivity and positive predictive value but good specificity for detecting hypercapnia in patients with MND (moderate-quality evidence).

ELBG CO$_2$ tension > 6 kPa (RS) vs MIP
2.2.2.11 Maximal inspiratory pressure (MIP) at a cut-off of 25% of predicted showed poor sensitivity and positive predictive value but good specificity for detecting hypercapnia in patients with MND (moderate-quality evidence).

Evidence statements 2.2.2.12 to 2.2.2.16 refer to GRADE profile 4.

pCO$_2$ > 45 mmHg (RS) vs FVC
2.2.2.12 Forced vital capacity (FVC) at a cut-off of 80% of predicted showed reasonably good sensitivity and specificity but poor positive predictive value for detecting hypercapnia in patients with MND (area under the curve [AUC] showed fair discriminative ability) (high-quality evidence).

pCO$_2$ > 45 mmHg (RS) vs Plmax
2.2.2.13 Maximal inspiratory pressure (Plmax) at a cut-off of 60% of predicted showed very good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in patients with MND (AUC showed poor discriminative ability) (high-quality evidence).
pCO₂ > 45 mmHg (RS) vs PEmax

2.2.2.14 Maximal expiratory pressure (PEmax) at a cut-off of 60% of predicted showed good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in patients with MND (AUC showed poor discriminative ability) (high-quality evidence).

pCO₂ > 45 mmHg (RS) vs MOP

2.2.2.15 Mouth occlusion pressure (MOP) at 100 ms at a cut-off of 80% of predicted showed poor sensitivity, specificity and positive predictive value for detecting hypercapnia in patients with MND (AUC showed poor discriminative ability) (moderate-quality evidence).

pCO₂ > 45 mmHg (RS) vs PNampl

2.2.2.16 Phrenic nerve motor response amplitude (PNampl) at a cut-off of -0.4 mV showed good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in patients with MND (AUC showed fair discriminative ability) (high-quality evidence).

Detecting hypoxaemia in patients with MND overall

Nocturnal O₂ saturation < 90% (RS) vs MOP (see GRADE profile 5)

2.2.2.17 Mouth occlusion pressure (MOP) at a cut-off of 100% showed reasonably good specificity and good positive predictive value but poor sensitivity for detecting hypoxaemia in patients with MND (very-low-quality evidence).

Detecting abnormal diaphragmatic strength in patients with MND overall

Evidence statements 2.2.2.18 to 2.2.2.25 refer to GRADE profile 6.

Pdi-sniff < 70 cmH₂O (RS) vs supine FVC

2.2.2.18 Supine forced vital capacity (FVC) at a cut-off of < 75% of predicted showed very good sensitivity, specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).
2.2.2.19  Supine forced vital capacity (FVC) at a cut-off of < 50% of predicted showed very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

Pdi-sniff < 70 cmH₂O (RS) vs upright FVC

2.2.2.20  Upright forced vital capacity (FVC) at a cut-off of < 75% of predicted showed good sensitivity and very good specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

2.2.2.21  Upright forced vital capacity (FVC) at a cut-off of < 50% of predicted showed very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

Pdi-sniff < 70 cmH₂O (RS) vs MIP

2.2.2.22  Maximal inspiratory pressure (MIP) at a cut-off of < −80 cmH₂O showed very good sensitivity, specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

Pdi-sniff < 70 cmH₂O (RS) vs PaCO₂

2.2.2.23  Partial pressure of CO₂ in arterial blood (PaCO₂) at a cut-off of > 45 mmHg showed very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

Pdi-sniff < 70 cmH₂O (RS) vs accessory muscle use

2.2.2.24  Accessory muscle use (visible contractions of the sternocleidomastoid or scalene muscles in the supine position) showed good sensitivity and very good specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).
Abdominal paradox (the presence of inward movement of the abdomen during inspiration in the supine position) showed very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (low-quality evidence).

Subgroup analysis: detecting hypercapnia in patients with MND with bulbar symptoms

Evidence statements 2.2.2.26 to 2.2.2.33 refer to GRADE profile 7.

\[ pCO_2 > 45 \text{ mmHg (RS) vs FVC} \]

2.2.2.26 Forced vital capacity (FVC) at a cut-off of 80% of predicted showed good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed fair discriminative ability) (moderate-quality evidence).

2.2.2.27 Forced vital capacity (FVC) at a cut-off of 63.4% of predicted showed good sensitivity and specificity but poor positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed fair discriminative ability) (moderate-quality evidence).

\[ pCO_2 > 45 \text{ mmHg (RS) vs PImax} \]

2.2.2.28 Maximal inspiratory pressure (PImax) at a cut-off of 60% of predicted showed very good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed poor discriminative ability) (moderate-quality evidence).

\[ pCO_2 > 45 \text{ mmHg (RS) vs PEmax} \]

2.2.2.29 Maximal expiratory pressure (PEmax) at a cut-off of 60% of predicted showed good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed no discriminative ability) (moderate-quality evidence).
**pCO₂ > 45 mmHg (RS) vs MOP**

2.2.2.30 Mouth occlusion pressure (MOP) at 100 ms at a cut-off of 80% of predicted showed reasonably good specificity but poor sensitivity and positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed poor discriminative ability) (moderate-quality evidence).

**pCO₂ > 45 mmHg (RS) vs PNampl**

2.2.2.31 Phrenic nerve motor response amplitude (PNampl) at a cut-off of −0.4 mV showed good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed good discriminative ability) (moderate-quality evidence).

2.2.2.32 Phrenic nerve motor response amplitude (PNampl) at a cut-off of −0.25 mV showed good sensitivity and specificity but poor positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed fair discriminative ability) (moderate-quality evidence).

2.2.2.33 Forced vital capacity (FVC) together with phrenic nerve motor response amplitude (PNampl) showed good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with bulbar symptoms (AUC showed good discriminative ability) (moderate-quality evidence).

**Subgroup analysis: detecting hypercapnia in patients with MND with spinal symptoms**

Evidence statements 2.2.2.34 to 2.2.2.39 refer to GRADE profile 7.

**pCO₂ > 45 mmHg (RS) vs FVC**

2.2.2.34 Forced vital capacity (FVC) at a cut-off of 80% of predicted showed good specificity but poor sensitivity and positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed poor discriminative ability) (moderate-quality evidence).
pCO₂ > 45 mmHg (RS) vs PImax

2.2.2.35 Maximal inspiratory pressure (PImax) at a cut-off of 60% of predicted showed very good sensitivity but poor specificity and positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed fair discriminative ability) (high-quality evidence).

pCO₂ > 45 mmHg (RS) vs PEmax

2.2.2.36 Maximal expiratory pressure (PEmax) at a cut-off of 60% of predicted showed good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed poor discriminative ability) (moderate-quality evidence).

pCO₂ > 45 mmHg (RS) vs MOP

2.2.2.37 Mouth occlusion pressure (MOP) at 100 ms at a cut-off of 80% of predicted showed poor sensitivity, specificity and positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed no discriminative ability) (moderate-quality evidence).

pCO₂ > 45 mmHg (RS) vs PNampl

2.2.2.38 Phrenic nerve motor response amplitude (PNampl) at a cut-off of −0.4 mV showed good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed fair discriminative ability) (moderate-quality evidence).

2.2.2.39 Phrenic nerve motor response amplitude (PNampl) at a cut-off of −0.37 mV showed good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed fair discriminative ability) (moderate-quality evidence).
Subgroup analysis: detecting respiratory impairment in MND patients with cognitive impairment and/or a diagnosis of dementia

No study was identified that addressed the identification and assessment of respiratory impairment in patients with MND with cognitive impairment and/or a diagnosis of dementia.

GRADE profiles

GRADE profile 2 Detecting hypercapnia (defined as PaCO$_2$ ≥ 6 kPa)

<table>
<thead>
<tr>
<th>Outcome (reference standard): Hypercapnia (defined as PaCO$_2$ ≥ 6 kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies (study design)</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Index test: VC &lt; 49% plus SNIP &lt; 26% (n = 69)</td>
</tr>
<tr>
<td>Index test: Maximal inspiratory pressure (MIP)</td>
</tr>
<tr>
<td>Index test: Maximal expiratory pressure (MEP)</td>
</tr>
</tbody>
</table>

Mean (SD) duration of disease at study entry: bulbar = 26.3 (23.7) months; non-bulbar = 23.7 (11.4) months.

CI, confidence interval; N/A, not applicable; NPV, negative predictive value; PaCO$_2$, partial pressure of CO$_2$ in arterial blood; PPV, positive predictive value; SD, standard deviation; SNIP, sniff nasal inspiratory pressure; VC, vital capacity. N = no serious; S = serious.

$^a$ Cut-off values derived from receiver operating characteristic (ROC) analysis.

$^b$ Unable to assess inconsistency as diagnostic accuracy not reported; downgraded 1 level.

$^c$ Unable to assess imprecision as CI not reported; downgraded 1 level.

[C] = Chaudri et al. (2000).
**GRADE profile 3 Detecting hypercapnia [defined as earlobe blood gas (ELBG) \( \text{CO}_2 \) tension > 6 kPa]**

Outcome (reference standard): Ventilatory failure (hypercapnia) [defined as ELBG \( \text{CO}_2 \) tension of >6 kPa]

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>Prevalence (%)</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV (%) (95% CI)</th>
<th>NPV (%) (95% CI)</th>
<th>Other analysis</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong>: CMS Pdi (cut-off: 7 cmH2O) (n = 65)</td>
<td>29.2</td>
<td>89 (67–99)</td>
<td>78 (64–89)</td>
<td>63 (44–78)</td>
<td>95 (82–99)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
<tr>
<td><strong>Index test</strong>: Sniff Pdi (cut-off: 30 cmH2O) (spinal group; n = 65)</td>
<td>29.2</td>
<td>90 (67–99)</td>
<td>87 (74–95)</td>
<td>74 (53–87)</td>
<td>95 (84–99)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
<tr>
<td><strong>Index test</strong>: Sniff Pdi (cut-off: 40 cmH2O) (bulbar group; n = 16)</td>
<td>12.5</td>
<td>50 (1–99)</td>
<td>57 (29–82)</td>
<td>14 (3–51)</td>
<td>89 (52–99)</td>
<td>N/A</td>
<td>Sb</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Index test</strong>: Sniff Poes (cut-off: 32 cmH2O) (n = 65)</td>
<td>29.2</td>
<td>74 (49–91)</td>
<td>91 (79–97)</td>
<td>78 (55–91)</td>
<td>89 (77–99)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Index test</strong>: SNP (%) (cut-off: 32% predicted) (n = 56)</td>
<td>28.6</td>
<td>81 (54–96)</td>
<td>85 (70–94)</td>
<td>68 (46–85)</td>
<td>92 (78–98)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Index test</strong>: Cough Pgas (cut-off: 55 cmH2O) (n = 65)</td>
<td>29.2</td>
<td>68 (43–87)</td>
<td>78 (64–89)</td>
<td>68 (46–85)</td>
<td>86 (71–95)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Index test</strong>: VC (%) (cut-off: 50% predicted) (n = 65)</td>
<td>29.2</td>
<td>53 (29–76)</td>
<td>89 (75–96)</td>
<td>67 (42–85)</td>
<td>82 (68–91)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Index test</strong>: FEV1 (%) (cut-off: 50% predicted) (n = 57)</td>
<td>24.6</td>
<td>50 (23–77)</td>
<td>88 (75–96)</td>
<td>58 (32–81)</td>
<td>84 (71–94)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Index test</strong>: MIP (%) (cut-off: 25% predicted) (n = 64)</td>
<td>28.1</td>
<td>55 (31–78)</td>
<td>83 (68–92)</td>
<td>56 (34–75)</td>
<td>83 (69–92)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Mean duration of disease not reported.

CI, confidence interval; CMS Pdi, transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; Cough Pgas, cough gastric pressure; FEV1 = forced expiratory volume in 1 second; MIP, maximal inspiratory pressure; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value; Sniff Pdi = maximal sniff transdiaphragmatic pressure; Sniff Poes = maximal sniff oesophageal pressure; SNP, maximal sniff nasal pressure; VC, vital capacity.

N = no serious; S = serious.

\(^a\) Cut-off values derived from ROC analysis.

\(^b\) Risk of bias as small study sample; downgraded 1 level.

\(^c\) Wide CIs for estimates of test accuracy (any CIs that covered the range of ≥ 40%); downgraded 1 level.

[\(\text{L}\] = Lyall et al. (2001b).
### GRADE profile 4 Detecting hypercapnia (defined as pCO₂ > 45 mmHg)

#### Outcome (reference standard): Hypercapnia [defined as pCO₂ > 45 mmHg]

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>Prevalence (%)</th>
<th>Sensitivity (%) (95% CI)</th>
<th>Specificity (%) (95% CI)</th>
<th>PPV (%) (95% CI)</th>
<th>NPV (%) (95% CI)</th>
<th>Other analysis (%)</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong>: FVC (cut-off: 80% predicted) (n = 199)</td>
<td>12.1</td>
<td>66.7 (45–84)</td>
<td>66.3 (59–73)</td>
<td>21.3 (14–32)</td>
<td>93.6 (88–97)</td>
<td>0.723</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
<tr>
<td><strong>Index test</strong>: PImax (cut-off: 60% predicted) (n = 199)</td>
<td>12.1</td>
<td>100 (86–100)</td>
<td>26.9 (20–34)</td>
<td>15.8 (11–22)</td>
<td>100 (92–100)</td>
<td>0.671</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
<tr>
<td><strong>Index test</strong>: PEmax (cut-off: 60% predicted) (n = 199)</td>
<td>12.1</td>
<td>75 (53–90)</td>
<td>52 (44–59)</td>
<td>17.7 (12–26)</td>
<td>93.8 (87–98)</td>
<td>0.629</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
<tr>
<td><strong>Index test</strong>: MOP at 100 ms (P0.1) (cut-off: 80% predicted) (n = 199)</td>
<td>12.1</td>
<td>45.8 (26–67)</td>
<td>56.6 (49–64)</td>
<td>12.6 (7–21)</td>
<td>88.4 (81–90)</td>
<td>0.546</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: PNampl (cut-off: −0.4mV) (n = 199)</td>
<td>12.1</td>
<td>75 (53–90)</td>
<td>62.9 (55–70)</td>
<td>21.7 (14–32)</td>
<td>94.8 (89–98)</td>
<td>0.772</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
</tbody>
</table>

Mean (SD) duration of disease at study entry = 17.2 (15.6) months (range 1–72 months)

AUC, area under the curve; CI, confidence interval; FVC, forced vital capacity; MOP, mouth occlusion pressure; NPV, negative predictive value; pCO₂, partial pressure of pCO₂; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; PNampl, phrenic nerve motor response amplitude; PPV, positive predictive value. N = no serious; S = serious.

a Cut-off values were based on normative limits commonly used in clinical practice.

b Wide CIs for estimates of test accuracy (any CIs that covered the range of ≥ 40%); downgraded 1 level.

[P] = Pinto et al. (2009).
**GRADE profile 5 Detecting hypoxaemia (defined as nocturnal O₂ saturation < 90% measured by pulse oximetry)**

Outcome (reference standard): Hypoxaemia [defined as nocturnal O₂ saturation < 90% measured by pulse oximetry]

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>Prevalence (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Other analysis</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cohort [P]</td>
<td>NR</td>
<td>44</td>
<td>66</td>
<td>80</td>
<td>NR</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>S⁵</td>
<td>S⁶ S⁷ S⁸ N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

CI, confidence interval; MOP, mouth occlusion pressure; N/A, not applicable; NPV, negative predictive value; NR, not recorded; PPV, positive predictive value.
N = no serious; S = serious.

a Cut-off value derived from ROC analysis.
b Unable to assess inconsistency as full details of diagnostic accuracy not reported; downgraded 1 level.
c Unable to assess imprecision as full details of calculation of confidence intervals not available; downgraded 1 level.
d Pre-test probabilities (prevalence) not reported, risk of bias; downgraded 1 level.

[P] = Pinto et al. (1999).
### GRADE profile 6 Detecting abnormal diaphragmatic strength [defined as maximal sniff transdiaphragmatic pressure (Pdi-sniff) < 70 cmH₂O]

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>Prevalence (%)</th>
<th>Sensitivity (% (95% CI))</th>
<th>Specificity (% (95% CI))</th>
<th>PPV (% (95% CI))</th>
<th>NPV (% (95% CI))</th>
<th>Other analysis</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index test</strong>: Supine FVC (cut-off: &lt; 75% predicted) (n = 25)</td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>100 (85–100)</td>
<td>100 (16–100)</td>
<td>100 (86–100)</td>
<td>100 (16–100)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: Supine FVC (cut-off: &lt; 50% predicted) (n = 25)</td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>53 (31–73)</td>
<td>100 (16–100)</td>
<td>100 (76–100)</td>
<td>18 (2–45)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
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<tr>
<td><strong>Index test</strong>: Upright FVC (cut-off: &lt; 75% predicted) (n = 25)</td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>83 (61–95)</td>
<td>100 (16–100)</td>
<td>100 (83–100)</td>
<td>33 (4–77)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: Upright FVC (cut-off: &lt; 50% predicted) (n = 25)</td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>30 (13–53)</td>
<td>100 (16–100)</td>
<td>100 (65–100)</td>
<td>22 (1–35)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
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<tr>
<td><strong>Index test</strong>: MIP (cut-off: &lt; −80 cmH₂O) (n = 25)</td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>91 (68–97)</td>
<td>100 (16–100)</td>
<td>100 (85–100)</td>
<td>50 (5–85)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: PaCO₂ (cut-off: &gt; 45 mmHg) (n = 25)</td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>33 (15–55)</td>
<td>100 (16–100)</td>
<td>100 (83–100)</td>
<td>14 (1–36)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: Accessory muscle use (n = 25)</td>
<td></td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>84 (61–95)</td>
<td>100 (16–100)</td>
<td>100 (83–100)</td>
<td>40 (4–78)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Index test</strong>: Abdominal paradox (n = 25)</td>
<td></td>
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</tr>
<tr>
<td>1 Cohort [L] 92</td>
<td>38 (19–60)</td>
<td>100 (16–100)</td>
<td>100 (69–100)</td>
<td>13 (2–38)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD) duration of disease at study entry = 2.8 (2.0) months (range 0.4–13.1 months).

CI, confidence interval; FVC, forced vital capacity; MIP, maximal inspiratory pressure; N/A, not applicable; NPV, negative predictive value; PaCO₂, partial pressure of CO₂ in arterial blood; Pdi-sniff, maximal sniff transdiaphragmatic pressure; PPV, positive predictive value.

N = no serious; S = serious.

a Cut-off values derived from ROC analysis.
b Cut-off values based on normative limits commonly used in clinical practice.
c Cut-off defined as visible contractions of the sternocleidomastoid or scalene muscles in the supine position.
d Cut-off defined as the presence of inward movement of the abdomen during inspiration in the supine position.
e Wide CIs for estimates of test accuracy (any CIs that covered the range of ≥ 40%); downgraded 1 level.
f High pre-test probabilities, risk of bias; downgraded 1 level.

[L] = Lechtzin et al. (2002).
### Subgroup analysis: bulbar group and spinal group

#### Outcome (reference standard): Hypercapnia [defined as pCO₂ > 45 mmHg]

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>Prevalence (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%) (95% CI)</th>
<th>NPV (%) (95% CI)</th>
<th>Other analysis</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulbar group; Index test: FVC (cut-off: 80% predicted) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>50.0 (95% CI 44–51)</td>
<td>58.6 (44–71)</td>
<td>52.5 (52–77)</td>
<td>16.1 (9–27)</td>
<td>100 (54–100)</td>
<td>AUC = 0.787 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group; Index test: PImax (cut-off: 60% predicted) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>100.0 (95% CI 69–100)</td>
<td>10.3 (4–21)</td>
<td>10.3 (4–21)</td>
<td>16.1 (9–27)</td>
<td>100 (54–100)</td>
<td>AUC = 0.531 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group; Index test: PEmax (cut-off: 60% predicted) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>80.0 (95% CI 44–97)</td>
<td>31.0 (19–44)</td>
<td>31.0 (19–44)</td>
<td>16.1 (9–27)</td>
<td>100 (54–100)</td>
<td>AUC = &lt;0.5 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group; Index test: MOP at 100 ms (P0.1) (cut-off: 80% predicted) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>50.0 (95% CI 19–81)</td>
<td>65.5 (52–77)</td>
<td>65.5 (52–77)</td>
<td>16.1 (9–27)</td>
<td>90 (68–99)</td>
<td>AUC = &lt;0.5 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group; Index test: PNampl (cut-off: −0.4 mV) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>80.0 (95% CI 44–97)</td>
<td>58.6 (44–71)</td>
<td>58.6 (44–71)</td>
<td>25 (13–42)</td>
<td>94.4 (81–99)</td>
<td>AUC = 0.810 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group: further logistic regression model; Index test: FVC (cut-off: 63.4% predicted) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>70.0 (95% CI 55–99)</td>
<td>84.4 (52–77)</td>
<td>84.4 (52–77)</td>
<td>43.3 (27–67)</td>
<td>94.2 (86–99)</td>
<td>AUC = 0.787 N N N N Moderate</td>
<td></td>
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</tr>
<tr>
<td>Bulbar group: further logistic regression model; Index test: PNampl (cut-off: −0.25 mV) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>80.0 (95% CI 35–93)</td>
<td>72.4 (72–93)</td>
<td>72.4 (72–93)</td>
<td>33.3 (23–67)</td>
<td>95.5 (84–99)</td>
<td>AUC = 0.77 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar group: further logistic regression model; Index test: FVC + PNampl (cut-offs: unclear) (n = 68)</td>
<td>1 Cohort [P]</td>
<td>14.7</td>
<td>90.0 (95% CI 44–97)</td>
<td>65.5 (59–83)</td>
<td>65.5 (59–83)</td>
<td>31 (18–53)</td>
<td>97.4 (85–99)</td>
<td>AUC = 0.83 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal group; Index test: FVC (cut-off: 80% predicted) (n = 131)</td>
<td>1 Cohort [P]</td>
<td>10.7</td>
<td>50.0 (95% CI 23–77)</td>
<td>73.5 (64–81)</td>
<td>73.5 (64–81)</td>
<td>18.4 (9–33)</td>
<td>92.5 (85–97)</td>
<td>AUC = 0.680 N N N N Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal group; Index test: PImax (cut-off: 60% predicted) (n = 131)</td>
<td>1 Cohort [P]</td>
<td>10.7</td>
<td>100.0 (95% CI 77–100)</td>
<td>35.0 (26–44)</td>
<td>35.0 (26–44)</td>
<td>15.6 (9–24)</td>
<td>100 (91–100)</td>
<td>AUC = 0.730 N N N N N High</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### Spinal group; Index test: PEmax (cut-off: 60% predicted) (n = 131)

<table>
<thead>
<tr>
<th>1 Cohort [P]</th>
<th>10.7</th>
<th>71.4</th>
<th>62.4</th>
<th>18.5</th>
<th>94.8</th>
<th>AUC = 0.687</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S±</th>
<th>N</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(42–92)</td>
<td>(53–71)</td>
<td>(87–99)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Spinal group; Index test: MOP at 100 ms (P0.1) (cut-off: 80% predicted) (n = 131)

<table>
<thead>
<tr>
<th>1 Cohort [P]</th>
<th>10.7</th>
<th>42.9</th>
<th>52.1</th>
<th>9.7</th>
<th>88.4</th>
<th>AUC = &lt;0.5</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S±</th>
<th>N</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(18–71)</td>
<td>(43–61)</td>
<td>(5–19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Spinal group; Index test: PNampl (cut-off: −0.4 mV) (n = 131)

<table>
<thead>
<tr>
<th>1 Cohort [P]</th>
<th>10.7</th>
<th>71.4</th>
<th>65</th>
<th>19.6</th>
<th>95</th>
<th>AUC = 0.797</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S±</th>
<th>N</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(42–92)</td>
<td>(56–74)</td>
<td>(11–33)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Mean (SD) duration of disease at study entry: bulbar group, 12.3 (7.5) months (range 1–45 months); spinal group, = 19.8 (18) months (range 1–72 months)

AUC, area under the curve; CI, confidence interval; FVC, forced vital capacity; MOP, mouth occlusion pressure; NPV, negative predictive value; pCO2, partial pressure of CO2; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; PNampl, phrenic nerve motor response amplitude; PPV, positive predictive value; N = no serious; S = serious.

* Cut-off values were based on normative limits commonly used in clinical practice.

b Further logistic regression analysis was carried out with tests that achieved AUC ≥ 0.70 in order to define new cut-off values that were more accurate than the generally accepted normative limits.

c Wide CIs for estimates of test accuracy (any CIs that covered the range of ≥ 40%); downgraded 1 level.

[P] = Pinto et al. (2009).
Table 5 Summary matrix of GRADE profiles

Shown are comparisons of the sensitivity, specificity and positive predictive value of different tests with different reference standards for hypercapnia, abnormal diaphragmatic strength and hypoxaemia

<table>
<thead>
<tr>
<th>Hypercapnia</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>Q</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC &lt;49%+ SNIP &lt;26%</td>
<td>90</td>
<td>73.5</td>
<td>40.9</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (50%)</td>
<td>67</td>
<td>89</td>
<td>53</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1 (50%)</td>
<td>58</td>
<td>88</td>
<td>50</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP (25%)</td>
<td>56</td>
<td>83</td>
<td>55</td>
<td>M</td>
<td>H</td>
<td>100</td>
<td>26.9</td>
</tr>
<tr>
<td>SNP (32%)</td>
<td>68</td>
<td>95</td>
<td>81</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniff Pdi (30 cmH2O)*</td>
<td>74</td>
<td>67</td>
<td>90</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniff Pdi (40 cmH2O)</td>
<td>57</td>
<td>50</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sniff Poes (32 cmH2O)</td>
<td>78</td>
<td>91</td>
<td>74</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough Pgas (50 cmH2O)</td>
<td>57</td>
<td>78</td>
<td>68</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMS Pdi (7 cmH2O)</td>
<td>63</td>
<td>78</td>
<td>89</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| CMS Pdi, transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; Cough Pgas, cough gastric pressure; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; H, high (shaded cells); L, low; M, moderate; MIP, maximal inspiratory pressure; MOP, mouth occlusion pressure; PaCO2, partial pressure of CO2 in arterial blood; PEmax, maximal expiratory pressure; PImax, maximal inspiratory pressure; PNampl, phrenic nerve motor response amplitude; PPV, positive predictive value; Q, quality; Sen, sensitivity; Sniff Pdi, maximal sniff transdiaphragmatic pressure; Sniff Poes, maximal sniff oesophageal pressure; SNIP, sniff nasal inspiratory pressure; SNP, maximal sniff nasal pressure; Spe, specificity; VC, vital capacity

* Data from patients with spinal symptoms only.
## 2.2.3 Evidence to recommendations

The GDG acknowledged that it was particularly challenging to draw conclusions about which respiratory function tests to recommend based on the available evidence, because different reference standards were used to define respiratory impairment in the included studies.

The GDG therefore came to the consensus that only high-quality evidence should be used as the basis for developing recommendations (as indicated in table 5 and described in evidence statements 2.2.2.1, 2.2.2.4, 2.2.2.12 and 2.2.2.13). The GDG also agreed that, because of the potentially fatal consequences of not detecting respiratory impairment (that is, sudden respiratory failure, complications or death), respiratory function tests with high sensitivity (rather than high specificity) are most important. The GDG further agreed and came to the consensus that the patient’s baseline respiratory function should be established as part of the initial assessment to diagnose MND or soon after initial diagnosis. The GDG also agreed that the tests

### Abnormal diaphragmatic strength

<table>
<thead>
<tr>
<th>Test</th>
<th>PPV</th>
<th>Spe</th>
<th>Sen</th>
<th>Q</th>
<th>UFVC (75%)</th>
<th>UFVC (50%)</th>
<th>SFVC (75%)</th>
<th>SFVC (50%)</th>
<th>MIP &lt; −80 cmH₂O</th>
<th>PaCO₂ &gt; 45 mmHg</th>
<th>Accessory muscle use</th>
<th>Abdominal paradox</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q</td>
<td>100 100 83</td>
<td>100 100 30</td>
<td>100 100 100</td>
<td>100 100 53</td>
<td>100 100 91</td>
<td>100 100 33</td>
<td>100 100 84</td>
<td>100 100 38</td>
</tr>
</tbody>
</table>

### Hypoxaemia

<table>
<thead>
<tr>
<th>Q</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL</td>
<td>44</td>
<td>66</td>
<td>80</td>
</tr>
</tbody>
</table>

H, high; L, low; M, moderate; MIP, maximal inspiratory pressure; MOP, mouth occlusion pressure; PaCO₂, partial pressure of CO₂ in arterial blood; PPV, positive predictive value; Q, quality; Sen, sensitivity; Spe, specificity; UFVC, upright forced vital capacity; SFVC, supine forced vital capacity; VL, very low.
should be carried out every 3 months, although they may be performed more or less often depending on whether there are any symptoms and signs of respiratory impairment, the rate of disease progression and the patient’s preferences and circumstances.

**Pulse oximetry to measure oxygen saturation, and arterial or capillary blood gas analysis**

There was an absence of clear evidence about which respiratory function tests are best for detecting respiratory impairment. The GDG agreed that both oxygen saturation measured by pulse oximetry (SpO₂) (used as the reference standard in GRADE profile 5 for detecting hypoxaemia) and measurement of the arterial partial pressure of carbon dioxide (PaCO₂) by arterial or capillary blood gas analysis (used as the reference standard in GRADE profiles 2 and 3 for detecting hypercapnia) are standard tests for detecting respiratory impairment in current UK practice, especially for patients who cannot undertake other respiratory function tests that need interfaces (for example, patients with MND who have severe bulbar impairment or severe cognitive impairment). The GDG agreed that SpO₂ should be recommended as a first-line routine initial screening, because it is practical to use, less stressful for patients, and can be carried out by most healthcare professionals (that is, it is not restricted to respiratory physicians). A cut-off of less than 90% was used as the reference standard in GRADE profile 5 for nocturnal SpO₂. However, the GDG felt that the cut-off for daytime SpO₂ for patients with MND should be higher so that patients with respiratory impairment can be identified appropriately and earlier, in view of the potentially serious consequences of failing to identify such patients. Based on the expert knowledge and experience of members, the GDG agreed that further arterial or capillary blood gas analysis (PaCO₂) should be carried out if the patient’s SpO₂ (measured at rest and breathing room air):

- is less than or equal to 92% if they have known lung disease
- is less than or equal to 94% if they do not have lung disease.

The GDG also agreed that referral to a specialist respiratory service for nocturnal oximetry and/or a limited sleep study should be considered for
patients with sleep-related respiratory symptoms even if their SpO₂ is greater than 94% (or 92% for patients with lung disease).

The GDG came to a consensus that when arterial or capillary blood gas analysis is carried out, the PaCO₂ cut-off value should be greater than 6 kPa (based on the reference standard in GRADE profiles 2 and 3). As a PaCO₂ of more than 6 kPa indicates hypercapnia, the GDG agreed that patients whose PaCO₂ is above this threshold should be seen urgently (within 1 week) by a specialist respiratory service in order to prevent the possibility of serious consequences such as sudden respiratory failure or death. In some cases this might be an emergency admission.

In order to ensure that all patients at risk are appropriately identified, the GDG also agreed that if the patient’s PaCO₂ is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment (see recommendation 1.1.7), particularly orthopnoea, they should be referred to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study. Both the impact of respiratory impairment and treatment options should be discussed with the patient and (if the patient agrees) their family and carers.

(Forced) vital capacity

The GDG agreed that there was high-quality evidence that measurement of vital capacity (together with SNIP) (evidence statement 2.2.2.1) and forced vital capacity (evidence statement 2.2.2.12) was useful for detecting respiratory impairment. The GDG therefore concluded that this should be recommended as an option for a complementary respiratory function test, after pulse oximetry. The GDG further discussed and agreed that the difference between the measurement of vital capacity and forced vital capacity is very subtle and that either test can be used.

Based on the evidence, and to enhance the accuracy of detecting respiratory impairment, the GDG agreed that if the patient’s FVC or VC is less than 50% of the predicted value there should be discussion with the patient and possible referral to a specialist respiratory service for further assessment. In order to
detect respiratory impairment as early as possible, the GDG also came to the consensus that FVC or VC of less than 80% of the predicted value together with any of the symptoms or signs of respiratory impairment listed in recommendation 1.1.7 (table 1), particularly orthopnoea, should also elicit further discussion with the patient and possible referral to a specialist respiratory service for further assessment.

Maximal inspiratory pressure (MIP) and sniff nasal inspiratory pressure (SNIP)

The GDG discussed the high-quality evidence on the measurement of SNIP (together with VC) (evidence statements 2.2.2.1 and 2.2.2.4) and MIP (also called PImax) (evidence statement 2.2.2.13), and noted that two different units of measurement were used in the studies (that is, % of predicted value and cmH2O). The GDG noted that cmH2O is the actual unit of measurement provided by the machine for both SNIP and MIP. In addition, there are several different equations for calculating % of predicted value, which can give significantly different results, and therefore could result in confusion. Hence the GDG agreed that the actual unit provided by the machine (that is, cmH2O) should be used in the recommendations.

SNIP and MIP can be measured using the same machine, and patients may perform better on one test than on the other because of different symptoms of MND. The GDG therefore came to the consensus that, where possible, to enhance the accuracy of detecting respiratory impairment, both tests should be recommended as options for complementary respiratory function tests after pulse oximetry. This should help to ensure that all patients at risk of respiratory impairment are identified. Again, in order to detect respiratory impairment as early as possible, the GDG agreed (based on the knowledge, experience and expertise of its members) that, for both SNIP and MIP, any of the following three results should elicit further discussion with the patient and possible referral to a specialist respiratory service for further assessment (if both tests are performed, the assessment should be based on the better respiratory function reading):

- SNIP or MIP less than 40 cmH2O
• SNIP or MIP less than 65 cmH₂O for men or 55 cmH₂O for women plus any symptoms or signs of respiratory impairment (see table 1 in recommendation 1.1.7), particularly orthopnoea

• Repeated regular tests show a rate of decrease of SNIP or MIP of more than 10 cmH₂O per 3 months.

**Transdiaphragmatic pressure (CMS Pdi), maximal sniff transdiaphragmatic pressure (Sniff Pdi) and phrenic nerve motor response amplitude (PNampl)**

The GDG agreed that there was high-quality evidence that transdiaphragmatic pressure after bilateral cervical phrenic nerve stimulation (CMS Pdi), maximal sniff transdiaphragmatic pressure (Sniff Pdi) and phrenic nerve motor response amplitude (PNampl) showed good sensitivity and predictive value in detecting respiratory impairment. However, the GDG also noted that these respiratory muscle tests are not commonly used in routine UK clinical practice because of their complexity and technicality. The GDG also agreed that the results of these tests would not provide any extra information compared with that obtained using pulse oximetry, arterial blood gas analysis and measurements of FVC, SNIP and/or MIP. Therefore the GDG came to the consensus that no recommendations should be made on these three tests.

**Subgroup: patients with severe bulbar impairment**

The GDG agreed that there was no high-quality evidence on respiratory function tests for patients with MND with severe bulbar impairment. The GDG noted that the interfaces used for measuring FVC, SNIP and MIP may not be suitable for such patients, and agreed that in these circumstances it would not be appropriate to carry out such tests. Therefore the GDG came to the consensus that, as for patients without severe bulbar impairment, measurement of SpO₂ should be recommended as first-line routine initial screening, followed by arterial or capillary blood gas analysis to measure PaCO₂ if appropriate. The recommendations on cut-off values for both SpO₂ and PaCO₂ should be the same as for patients without severe bulbar impairment. Recommendations on what to do if the patient’s SpO₂ is above the cut-off but they have sleep-related respiratory symptoms, or their PaCO₂ is below the cut-off but they have any symptoms or signs of respiratory
impairment (particularly orthopnoea), should also be the same as for patients without severe bulbar impairment.

**Subgroup: patients with severe cognitive problems that may be related to respiratory impairment**

No study was identified that addressed the identification and assessment of respiratory impairment in patients with MND who have severe cognitive problems that may be related to respiratory impairment. Since these patients are similar to patients with severe bulbar impairment in that the interfaces used for measuring FVC, SNIP and MIP may not be suitable, the GDG came to the consensus that, for patients with severe cognitive problems that may be related to respiratory impairment, the recommendations should be the same as those for patients with severe bulbar impairment.

**Subgroup: patients with a diagnosis of dementia**

No study was identified that addressed the identification and assessment of respiratory impairment in patients with MND who have a diagnosis of dementia. The GDG acknowledged that respiratory function tests may be inappropriate for this particular subgroup because of issues such as consent (see ‘Dementia’, NICE clinical guideline 42), difficulty in carrying out the tests, the patient’s ability to understand, tolerate and agree to undertake the tests, the impact on carers, and whether the patient is capable of receiving non-invasive ventilation. Hence the GDG came to the consensus that no specific recommendations should be made on which respiratory function tests to carry out for this subgroup, and that decisions should be based on the particular patient's needs and circumstances.
2.2.4 Recommendations

Recommendation 1.1.8
As part of the initial assessment to diagnose MND, or soon after diagnosis, a healthcare professional from the multidisciplinary team who has appropriate competencies should perform the following tests (or arrange for them to be performed) to establish the patient's baseline respiratory function:

- oxygen saturation measured by pulse oximetry (SpO₂)
  - this should be a single measurement of SpO₂ with the patient at rest and breathing room air
  - if it is not possible to perform pulse oximetry locally, refer the patient to a specialist respiratory service

then one or both of the following:

- forced vital capacity (FVC) or vital capacity (VC)\(^8\)
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP).

Recommendation 1.1.9
If the patient has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment:

- ensure that SpO₂ is measured (at rest and breathing room air)
- do not perform the other respiratory function tests (FVC, VC, SNIP and MIP) if interfaces are not suitable for the patient.

\(^8\) The difference between the measurement of vital capacity and forced vital capacity is very subtle and so either can be used.
**Recommendation 1.1.10**

A healthcare professional with appropriate competencies should perform the respiratory function tests every 3 months, although tests may be performed more or less often depending on:

- whether there are any symptoms and signs of respiratory impairment (see recommendation 1.1.7)
- the rate of progression of MND
- the patient’s preference and circumstances.

**Recommendation 1.1.11**

Perform arterial or capillary blood gas analysis if the patient’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 patient to a specialist respiratory service.

**Recommendation 1.1.12**

If the patient’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 specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study **and**
- discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.
Recommendation 1.1.13
If the patient’s arterial partial pressure of carbon dioxide (PaCO₂) is greater than 6 kPa:

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

Recommendation 1.1.14
If the patient’s PaCO₂ is less than or equal to 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnoea (see recommendation 1.1.7):

- refer them to a specialist respiratory service for nocturnal (overnight) oximetry and/or a limited sleep study and
- discuss both the impact of respiratory impairment and treatment options with the patient and (if the patient agrees) their family and carers.
Recommendation 1.1.15
If any of the results listed in table 2 is obtained, discuss with the patient and (if the patient agrees) their family and carers:

- the impact of respiratory impairment
- treatment options
- possible referral to a specialist respiratory service for further assessment.

Table 2 Results of respiratory function tests

<table>
<thead>
<tr>
<th>Forced vital capacity (FVC) or vital capacity (VC)</th>
<th>Sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• FVC or VC less than 50% of predicted value</td>
<td>• SNIP or MIP less than 40 cmH₂O</td>
</tr>
<tr>
<td>• FVC or VC less than 80% of predicted value plus any symptoms or signs of respiratory impairment (see recommendation 1.1.7), particularly orthopnoea</td>
<td>• SNIP or MIP less than 65 cmH₂O for men or 55 cmH₂O for women plus any symptoms or signs of respiratory impairment (see recommendation 1.1.7), particularly orthopnoea</td>
</tr>
<tr>
<td></td>
<td>• Repeated regular tests show a rate of decrease of SNIP or MIP of more than 10 cmH₂O per 3 months</td>
</tr>
</tbody>
</table>

Recommendation 1.1.16
Base decisions on respiratory function tests for a patient with a diagnosis of dementia on considerations specific to their needs and circumstances, such as:

- their ability to give consent
- 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.

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2.3 Clinical and cost effectiveness of non-invasive ventilation for the treatment of respiratory impairment in patients with motor neurone disease

2.3.1 Evidence review

A total of 2672 studies were retrieved by the systematic searches. Of these, only 12 studies met the inclusion and exclusion criteria (for review protocol and inclusion/exclusion criteria, see appendix 9.2). Of the 12 included studies, there was one randomised controlled trial and 11 observational studies. No study was identified that addressed the adverse effects of non-invasive ventilation. The 12 included studies were grouped by key outcomes and presented in GRADE profiles. Evidence on individual outcomes was appraised by using GRADE methodology (see appendix 9.2), and evidence statements were drawn to further summarise the evidence. The 12 included studies and the outcomes that were included in the GRADE profiles are summarised in table 6.

Table 6 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparisons</th>
<th>Key outcomes presented in GRADE profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourke et al.</td>
<td>Respiratory criteria (both treatment and control groups): orthopnoea with PImax &lt; 60% of predicted, or symptomatic daytime hypercapnia</td>
<td>Quality of life: SF-36 (Mental Component Summary)</td>
</tr>
<tr>
<td>(2006) RCT</td>
<td>Comparison: NIV vs standard care without NIV (subgroup analysis available)</td>
<td>Symptom improvement: SAQLI</td>
</tr>
<tr>
<td>Pinto et al.</td>
<td>Respiratory criteria (both treatment and control groups): onset of abnormalities in diurnal gas exchanges</td>
<td></td>
</tr>
<tr>
<td>(1995) Cohort</td>
<td>Comparison: NIV (BiPAP) (group II) vs standard care (oxygen, bronchodilators and other palliative measures) (group I)</td>
<td>Respiratory muscle strength (6–12 months): FVC, VC, PO2, PCO2</td>
</tr>
<tr>
<td>Mustfa et al.</td>
<td>Respiratory criteria (both treatment and control groups): confirmation of respiratory muscle weakness such as orthopnoea, unrefreshing sleep, daytime somnolence and reduced appetite; daytime hypercapnia, even if asymptomatic; nocturnal desaturation (defined as SaO2 of &lt; 90% for &gt; 5% of sleep time)</td>
<td>Survival: total survival, % survival from onset of diurnal disorder of gas exchange</td>
</tr>
<tr>
<td>(2006) Cohort</td>
<td>Comparison: NIV vs no NIV (refused or intolerant)</td>
<td></td>
</tr>
<tr>
<td>Carrat et al.</td>
<td>Respiratory criteria (both treatment and control groups): FVC &lt; 75%; nocturnal respiratory insufficiency at polysomnography</td>
<td>Survival: 1-year survival rates</td>
</tr>
<tr>
<td>(2009) Cohort</td>
<td>Comparison: NIV vs no NIV (refused or intolerant)</td>
<td></td>
</tr>
<tr>
<td>Kleopa et al.</td>
<td>Respiratory criteria (both treatment and control groups): FVC &lt; 50% of predicted; or fall in FVC of more than 15% within a 3-month period.</td>
<td>Survival: in months from initiation or offer of NIV</td>
</tr>
<tr>
<td>(1999) Cohort</td>
<td>Comparison: NIV vs no NIV (refused) vs NIV less tolerant (fewer hours) (subgroup analysis available)</td>
<td>Respiratory muscle strength: % FVC decline before and after initiation or offer of NIV</td>
</tr>
<tr>
<td>Study</td>
<td>Comparisons</td>
<td>Key outcomes presented in GRADE profiles</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sivori et al. (2007) Cohort</td>
<td>Respiratory criteria (both treatment and control groups): symptomatic</td>
<td>Survival: at 10, 20 and 30 months</td>
</tr>
<tr>
<td></td>
<td>ventilation impairment (dyspnoea, morning headache, fatigue) plus one of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>the following: PaCO₂ &gt; 45 mmHg, or nocturnal oxygen saturation by pulse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>oximetry ≤ 88% for 5 continuous minutes or PImax &lt; 60 cmH₂O or FVC &lt; 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison: NIV vs no NIV (refused)</td>
<td></td>
</tr>
<tr>
<td>Lo Coco et al. (2006) Cohort</td>
<td>Respiratory criteria (both treatment and control groups): dyspnoea,</td>
<td>Survival: median (months) after initiation of NIV</td>
</tr>
<tr>
<td></td>
<td>morning headache, daytime hypersomnolence, or one of the following: FVC</td>
<td>Factors influencing NIV tolerance</td>
</tr>
<tr>
<td></td>
<td>&lt; 50% of predicted, MIP &lt; −60 cmH₂O, PaCO₂ ≥ 45 mmHg, nocturnal desaturation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison: NIV vs NIV less tolerant (fewer hours)</td>
<td></td>
</tr>
<tr>
<td>Aboussouan et al. (1997) Cohort</td>
<td>Respiratory criteria (both treatment and control groups): orthopnoea,</td>
<td>Survival: hazard ratios</td>
</tr>
<tr>
<td></td>
<td>hypercapnia or both; PCO₂ ≥ 45 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison: NIV vs NIV less tolerant (fewer hours)</td>
<td></td>
</tr>
<tr>
<td>Farrero et al. (2005) Cohort</td>
<td>Respiratory criteria (both treatment and control groups): occurrence of</td>
<td>Survival of subgroups: mean (months) after initiation of NIV</td>
</tr>
<tr>
<td></td>
<td>any of the following: FVC ≤ 50% of predicted or a decrease in FVC of ≥ 500</td>
<td></td>
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<tr>
<td></td>
<td>ml on two consecutive visits, SpO₂ &lt; 90% during 5 consecutive minutes, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypercapnia (PaCO₂ &gt; 45 mmHg)</td>
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<tr>
<td></td>
<td>Comparison: NIV for patients with non-bulbar MND vs NIV for patients with</td>
<td></td>
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<tr>
<td></td>
<td>bulb MND</td>
<td></td>
</tr>
<tr>
<td>Berlowitz et al. (2006) Cohort</td>
<td>Respiratory criteria (both treatment and control groups): respiratory</td>
<td>Survival: median (months) after initiation of treatment</td>
</tr>
<tr>
<td></td>
<td>failure (NIV or tracheostomy)</td>
<td></td>
</tr>
<tr>
<td>Kaub-Wittermer et al. (2003) Cross-sectional</td>
<td>Respiratory criteria (both treatment and control groups): patients</td>
<td>Carer’s burden</td>
</tr>
<tr>
<td>survey</td>
<td>recorded to be ventilated (NIV or tracheostomy)</td>
<td></td>
</tr>
<tr>
<td>Newson-Davis et al. (2001) Cohort</td>
<td>Respiratory criteria:</td>
<td>Cognitive performance: list learning, list recall verbal fluency, KOLT</td>
</tr>
<tr>
<td></td>
<td>• Treatment group: reduced VC (&lt; 80% of predicted); nocturnal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>polysomnography showing episodes of nocturnal</td>
<td></td>
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<tr>
<td></td>
<td>hypoventilation causing arousals; evidence of abnormal daytime blood</td>
<td></td>
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<tr>
<td></td>
<td>gas (e.g. PaCO₂ &gt; 49 mmHg); bicarbonate &gt; 28 mmol/l; daytime somnolence</td>
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<tr>
<td></td>
<td>using Epworth sleepiness scale</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Control group: matched for age and disease severity but with no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>respiratory difficulty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparison: NIV vs no NIV way no NIV</td>
<td></td>
</tr>
</tbody>
</table>

BiPAP, bilevel positive airway pressure; FVC, forced vital capacity; KOLT, Kendrick object learning test; MIP, maximal inspiratory pressure; NIV, non-invasive ventilation; PaCO₂, partial pressure of CO₂ in arterial blood; PCO₂, partial pressure of carbon dioxide; PImax, maximal inspiratory pressure; PO₂, partial pressure of oxygen; RCT, randomised controlled trial; SaO₂, arterial oxygen saturation; SAQLI, sleep apnoea quality-of-life index; SF-36, short form-36, SpO₂, oxygen saturation measured by pulse oximetry; VC, vital capacity.

### 2.3.2 Evidence statements

**All patients with MND**

**Key outcome: survival**

#### 2.3.2.1 Low-quality evidence from a randomised controlled trial (main evidence) and very-low-quality evidence from observational studies (supporting evidence) showed that NIV improved survival
(compared with no NIV) in patients with MND with respiratory impairment. [GRADE profile 8]

2.3.2.2 Very-low-quality evidence from an observational study showed that even patients who were less tolerant of NIV (treatment for less than 4 hours per day) had improved survival compared with patients who did not use NIV. [GRADE profile 9]

2.3.2.3 Very-low-quality evidence from observational studies showed a positive trend between survival and hours of NIV use. [GRADE profile 10]

2.3.2.4 Very-low-quality evidence from one observational study showed that patients with tracheostomy had longer survival than patients with NIV. [GRADE profile 11]

Key outcome: quality of life
2.3.2.5 Low-quality evidence from a randomised controlled trial (main evidence) that showed NIV improved quality of life (SF-36 mental component summary) compared with no NIV in patients with MND. [GRADE profile 12]

Key outcome: respiratory muscle strength
2.3.2.6 There was conflicting very-low-quality evidence on the effectiveness of NIV in improving respiratory muscle strength in patients with MND. [GRADE profiles 13 and 14]

- Some very-low-quality evidence from observational studies showed that NIV significantly slowed down the decline of FVC compared with no NIV in patients with MND with respiratory impairment.

- Some very-low-quality evidence from observational studies showed that NIV did not improve FVC (% of predicted), VC (% of predicted), PO2 or PCO2 compared with no NIV in patients with MND after the onset of abnormalities in diurnal gas exchanges.
• Some very-low-quality evidence from observational studies showed that minimal NIV (less than 4 hours per day) significantly slowed down the decline of FVC compared with no NIV in patients with MND with respiratory impairment.

Key outcome: symptom improvement or relief

2.3.2.7 Low-quality evidence from a randomised controlled trial (main evidence) showed that NIV improved sleep quality (compared with no NIV) in patients with MND with respiratory impairment, and very low-quality evidence from an observational study showed that NIV improved cognitive performance (compared with no NIV) in patients with MND. [GRADE profile 15]

Subgroup analysis: patients with and without bulbar impairment

Key outcome: survival

2.3.2.8 Low-quality evidence from a randomised controlled trial (main evidence) showed that NIV (compared with no NIV) improved survival for patients with MND with respiratory impairment who had good bulbar function, but not for those with poor bulbar function. However, very-low-quality evidence from an observational study (supporting evidence) showed that NIV (compared with no NIV) improved survival in both bulbar and non-bulbar groups [GRADE profile 16]

2.3.2.9 Very-low-quality evidence from an observational study showed that patients with MND with respiratory impairment who had no bulbar impairment had longer survival after the initiation of NIV than patients with bulbar impairment. [GRADE profile 17]

2.3.2.10 Very-low-quality evidence from an observational study showed that NIV provided survival benefit to a subgroup of patients with bulbar impairment and hypercapnia (compared with patients with bulbar impairment and normocapnia). [GRADE profile 17]

2.3.2.11 Very-low-quality evidence from an observational study showed that NIV improved survival in patients with MND with limb involvement
but not in patients with bulbar involvement (comparison was with patients who were less tolerant of NIV – that is, treatment for less than 4 hours per day). [GRADE profile 18]

Key outcome: quality of life
2.3.2.12 Low-quality evidence from a randomised controlled trial (main evidence) showed that NIV improved quality of life (SF-36 mental component summary) in patients with MND with good bulbar function, but not in those with poor bulbar function. [GRADE profile 19]

Key outcome: Symptom improvement or relief
2.3.2.13 Low-quality evidence from a randomised controlled trial (main evidence) showed that NIV improved sleep quality in patients with MND, regardless of bulbar function. [GRADE profile 20]

Other factors/outcomes
Key outcome: factors that influence tolerance of NIV
2.3.2.14 Very-low-quality evidence from an observational study showed that bulbar involvement influenced patients’ tolerance of NIV. [GRADE profile 21]

Key outcome: carer’s burden
2.3.2.15 Very-low-quality evidence from an observational study showed that carers of patients with MND with tracheostomy were more likely to give up working compared with carers of patients with NIV. However, there was no difference between the two groups in carers’ health problems. [GRADE profile 22]

Subgroup: patients with a diagnosis of dementia
No study was identified that addressed the clinical effectiveness of NIV in patients with MND with a diagnosis of dementia.
GRADE profiles for all patients with MND

Key outcome: survival

**GRADE profile 8 Clinical effectiveness of NIV (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: Survival (days) after randomisation</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>RCT</td>
<td>NIV (22)</td>
<td>No NIV(^a) (19)</td>
<td>Median (range): NIV = 219 (75–1382) SC = 171 (1–878) p = 0.0062</td>
<td>S (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

| **Outcome: Survival at 6 months and 1 year after the onset of abnormalities in diurnal gas exchange** | | | | | | | | | | |
| 1 | Cohort | NIV (10) | No NIV\(^c\) (10) | Log-rank test: p = 0.0006 | N | N | N | S (iii) | S (iv) | Very low |

| **Outcome: Survival at the end of study period (Kaplan–Meier, hazard ratio)** | | | | | | | | | | |
| 1 | Cohort | NIV (9/18) (50.0%) | No NIV\(^c\) (20/21) (95.2%) | HR = 3.4 (95% CI: 1.5 to 7.9) | N | N | N | S (iii) | N | Very low |

| **Outcome: Survival at 1 year (adjusted hazard ratio)** | | | | | | | | | | |
| 1 | Cohort | NIV (4/13) (30.8%) | No NIV\(^c\) (0/13) (0%) | HR = 24.8 (95% CI: 14.4 to 54.0) p = 0.0001 | N | N | N | S (iii) | N | Very low |

| **Outcome: Survival at 1 year** | | | | | | | | | | |
| 1 | Cohort | NIV (12/16) (75%) | No NIV\(^c\) (0/12) (0%) | RR = 2.25 (95% CI: 0.96 to 5.23) ARI = 41.7% | N | N | N | S (iii) | N | Very low |

| **Outcome: Survival (months) from initiation of NIV** | | | | | | | | | | |
| 1 | Cohort | NIV (38) | No NIV\(^c\) (38) | Mean (SD): NIV = 14.2 (13.0) No NIV = 4.6 (12.7) p < 0.001 | N | N | N | S (iii) | N | Very low |

| **Outcome: Survival at 21–30 months after initiation of NIV** | | | | | | | | | | |
| 1 | Cohort | NIV\(^d\) (5/29) (17.2%) | No NIV\(^d\) (0/68) (0%) | RR = infinity ARI = 17.2% | S (v) | N | N | S (iii) | N | Very low |

| **Outcome: Survival at 11–20 months after initiation of NIV** | | | | | | | | | | |
| 1 | Cohort | NIV\(^d\) (10/29) (34.5%) | No NIV\(^d\) (11/68) (16.2%) | RR = 2.13 (95% CI: 1.01 to 4.46) ARI = 18.3% | S (v) | N | N | S (iii) | N | Very low |

ARI, absolute risk increase; CI, confidence interval; HR, hazard ratio; NIV, non-invasive ventilation; RCT, randomised control trial; RR, relative risk; SC, standard care.
N = no serious; S = serious.
\(^a\) Standard care without NIV. Standard care: pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.
\(^b\) Standard care (oxygen, bronchodilators and other palliative measures).
\(^c\) Patients who declined or were intolerant of NIV.
\(^d\) In the NIV group, 18/29 were also on riluzole.
\(^e\) In the No NIV group, patients declined NIV but 26/68 were on riluzole.
(i) Study with no blinding.
(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control group for power calculation or optimal information size (OIS); downgraded 1 level.
(iii) Unable to assess sample size (OIS), small study sample; downgraded 1 level.
(iv) Only p value was reported, no hazard ratio or relative risk at different time points; downgraded 1 level.
(v) Different baseline care, some patients were on riluzole and some were not; downgraded 1 level.

[B] = Bourke et al. (2006)
[P] = Pinto et al. (1995)
[C] = Carrat et al. (2009)
[S] = Sivori et al. (2007)

**GRADE profile 9 Clinical effectiveness of NIV (NIV less tolerant vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NIV\footnote{a}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV less tolerant\footnote{a} (38)</td>
<td>No NIV\footnote{b} (52)</td>
<td>Mean (SD): NIV less tolerant = 7.0 (6.7) No NIV = 4.6 (2.7) p = 0.038</td>
<td>N N N S (i)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Very low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation.
N = no serious; S = serious.
\footnote{a} Patients in the NIV less tolerant group received < 4 hours of NIV per day.
\footnote{b} Patients who declined NIV.

(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level.


**GRADE profile 10 Clinical effectiveness of NIV (NIV vs NIV less tolerant)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Very low</td>
</tr>
<tr>
<td>1 [LC]</td>
<td>Cohort</td>
<td>NIV (44)</td>
<td>NIV less tolerant\footnote{a} (27)</td>
<td>Median (months) (IQR): NIV = 18 (7–28) NIV less tolerant = 6 (3–12) p = 0.0001</td>
<td>N N N S (i)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>Very low</td>
</tr>
</tbody>
</table>

**Outcome: Survival from onset of respiratory insufficiency**

| 1 \[A\] | Cohort | NIV (9/18) (50%) | NIV less tolerant\footnote{a} (1/21) (4.8%) | RR = 10.5 (95% CI: 1.47 to 75.12) ARI = 45.2% | N N N S (i) | N | N | N | S | Very low |

ARI, absolute risk increase; CI, confidence interval; IQR, interquartile range; NIV, non-invasive ventilation; RR, relative risk.
N = no serious; S = serious.
\footnote{a} Patients in the NIV less tolerant group received < 4 hours of NIV per day.

(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level.

[LC] = Lo Coco et al. (2006)
### GRADE profile 11 Clinical effectiveness of NIV (NIV vs tracheostomy ventilation)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (36)</td>
<td>TV (11)</td>
<td>Median (months): NIV = 32; TV = 41 p = 0.0497</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation; TV = tracheostomy ventilation. N = no serious; S = serious.
(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level.
[Be] = Berlowitz et al. (2006)

### Key outcome: quality of life

**GRADE profile 12 Clinical effectiveness of NIV (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (22)</td>
<td>No NIV (19)</td>
<td>Median (range): NIV = 168 (45–1357) SC = 99 (0–690) p = 0.0017</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

Outcome: SF-36 (mental component summary) – duration (days) maintained at > 75% of baseline

Outcome: SF-36 (mental component summary) – time-weighted improvement (at 12 months or until death)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (22)</td>
<td>No NIV (19)</td>
<td>Median (range): NIV = 2.31 (0–11.54) SC = 0 (0–52.3) p = 0.0082</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation; RCT, randomised controlled trial; SC, standard care. N = no serious; S = serious.
a Standard care without NIV. Standard care: pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.
b Data are median (range) values of AUC (area under the curve) above baseline divided by time from randomisation until death.
(i) Study with no blinding.
(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control groups for power calculation or optimal information size; downgraded 1 level.
[B] = Bourke et al. (2006)
### Key outcome: respiratory muscle strength

**GRADE profile 13: Clinical effectiveness of NIV (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
</table>
| **Outcome: Decline in FVC (% predicted) after initiation of NIV**

1 [K]

| | Cohort | NIV (38) | No NIV\(^a\) (52) | Mean (SD): NIV = −3.5 (5.3) No NIV = −8.3 (5.0) | N | N | N | S (i) | N | Very low |

**Outcome: FVC (% predicted) after onset of abnormalities in diurnal gas exchange (at 6–12 months)**

1 [P]

| | Cohort | NIV (10) | No NIV\(^b\) (10) | Mean (SD): NIV = 43.9 (14.0) SC = 44.1 (15.0) | p = 0.9 | N | N | N | S (i) | N | Very low |

**Outcome: VC (% predicted) after onset of abnormalities in diurnal gas exchange (at 6–12 months)**

1 [P]

| | Cohort | NIV (10) | No NIV\(^b\) (10) | Mean (SD): NIV = 40.0 (21.0) SC = 35.8 (5.1) | p = 0.06 | N | N | N | S (i) | N | Very low |

**Outcome: PO\(_2\) (mmHg) after onset of abnormalities in diurnal gas exchange (at 6–12 months)**

1 [P]

| | Cohort | NIV (10) | No NIV\(^b\) (10) | Mean (SD): NIV = 73.8 (5.5) SC = 80.4 (6.9) | p = 0.06 | N | N | N | S (i) | N | Very low |

**Outcome: PCO\(_2\) (mmHg) after onset of abnormalities in diurnal gas exchange (at 6–12 months)**

1 [P]

| | Cohort | NIV (10) | No NIV\(^b\) (10) | Mean (SD): NIV = 46.0 (3.4) SC = 45.2 (4.5) | p = 0.7 | N | N | N | S (i) | N | Very low |

FVC, forced vital capacity; NIV, non-invasive ventilation; PCO\(_2\), partial pressure of CO\(_2\); PO\(_2\), partial pressure of O\(_2\); SC, standard care; VC, vital capacity.

\(^a\) Patients who declined or were intolerant of NIV.

\(^b\) Patients received standard care (oxygen, bronchodilators and other palliative measures).

(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level.


[P] = Pinto et al. (1995)
### GRADE profile 14 Clinical effectiveness of NIV (NIV less tolerant vs no NIV)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV less tolerant&lt;sup&gt;a&lt;/sup&gt; (32)</td>
<td>No NIV&lt;sup&gt;b&lt;/sup&gt; (52)</td>
<td>Mean (SD): NIV less tolerant = −5.9 (4.8) No NIV = −8.3 (5.0) p = 0.02</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; NIV, non-invasive ventilation.
N = no serious; S = serious.
<sup>a</sup>Patients in the NIV less tolerant group received < 4 hours of NIV per day.
<sup>b</sup>Patients who declined or were intolerant of NIV.
(i) Cannot assess imprecision; downgraded 1 level.

---

FVC, forced vital capacity; NIV, non-invasive ventilation.
N = no serious; S = serious.
<sup>a</sup>Patients in the NIV less tolerant group received < 4 hours of NIV per day.
<sup>b</sup>Patients who declined or were intolerant of NIV.
(i) Cannot assess imprecision; downgraded 1 level.
### Key outcome: symptom improvement or relief

**GRADE profile 15 Clinical effectiveness of NIV (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: Sleep apnoea quality-of-life index (SAQLI) symptoms domain – duration (days) maintained at &gt; 75% of baseline</strong></td>
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<tr>
<td>1</td>
<td>RCT</td>
<td>NIV (22)</td>
<td>No NIV(^a) (19)</td>
<td>Median (range): NIV = 192 (48–1357) SC = 46 (0–703) p = 0.0013</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Outcome: Sleep apnoea quality-of-life index (SAQLI) symptoms domain – time-weighted improvement (from AUC)</strong></td>
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</tr>
<tr>
<td>1</td>
<td>RCT</td>
<td>NIV (22)</td>
<td>No NIV(^a) (19)</td>
<td>Median (range): NIV = 1.07 (0–3.20) SC = 0 (0–1.14) p &lt; 0.0001</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
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<tr>
<td><strong>Outcome: Change in cognitive performance – list learning (at 6 weeks)</strong></td>
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</tr>
<tr>
<td>1</td>
<td>Cohort</td>
<td>NIV (9)</td>
<td>No NIV(^b) (10)</td>
<td>Mean change scores: NIV = +14.85 No NIV = −0.59 p = 0.01</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Outcome: Change in cognitive performance – list recall (at 6 weeks)</strong></td>
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</tr>
<tr>
<td>1</td>
<td>Cohort</td>
<td>NIV (9)</td>
<td>No NIV(^b) (10)</td>
<td>Mean change scores: NIV = +8.95 No NIV = −9.19 p = 0.026</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>Outcome: Change in cognitive performance – Kendrick object learning test (KOLT) (at 6 weeks)</strong></td>
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</tr>
<tr>
<td>1</td>
<td>Cohort</td>
<td>NIV (9)</td>
<td>No NIV(^b) (10)</td>
<td>Mean change scores: NIV = +5.86 No NIV = −4.0 p = 0.007</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation; RCT, randomised controlled trial; SC, standard care.  
N = no serious; S = serious.  
\(^a\) Patients received standard care comprising pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.  
\(^b\) Patients in the control group were matched for age and disease severity with treatment group but with no respiratory difficulty.  
\(^c\) Data are median (range) values of AUC (area under the curve) above baseline divided by time from randomisation until death.  
(i) Study with no blinding.  
(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control group for power calculation or optimal information size (OIS); downgraded 1 level.  
(iii) Indirect comparator, as the control group had no respiratory difficulty; downgraded 1 level.  
(iv) Unable to assess sample size (OIS), small study sample; downgraded 1 level.  
[B] = Bourke et al. (2006)  
[ND] = Newsom-Davis et al. (2001)
**GRADE profiles for subgroup analysis: bulbar and non-bulbar impairment**

**Key outcome: survival**

**GRADE profile 16 Clinical effectiveness of NIV for patients with bulbar and non-bulbar impairment (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: GOOD BULBAR FUNCTION</strong>: Survival (days) after randomisation</td>
<td>1 [B]</td>
<td>RCT</td>
<td>NIV (11)</td>
<td>No NIV (9)</td>
<td>Median (range); NIV = 216 (94–681) SC = 11 (1–283) p = 0.0059</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Outcome: POOR BULBAR FUNCTION</strong>: Survival (days) after randomisation</td>
<td>1 [B]</td>
<td>RCT</td>
<td>NIV (11)</td>
<td>No NIV (10)</td>
<td>Median (range); NIV = 222 (75–1382) SC = 261 (6–876) p = 0.92</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Outcome: MODERATE OR SEVERE BULBAR</strong>: Survival (months) from initiation of NIV</td>
<td>1 [A]</td>
<td>Cohort</td>
<td>NIV (6)</td>
<td>No NIV (14)</td>
<td>HR = 2.7 (95% CI: 1.1 to 10.6)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
</tr>
<tr>
<td><strong>Outcome: BULBAR ONSET</strong>: Survival (months) from initiation of NIV</td>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV (14)</td>
<td>No NIV (17)</td>
<td>NIV had longer mean survival compared with No NIV (p = 0.01) (actual means not reported)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
</tr>
<tr>
<td><strong>Outcome: LIMB ONSET</strong>: Survival (months) from initiation of NIV</td>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV (24)</td>
<td>No NIV (9)</td>
<td>NIV had longer mean survival compared with No NIV (p &lt; 0.001) (actual means not reported)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (iii)</td>
<td>S (iv)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio; NIV, non-invasive ventilation; RCT, randomised controlled trial; SC, standard care.

N = no serious; S = serious.

a Bulbar function was assessed with a simple 6-point clinical scale, dichotomised into normal to moderate bulbar impairment (score 4–6) and severe bulbar impairment (score 0–3).

b Standard care without NIV, comprising pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.

c Classification of bulbar and limb was based on the area of disease onset.

d Patients who declined or were intolerant of NIV.

(i) Study with no blinding.

(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control group for power calculation or optimal information size (OIS); downgraded 1 level.

(iii) Unable to assess sample size (OIS), small study sample; downgraded 1 level.

(iv) Only p value was reported, median survival not reported; downgraded 1 level.

[B] = Bourke et al. (2006)


### GRADE profile 17 Clinical effectiveness of NIV for patients with bulbar and non-bulbar impairment (bulbar vs non-bulbar)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: BULBAR VS NON-BULBAR</strong>: Survival (months) from initiation of NIV</td>
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<td></td>
</tr>
<tr>
<td>1 [F]</td>
<td>Cohort</td>
<td>NIV bulbar(^b) (27)</td>
<td>NIV non-bulbar (30)</td>
<td>Mean (SD): NIV bulbar = 15 (2) NIV non-bulbar = 27 (4) (p = 0.03)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Hyper, hypercapnic; NIV, non-invasive ventilation; Normo, normocapnic. 
\( N = \) no serious; \( S = \) serious. 
\(^a\) Definition for bulbar and non-bulbar: the presence of deglutition or phonation alterations. 
\(^b\) The NIV bulbar group only included bulbar patients who tolerated NIV. 
(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level. 
[F] = Farrero et al. (2005)

### GRADE profile 18 Clinical effectiveness of NIV for patients with bulbar and non-bulbar impairment (NIV vs NIV less tolerant)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: BULBAR ONSET</strong>: Survival (months) from initiation of NIV</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV (14)</td>
<td>NIV less tolerant(^b) (12)</td>
<td>No significant difference between NIV and NIV less tolerant (p = 0.07) (actual means not reported)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>S (ii)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation. 
\( N = \) no serious; \( S = \) serious. 
\(^a\) Classification of bulbar and limb was based on the area of disease onset. 
\(^b\) Patients in the NIV less tolerant group received < 4 hours of NIV per day. 
(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level. 
(ii) Only the \( p \) value was reported, median survival not reported; downgraded 1 level. 

| **Outcome: LIMB ONSET**: Survival (months) from initiation of NIV |
| 1 [K] | Cohort | NIV (24) | NIV less tolerant\(^b\) (20) | NIV had longer mean survival compared with NIV less tolerant \(p = 0.006\) (actual means not reported) | N | N | N | S (i) | S (ii) | Very low |
**Key outcome: quality of life**

**GRADE profile 19 Clinical effectiveness of NIV for patients with bulbar and non-bulbar impairment (NIV vs no NIV)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Treatment (n)</th>
<th>Control (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (11)</td>
<td>No NIV (9)</td>
<td>Median (range): NIV = 199 (48–552) SC = 4 (0–196) p = 0.001</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Outcome: GOOD BULBAR FUNCTION</strong>: SF-36 (mental component summary) – duration (days) maintained at &gt; 75% of baseline</td>
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<tr>
<td></td>
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<td>NIV (11)</td>
<td>No NIV (10)</td>
<td>Median (range): NIV = 127 (45–1357) SC = 164 (2–690) p = 0.64</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
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<tr>
<td><strong>Outcome: POOR BULBAR FUNCTION</strong>: SF-36 (mental component summary) – duration (days) maintained at &gt; 75% of baseline</td>
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<td></td>
<td>NIV (11)</td>
<td>No NIV (9)</td>
<td>Median (range): NIV = 2.18 (0–11.54) SC = 0 (0–1.39) p = 0.0052</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
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<tr>
<td><strong>Outcome: GOOD BULBAR FUNCTION</strong>: SF-36 (mental component summary) – time-weighted improvement (at 12 months or until death)</td>
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<tr>
<td></td>
<td></td>
<td>NIV (11)</td>
<td>No NIV (10)</td>
<td>Median (range): NIV = 4.47 (0–7.75) SC = 0.88 (0–5.23) p = 0.24</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Outcome: POOR BULBAR FUNCTION</strong>: SF-36 (mental component summary) – time-weighted improvement (at 12 months or until death)</td>
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</table>

NIV, non-invasive ventilation; RCT, randomised control trial; SC, standard care.
N = no serious; S = serious.

* Bulbar function was assessed with a simple 6-point clinical scale, dichotomised into normal to moderate bulbar impairment (score 4–6) and severe bulbar impairment (score 0–3).

* Standard care without NIV, comprising pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.

* Data are median (range) values of AUC (area under the curve) above baseline divided by time from randomisation until death.

(i) Study with no blinding.

(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control group for power calculation or optimal information size; downgraded 1 level.

[B] = Bourke et al. (2006)
**Key outcome: symptom improvement or relief**

**GRADE profile 20 Clinical effectiveness of NIV for patients with bulbar and non-bulbar impairment (NIV vs no NIV)**

| Outcome: GOOD BULBAR FUNCTION\(^a\): Sleep apnoea quality-of-life index (SAQLI) symptoms domain – duration (days) maintained at > 75% of baseline |
|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration |
| 1 \[B\] | RCT | NIV (11) | No NIV\(^b\) (9) | Median (range): NIV = 205 (69–629) SC = 4 (0–143) p = 0.0004 | N (i) | N | N | S (ii) | N | Low |

| Outcome: POOR BULBAR FUNCTION\(^a\): SAQLI symptoms domain – duration (days) maintained at > 75% of baseline |
|---|---|---|---|---|---|---|---|---|
| 1 \[B\] | RCT | NIV (11) | No NIV\(^b\) (10) | Median (range): NIV = 143 (48–1357) SC = 100 (2–703) p = 0.26 | N (i) | N | N | S (ii) | N | Low |

| Outcome: GOOD BULBAR FUNCTION\(^a\): SAQLI symptoms domain – time-weighted improvement (from AUC) |
|---|---|---|---|---|---|---|---|---|
| 1 \[B\] | RCT | NIV (11) | No NIV\(^b\) (9) | Median (range): NIV = 1.73 (0.52–2.95) SC = 0 (0–0) p < 0.0001 | N (i) | N | N | S (ii) | N | Low |

| Outcome: POOR BULBAR FUNCTION\(^a\): SAQLI symptoms domain – time-weighted improvement (from AUC) |
|---|---|---|---|---|---|---|---|---|
| 1 \[B\] | RCT | NIV (11) | No NIV\(^b\) (10) | Median (range): NIV = 0.90 (0–3.20) SC = 0.04 (0–1.14) p = 0.018 | N (i) | N | N | S (ii) | N | Low |

AUC, area under the curve; NIV, non-invasive ventilation; RCT, randomised control trial; SC, standard care. 
N = no serious; S = serious.

\(^a\) Bulbar function was assessed with a simple 6-point clinical scale, dichotomised into normal to moderate bulbar impairment (score 4–6) and severe bulbar impairment (score 0–3).

\(^b\) Standard care without NIV, comprising pneumococcal and annual influenza vaccines, assisted cough techniques, advice on posture during sleep, bed raiser and adjustable beds when required, palliative care during end of life.

\(^c\) Data are median (range) values of AUC above baseline divided by time from randomisation until death.

(i) Study with no blinding.

(ii) Uncertainty in terms of precision, total number of events less than 300, and no information on estimations for median survival time for treatment and control group for power calculation or optimal information size; downgraded 1 level.

\[B\] = Bourke et al. (2006)
GRADE profiles for other factors or outcomes

**Key outcome: factors that influence NIV tolerance**

**GRADE profile 21 Clinical effectiveness of NIV (NIV vs NIV less tolerant)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Group 1 (n)</th>
<th>Group 2 (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (35/44)</td>
<td>NIV less toleranta (15/27)</td>
<td>Mild to moderate bulbar involvement (vs severe bulbar involvement) OR = 6.09 (95% CI: 1.18, 31.52)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

NIV, non-invasive ventilation; OR, odds ratio. N = no serious; S = serious.
a Patients in the NIV less tolerant group received < 4 hours of NIV per day.
(i) Unable to assess sample size (optimal information size), small study sample; downgraded 1 level.
[LC] = Lo Coco et al. (2006)

**Key outcome: carers’ burden**

**GRADE profile 22: carers’ burden (NIV vs tracheostomy)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Design</th>
<th>Group 1 (n)</th>
<th>Group 2 (n)</th>
<th>Results</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other consideration</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIV (6/32)</td>
<td>TV (12/20)</td>
<td>RR = 0.31 (95% CI: 0.14 to 0.70) ARR = 41%</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NIV (20/32)</td>
<td>TV (14/20)</td>
<td>RR = 0.89 (95% CI: 0.60 to 1.32) ARR = 7%</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

ARR, absolute risk reduction; NIV, non-invasive ventilation; RR, relative risk; TV, tracheostomy ventilation. N = no serious; S = serious.
(i) = unable to assess sample size (optimal information size), small study sample, downgraded 1 level.

### 2.3.3 Health economic modelling

A search for cost-effectiveness studies identified one relevant published paper that examined non-invasive ventilation (NIV) in patients with MND. Using a quality checklist to assess its applicability and limitations, it was concluded that this study was not applicable to the decision problem (see appendix 9.7). Other cost-effectiveness papers were used to explore approaches to
modelling strategies and to inform the model’s structure; two of these were reviewed in detail for this guideline (see appendix 9.7).

Models

Two models were developed to estimate the cost effectiveness of NIV: the first was based on a Markov model and the second was based on a randomised control trial (RCT). The following criteria were used for both models:

- The estimate of the efficacy of NIV in patients with MND (that is, the percentage of patients with MND who can tolerate NIV) was based on the results of the Bourke et al. (2006) study and adjusted based on reported tolerance in other studies and the experience of GDG members. See appendix 9.7 for more details.
- Patients accrued costs and utilities depending on their pathway through the model.
- Costs were obtained from NHS reference costs and published papers.
- Costs of equipment such as ventilator machines were obtained from GDG expert opinion.

There was no information from either the literature or GDG members on the costs or quality-of-life outcomes resulting from adverse events of NIV. More details of the rationale for both models, the efficacy of NIV, and chosen utilities and costs are presented in appendix 9.7.

Markov model

This first model was based on a decision-analytic methodology using Markov-modelling-based transition probabilities obtained from a Health Technology Assessment (HTA) report (Stewart 2000). This HTA report assumed that patients with MND can progress and regress in a stepwise manner through the model. However, the GDG considered that patients can only progress and cannot revert to an earlier health state in the model.

Disease-specific health states were defined and transition probabilities were assigned for movement between the health states over a discrete time period (or Markov cycle). Once the model structure (health states, transitions) was
set, estimates of resource use and health outcomes associated with the states and transitions between states in the model were incorporated. EQ-5D utilities were obtained from published sources that linked quality of life to progression of MND.

**RCT model**
The second economic model was designed to closely reflect an RCT carried out by Bourke et al. (2006), which investigated the effects of NIV on survival and quality of life in patients with MND. Patients diagnosed with MND with respiratory failure received no NIV (current best practice; n = 19) or NIV (n = 22). Death was the absorbing state in both arms. Data on quality of life obtained using SF-36 from the RCT by Bourke et al. (2006) were converted into EQ-5D values using the mapping technique of Ara and Brazier (2008).

**Types of analysis**
Using the Markov model, both deterministic analysis (using only point estimates) and probabilistic analysis (using a range of values and simulation to account for uncertainty) were conducted to examine cost effectiveness. Additional analysis included cost-effectiveness acceptability curves, which assess the probability that a treatment or intervention is cost effective at a particular cost per quality-adjusted life-year (QALY) gained – in this case £30,000 per QALY. Finally, value of information analysis was conducted, which places a monetary value on how much it is worth to society to resolve the uncertainty in the cost-effectiveness analysis by conducting further research.

**Results**
The results of the cost-effectiveness analysis using the Markov model are summarised in table 7.
### Table 7 Results of cost-effectiveness analysis of NIV using a Markov model

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Deterministic ICER (per QALY gained)</th>
<th>Probability of being cost effective at £30,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NIV vs NIV</td>
<td>£34,639</td>
<td>12.7%</td>
</tr>
<tr>
<td>Standard care vs NIV</td>
<td>£21,556</td>
<td>90%</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; NIV, non-invasive ventilation; QALY, quality-adjusted life year.

The figure obtained from the value of information analysis was approximately £40 million. This represents the amount that society would be willing to pay to resolve uncertainty in the cost-effectiveness analysis by undertaking further research on the use of NIV in patients with MND (see appendix 9.7 for more details of value of Information analysis).

Incremental cost-effectiveness ratios (ICERs) were obtained using the RCT model by calculating the cost difference and QALY gain obtained when comparing the NIV and No NIV strategies. The base-case ICERs were between £13,327 and £30,439 per QALY gained when the ‘No NIV’ quality-of-life profile was varied. Appendix 9.7 gives details of a deterministic sensitivity analysis in which cost and QALYs were varied for the ‘No NIV’ strategy.

The evidence presented indicates that NIV is cost effective in a modelled population. However, there is considerable uncertainty around the estimates, and so the results should be interpreted with caution. The RCT model in particular is highly speculative. Nonetheless, together with the available evidence, the results are useful and give indications to inform the GDG.

**Discussion**

The GDG discussed the cost-effectiveness results from the two analyses presented. The GDG noted that the Markov model was based on robust methodology and data and that it was of high quality. However, the GDG had concerns that the structure of the Markov model did not accurately capture an improvement in quality of life, and so may underestimate the quality-of-life benefits attributable to NIV. The GDG also noted that the RCT model lacked data on quality of life after randomisation for some subjects because of early deaths in the ‘No NIV’ arm before the scheduled quality of-life-assessment.
The GDG was mindful that the results of the RCT model were highly speculative. The GDG also noted that a limitation of both models was the instruments used to capture quality of life (SF-36 and EQ-5D), which are highly insensitive to the symptoms of MND. The GDG concluded that the ICER estimates obtained using the Markov model were on the high side, although they did indicate that NIV is cost effective, since more accurate capturing of the quality of life would reduce the ICERs much further. Therefore, given the severity of MND, the lack of alternative treatment options for respiratory impairment and the difficulty in measuring quality of life in patients with MND, the GDG considered that the use of NIV in the management of people with MND represents a cost-effective use of NHS resources.

2.3.4 Evidence to recommendations

The GDG acknowledged that the available evidence on the effectiveness of non-invasive ventilation for treating respiratory impairment in patients with MND is of low or very low quality. This is because MND is a rare but progressive condition, and so trials with statistical precision and blinding would be impossible and unethical. Hence the GDG agreed that the one RCT that was included provides the best evidence on the use of non-invasive ventilation for patients for MND, and that it is highly unlikely that a well-conducted RCT will be carried out in the future for the reasons mentioned.

Based on the evidence on improvements in survival, quality of life and symptoms (including cognitive performance), and the health economic evaluation (section 2.3.3), the GDG agreed that a trial of non-invasive ventilation should be offered to patients with MND who have respiratory impairment, after an informed discussion with the patient and (if the patient agrees) their family and carers about both the benefits and limitations of the intervention. The GDG also agreed that non-invasive ventilation should be continued only if symptomatic and/or physiological improvements are achieved.

Although there was low-quality evidence showing that patients with bulbar involvement did not benefit overall from non-invasive ventilation in terms of
survival, there was also very-low-quality evidence showing the opposite. Moreover, there was also low-quality and very-low-quality evidence (in subgroup analysis) demonstrating that non-invasive ventilation improved sleep-related symptoms in patients with bulbar involvement. Hence the GDG agreed that a trial of non-invasive ventilation should be considered for patients with severe bulbar impairment if the patient may benefit from an improvement in sleep-related symptoms that may be a result of hypoventilation. Although the evidence on the improvement in cognitive performance was of very low quality, the GDG agreed that that a trial of non-invasive ventilation should also be considered for patients with severe cognitive problems that may be related to respiratory insufficiency, since correction of hypoxia and/or hypercapnia may result in cognitive improvements. The GDG also agreed that non-invasive ventilation should be continued for patients with severe bulbar impairment or severe cognitive problems only if clinical reviews show an improvement in sleep-related symptoms (that may be a result of correction of hypoventilation).

No study was identified that addressed the clinical effectiveness of non-invasive ventilation in patients who have a diagnosis of dementia. The GDG acknowledged that non-invasive ventilation may be inappropriate for these patients because of issues such as their capacity to make decisions and give consent (see ‘Dementia’, NICE clinical guideline 42), the severity of their dementia and cognitive problems, their ability to understand the purpose of the interfaces, their acceptance of the treatment, and whether they are likely to achieve improvements in sleep-related symptoms and/or behavioural improvements. Hence, based on the expertise and experience of members, the GDG agreed that no specific recommendations should be made on whether to offer a trial of non-invasive ventilation to these patients. Instead, the GDG recommended that the neurologist from the multidisciplinary team should carry out an assessment before a decision is made for an individual patient, which should include discussions with the patient’s family and/or carers.
2.3.5 Recommendations

**Recommendation 1.1.17**
Offer a trial of non-invasive ventilation if the patient’s symptoms and signs and the results of the respiratory function tests indicate that the patient is likely to benefit from the treatment.

- Discuss both the benefits and limitations of the intervention with the patient and their family and carers.
- Only consider a trial of non-invasive ventilation for a patient who has severe bulbar impairment or severe cognitive problems that may be related to respiratory impairment if they may benefit from an improvement in sleep-related symptoms or correction of hypoventilation.

**Recommendation 1.1.20**
When starting non-invasive ventilation:

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

**Recommendation 1.1.21**
Continue non-invasive ventilation if the clinical reviews show:

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

**Recommendation 1.1.22**
Discuss all decisions to continue or withdraw non-invasive ventilation with the patient and (if the patient agrees) their family and carers.
**Recommendation 1.1.23**

Before a decision is made on the use of non-invasive ventilation for a patient with a diagnosis of dementia, the neurologist from the multidisciplinary team should carry out an assessment that includes:

- the patient’s capacity to make decisions and to give consent\(^\text{10}\)
- the severity of dementia and cognitive problems
- whether the patient is likely to accept treatment
- whether the patient is likely to achieve improvements in sleep-related symptoms and/or behavioural improvements
- a discussion with the patient’s family and/or carers (with the patient’s consent if they have the capacity to give it).

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**2.4 Key elements in the management of the use of non-invasive ventilation for patients with motor neurone disease**

**2.4.1 Evidence review**

A total of 2678 studies were retrieved by the systematic searches. However, none of these studies were relevant to the review question, and hence no studies were included.

**2.4.2 Evidence statements**

No evidence was found on the key elements in the management of the use of non-invasive ventilation for patients with MND.

**2.4.3 Evidence to recommendations**

The GDG acknowledged that there is no evidence relating to the key elements in the management of the use of non-invasive ventilation for patients with MND. However, the GDG agreed that consensus recommendations based on the knowledge, experience and expertise of members need to be made on

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key elements of care, including: risk assessment before offering non-invasive ventilation, ongoing monitoring and review of the effectiveness of the treatment, initial acclimatisation to the use of non-invasive ventilation, and issues relating to device maintenance and emergency technical and clinical support.

The GDG further discussed that, to ensure continuity of care, regular respiratory assessment, provision and management of non-invasive ventilation and ongoing monitoring and clinical reviews should be provided by a multidisciplinary team within the context of a comprehensive multidisciplinary care plan. The coordination of care should be led by a healthcare professional within the team who has a specific interest in MND. The leader should also ensure that the care plan is communicated to relevant healthcare and social care professionals, including the patient’s primary care team, as well as to the patient and (where appropriate) their family and carers.

The GDG further discussed the composition of the multidisciplinary team, and agreed that it should include healthcare professionals who would be involved in respiratory monitoring and provision of non-invasive ventilation. These include a neurologist, a respiratory physician, MND and respiratory specialist nurses, a specialist respiratory physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist. The GDG agreed that these team members do not have to be at the same location.
2.4.4 Recommendations

Recommendation 1.1.1
A multidisciplinary team should coordinate and provide ongoing management and treatment for a patient with MND, including regular respiratory assessment and provision of non-invasive ventilation.

- The team should be led by a healthcare professional with a specific interest in MND. The leader should ensure that the patient’s multidisciplinary care plan (see recommendation 1.1.19) is coordinated and is communicated to relevant healthcare and social care professionals, including the patient’s primary care team, as well as to the patient and (where appropriate) their family and carers.

- The team should include a neurologist, a respiratory physician, an MND specialist nurse, a respiratory specialist nurse, a specialist respiratory physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist (team members do not have to be at the same location).

- Access to other healthcare professionals should be provided as needed.

- Team members who provide non-invasive ventilation should have appropriate competencies.
**Recommendation 1.1.18**

Before starting non-invasive ventilation, the multidisciplinary team should carry out and coordinate a patient-centred risk assessment, after discussion with the patient and their family and carers. This should consider:

- the most appropriate type of non-invasive ventilator and interfaces, based on the patient’s needs and lifestyle factors
- the patient’s tolerance of the treatment
- the risk, and possible consequences, of ventilator failure
- the power supply required, including battery back-up
- how easily the patient can get to hospital
- risks associated with travelling away from home (especially abroad)
- whether a humidifier is required
- issues relating to secretion management
- the availability of carers.
**Recommendation 1.1.19**

Before starting non-invasive ventilation, the multidisciplinary team should prepare a comprehensive care plan, after discussion with the patient and their family and carers (who should be offered a copy of the plan). This should cover:

- long-term support provided by the multidisciplinary team
- the initial frequency of respiratory function tests and monitoring of respiratory impairment
- the frequency of clinical reviews of symptomatic and physiological changes
- the provision of carers
- arrangements for device maintenance and 24-hour emergency clinical and technical support
- secretion management and respiratory physiotherapy assessment, including cough-assist therapy (if required)
- training in and support for the use of non-invasive ventilation for the patient and their family and carers
- regular opportunities to discuss the patient’s wishes in relation to continuing or withdrawing non-invasive ventilation, and other end-of-life considerations (see also recommendations 1.1.24 and 1.1.25).

2.5 **Information and support needs of patients with motor neurone disease and their families and carers**

2.5.1 **Evidence review**

A total of 616 studies were retrieved by the systematic searches. Of these, 11 studies were relevant to the review question, and hence were included. One topic-specific website was also identified (www.healthtalkonline.org) and was included as an individual study. Therefore 12 studies were included in the analysis. All relevant data and methodology from the 12 studies were extracted in evidence tables (see appendix 9.6), and the quality of the studies
was appraised using the NICE qualitative studies checklist. The included studies are summarised in table 8.

From the 12 evidence tables, further thematic analysis with ‘clustering method’ was adopted to further synthesise data across different types of qualitative research (Miles and Huberman 1994). The clustering method includes the process of coding, identifying similarities and common sequences, isolating commonalities and differences, and grouping generalisations.

The initial protocol was to use ‘Time-Ordered Meta Matrix’ (Miles and Huberman 1994) to map along the flow of the care pathway (for example, information and support needs of patients and carers at each key stage of the care pathway). However, this method was found to be not appropriate because: (i) there was a lack of data, and (ii) the evidence showed that different patients and carers have different views on when information should be given or discussed, and that this should be person-centred rather than prescriptive.

Therefore a ‘Thematic-Conceptual Meta Matrix’ (Miles and Rosenblum 1987) was adopted, and the matrix was modified to resemble the evidence profiles (that is, GRADE profiles). From the synthesis, a number of outcomes (or higher-level themes) were identified:

- **Outcome 1:** Timing, level of information and ways of communication.
- **Outcome 2:** Information needs of patients and carers.
- **Outcome 3:** Support needs (or assistance required) of patients and carers.
- **Outcome 4:** Carer-specific information needs.
- **Outcome 5:** Carer-specific support needs.
- **Outcome 6:** Decision making and end-of-life care (advance directives).
- **Outcome 7:** Knowledge and communication among healthcare professionals.
The three quality criteria in the evidence profiles are based on the NICE qualitative studies checklist, summarised as follows:

- **Study limitations:** including assessments on theoretical approach, study design, data collection and validity.
- **Indirectness:** including transferability (synonyms to ‘generalisability’ in quantitative research).
- **Other considerations:** including analysis and synthesis methods, and any other limitations that may be subjected to bias.

Overall, the evidence was of mixed quality with limitations. There were some good-quality interview studies, but some studies were subject to bias or lack of transferability (non-UK studies). As the evidence was only from patients who were still alive and able to participate in the studies, the evidence was biased towards this particular group of patients, and hence patients who had progressive MND with severe disability and who died in short period of time were under-represented.
Table 8 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study sample/characteristics</th>
<th>Key summary of outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthtalkonline (<a href="http://www.healthtalkonline.org">www.healthtalkonline.org</a>) Interview</td>
<td>Total number of patients and caregivers in study = 46 UK study</td>
<td>Information needs of patients and their carers</td>
</tr>
<tr>
<td>Silverstein et al. (1991) Structured questionnaire</td>
<td>Total number of patients in study = 38 US study</td>
<td>Preferences for specific evidence; wishes for participating in decisions.</td>
</tr>
<tr>
<td>Bolmsjö and Hermén (2003) Interview</td>
<td>Total number of families/close relatives in study = 16 Swedish study</td>
<td>Information on the disease; communication; knowledge of healthcare professionals; information on equipment and assistance.</td>
</tr>
<tr>
<td>Chio et al. (2008) Structured questionnaire</td>
<td>Total number of participants in study = 120 (60 patients; 60 carers) Italian study</td>
<td>Information on the disease, research and treatment; communication.</td>
</tr>
<tr>
<td>Hughes et al. (2005) Interview</td>
<td>Total number of participants in study = 29 (9 patients; 5 carers; 15 professionals) UK study</td>
<td>Experiences of services and suggestions for changes.</td>
</tr>
<tr>
<td>Johnston et al. (1996) Interview</td>
<td>Total number of patients in study = 50 UK study</td>
<td>Information needs; ways of communication.</td>
</tr>
<tr>
<td>McCluskey et al. (2004) Structured questionnaire</td>
<td>Total number of participants in study = 257 (144 patients; 113 carers) US study</td>
<td>Information needs; end-of-life care.</td>
</tr>
<tr>
<td>Williams et al. (2008) Interview</td>
<td>Total number of carers in study = 19 US study</td>
<td>Carer-specific Information and support needs.</td>
</tr>
<tr>
<td>Borasio et al. (2001) Structured questionnaire</td>
<td>Total number of professionals (neurologists) in study = 74 EU study</td>
<td>Communication; structure for delivering information; end-of-life care.</td>
</tr>
<tr>
<td>Moss et al. (1996) Interview</td>
<td>Total number of patients in study = 50 US study</td>
<td>End-of-life care.</td>
</tr>
<tr>
<td>Wicks and Frost (2008) Semi-structured questionnaire</td>
<td>Total number of participants in study = 334 (247 patients; 87 carers) US study</td>
<td>Information needs; preferences for information.</td>
</tr>
<tr>
<td>Cox (1992) Interview</td>
<td>Total number of participants in study = 28 (10 patients; 10 carers; 8 professionals) UK study</td>
<td>Knowledge of services; information and support needs.</td>
</tr>
</tbody>
</table>

2.5.2 Evidence statements

Key outcome: timing, level of information and ways of communication

2.5.2.1 Mixed-quality qualitative evidence showed that information should be provided to patients and carers as soon as possible through staged discussion, with a person-centred approach, and in a sensitive manner. [Evidence profile 23]
**Key outcome: information and support needs (patients and carers)**

2.5.2.2 *Mixed-quality qualitative evidence showed that patients and carers need information on the following: symptoms of MND; natural progression of the disease; aids and equipment; tests that will be carried out; health and social care services; access to services; ongoing research and new treatments; the risk of developing cognitive dysfunction and emotional lability.* [Evidence profile 24]

2.5.2.3 *Moderate-quality qualitative evidence showed that patients and carers need support in the following aspects: general domestic care, including financial support; use of different equipment; physical or mobility assistance; psychological and emotional support.* [Evidence profile 24]

**Key outcome: information and support needs (carer-specific)**

2.5.2.4 *Low-quality qualitative evidence showed that carers need information on possible psychological and cognitive symptoms of patients with MND.* [Evidence profile 25]

2.5.2.5 *Mixed-quality qualitative evidence showed that carers need support in the following aspects: the use and maintenance of equipment; respite care; carer coping strategies; counselling. They also to be able to communicate with healthcare professionals without the patient being present.* [Evidence profile 25]

**Key outcome: decision making and end-of-life care**

2.5.2.6 *Mixed-quality qualitative evidence showed that patients wanted shared decision making regarding end-of-life care, and wanted end-of-life care to be discussed and planned when appropriate.* [Evidence profile 26]

**Key outcome: knowledge and communication among healthcare professionals**

2.5.2.7 *Mixed-quality qualitative evidence showed that some healthcare professionals (those who were not specialists in MND but were involved in care provision) lacked knowledge of MND. It was also...*
felt that peer communication, including communication between primary and secondary care, should be better. [Evidence profile 27]

### Evidence profiles

#### Evidence profile 23 Timing, level of information and ways of communication

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample</th>
<th>Themes that emerged</th>
<th>Study limitations</th>
<th>Indirectness (transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x interview [HT]</td>
<td>P&amp;C = 46</td>
<td>Patients and carers have different views on 'how much' and 'when' information should be given or discussed. This should be based on the individual and be person-centred.</td>
<td>Overall comments:</td>
<td>• Good quality.  • Transferable to population addressed.</td>
<td></td>
</tr>
<tr>
<td>2 x interviews [H] [J]</td>
<td>P&amp;C = 64 Pr = 15.  Total = 79</td>
<td>Healthcare professionals should aim to give/discuss information as soon as possible.</td>
<td>Overall comments:</td>
<td>• [H] Good quality.  • [J] No report of data analysis and synthesis methods.  • Both studies were transferable to population addressed.</td>
<td></td>
</tr>
<tr>
<td>1 x structured questionnaire (self-report) [B]</td>
<td>Pr = 74</td>
<td>Emphasised 'staged discussion'.</td>
<td>Overall comments:</td>
<td>• Self-assessment bias (self-report using a pre-determined structured questionnaire).  • Transferable to population addressed.</td>
<td></td>
</tr>
<tr>
<td>2 x interviews [BH] [J]</td>
<td>P&amp;C = 66</td>
<td>Diagnosis and information should be communicated in a sensitive manner. For example, some common good points:  • Truthful, directness, honesty, kindness, empathy.  • Give opportunity for patients and carers to ask questions.</td>
<td>Overall comments:</td>
<td>• [BH] Good quality.  • [J] No report data of analysis and synthesis methods.  • Both studies were transferable to population addressed.</td>
<td></td>
</tr>
</tbody>
</table>

P&C, patients and carers; Pr, professionals

[HT] = [www.healthtalkonline.org](http://www.healthtalkonline.org) (formerly DIPEX): UK study, regular updates; patients and carers.

[H] = Hughes et al. (2005): UK study; patients, carers and professionals.

[J] = Johnston et al. (1996): UK study; patients only

[B] = Borasio et al. (2001): European study (European ALS Research Group); professionals only.

## Evidence profile 24 Information and support needs (patients and carers)

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample</th>
<th>Themes that emerged</th>
<th>Overall comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: Information needs (patients and carers)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 x interviews [HT] [H] [BH] [Co] [J] 2 x structured questionnaires [S] [C] 1 x structured questionnaire (self-report) [B]</td>
<td>P&amp;C = 304 Pr = 97 Total = 401</td>
<td>Information on causes and symptoms of MND, the natural progression of the disease and what to expect in the future, particularly the impact on mobility (arms and legs), respiratory function, speech, swallowing and communication.</td>
<td>Mixed quality: some studies were subject to self-assessment bias or lacked details of methodology. Transferability: not all were UK or European studies.</td>
</tr>
<tr>
<td>3 x interviews [HT] [BH] [W] 1 x structured questionnaire [S]</td>
<td>P&amp;C = 119</td>
<td>Information on aids and equipments (e.g. for mobility, eating, breathing, communication) and how to access them.</td>
<td>Good-quality interviews and structured questionnaire. Transferability: not all were UK or European studies.</td>
</tr>
<tr>
<td>1 x interview [HT] 1 x structured questionnaire [C] 1 x structured questionnaire (self-report) [B]</td>
<td>P&amp;C = 166 Pr = 74 Total = 240</td>
<td>Information on tests and investigations (including respiratory tests) what the tests/investigations are for, at what point they should be carried out, and explaining the results.</td>
<td>Mixed quality: two studies were of good quality ([HT], [C]), but [B] was subject to self-assessment bias or lacked details of methodology. Transferable to population addressed.</td>
</tr>
<tr>
<td>3 x interviews [HT] [W] [Co] 1 x structured questionnaire (self-report) [MC]</td>
<td>P&amp;C = 332</td>
<td>Information on health and social care services available, and how to access the services; for example, other supportive care, home help, charity organisations, hospices, specialist centres, community occupational therapy, support groups.</td>
<td>Mixed quality: some good-quality studies, but some were subject to self-assessment bias or lacked details of methodology. Transferability: not all studies were UK or European studies.</td>
</tr>
<tr>
<td>2 x interviews [HT] [H] 1 x structured questionnaire [C] 1 x structured questionnaire (self-report) [B]</td>
<td>P&amp;C = 180 Pr = 89 Total = 269</td>
<td>Information on ongoing research and new treatments.</td>
<td>Mixed quality: three studies were of good quality ([HT], [H], [C]), but [B] was subject to self-assessment bias or lacked details of methodology. Transferable to population addressed.</td>
</tr>
<tr>
<td>1 x structured questionnaire [C] 1 x structured questionnaire (self-report) [B]</td>
<td>P&amp;C = 120 Pr = 74 Total = 194</td>
<td>Information on symptomatic therapies that would improve quality of life.</td>
<td>Mixed quality: [HT] was of good quality, but [B] was subject to self-assessment bias or lacked details of methodology. Transferable to population addressed.</td>
</tr>
<tr>
<td>1 x interview [HT]</td>
<td>P&amp;C = 46</td>
<td>Information on social and financial support (benefits).</td>
<td>Good quality. Transferable to population addressed.</td>
</tr>
<tr>
<td>No. of studies and study design</td>
<td>Study sample</td>
<td>Themes that emerged</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>P&amp;C = 20 Pr = 8 Total = 28</td>
<td>Support needs and assistance required to manage daily living: care support, including domestic assistance and night-time assistance; physical and mobility assistance; use of different equipment, including ventilator support; psychological and emotional support; activities to improve ability; use of emergency call alarm; occupational therapy support; financial support.</td>
<td>Overall comments: Lack of detail of synthesis methods. Transferable to population addressed.</td>
</tr>
</tbody>
</table>

P&C, patients and carers; Pr, professionals.

[HT] = [www.healthtalkonline.org](http://www.healthtalkonline.org) (formerly DIPEX): UK study, regular updates; patients and carers.

[H] = Hughes et al. (2005): UK study; patients, carers and professionals.


[Co] = Cox (1992): UK study; patients, carers and professionals.

[J] = Johnston et al. (1996): UK study; patients only.


[C] = Chio et al. (2008): Italian study; patients and carers.

[B] = Borasio et al. (2001): European study (European ALS Research Group); professionals only.


### Evidence profile 25 Information and support needs (carer-specific)

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample</th>
<th>Themes that emerged</th>
<th>Study limitations</th>
<th>Indirectness (transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x semi-structured questionnaire (self-report) [WF]</td>
<td>C = 87</td>
<td>Information about the possibility of psychological symptoms such as cognitive dysfunction, uncontrollable laughter and crying.</td>
<td>Overall comments:</td>
<td>• Self-assessment bias (self-report using pre-determined structured questionnaire).</td>
<td>Transferability: not a UK or European study.</td>
</tr>
</tbody>
</table>

### Outcome: Information needs (carer-specific)

1 x semi-structured questionnaire (self-report) [WF]

C = 87

1 x interview [W]

C = 19

• To be able to speak to healthcare professionals alone (without the patient) about their concerns and the patient's needs.
• Information on how to use and maintain the aids and equipment.

### Outcome: Support needs (carer-specific)

1 x interview [Co]

C = 10

Pr = 8

Total = 18

Support needs and assistance required to manage daily living:
• psychological and emotional support and counselling to cope with strain, stress, frustration and isolation
• support from respite care
• education and coping strategies as a carer.

Overall comments:
• Lack of detail on synthesis methods.
• Transferable to population addressed.

C, carers; Pr, professionals.


[Co] = Cox (1992): UK study; patients, carers and professionals.
### Evidence profile 26 Decision making and end-of-life care

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample</th>
<th>Themes that emerged</th>
<th>Study limitations</th>
<th>Indirectness (transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
</table>
| 1 x structured questionnaire [S] | P = 38 | • 26 out of 37 patients wanted shared decision making  
• Patients’ preference was stable at 6 months’ follow-up. | | | Overall comments:  
• Good quality.  
• Transferability: not a UK or European study. |
| 2 x structured questionnaires (self-report) [B] [MC] | P&C = 257  
Pr = 74  
Total = 331 | • End-of-life options and ventilation should be discussed.  
• Out of 74 neurologists, 78% believed that advance directives are useful, and 55% discussed them with patients regularly.  
• Times when advance directives should be discussed:  
  – when patients ask for it  
  – when respiratory insufficiency is imminent  
  – when the first respiratory symptoms become apparent. | | | Overall comments:  
• Self-assessment bias (self-report using pre-determined structured questionnaire).  
• Transferability: one European and one US study. |
| 1 x interview [MO] | P = 50 | • 48 out of 50 patients answered questions about advance directives. The topics that were mentioned were:  
  – The option to stop ventilatory support under certain circumstances  
  – permanent unconsciousness  
  – inability to communicate  
  – would not want CPR  
  – burdensome to family  
  – no caregiver help available  
• Patients who had completed written advance directives were more likely to have verbally informed their family and healthcare professionals of their wishes and preference, compared with those who had not completed an advance directive. | | | Overall comments:  
• Lack of detail and incomplete reporting of methodology; not clear whether all analyses were reported.  
• Transferability: not a UK or European study. |

P, patients; P&C, patients and carers; Pr, professionals.
[B] = Borasio et al. (2001): European study (European ALS Research Group); professionals only.  
Evidence profile 27 Knowledge and communication among healthcare professionals

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample</th>
<th>Themes that emerged</th>
<th>Study limitations</th>
<th>Indirectness (transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 interviews [BH] [H]</td>
<td>P&amp;C = 30 Pr = 15 Total = 45</td>
<td>There is a lack of knowledge about MND among healthcare professionals (within the multidisciplinary team or supportive care staff) who are not specialists (neurologists).</td>
<td>Overall comments:</td>
<td>Both good quality.</td>
<td>Transferable to population addressed.</td>
</tr>
<tr>
<td>1 interview [H]</td>
<td>P&amp;C = 14 Pr = 15 Total = 29</td>
<td>There should be better communication and coordination among the multidisciplinary team, and between primary and secondary care.</td>
<td>Overall comments:</td>
<td>Good quality.</td>
<td>Transferable to population addressed.</td>
</tr>
<tr>
<td>1 structured questionnaire (self-report) [B]</td>
<td>Pr = 74</td>
<td>A plan for follow-up and support should be communicated to patients and carers after diagnosis.</td>
<td>Overall comments:</td>
<td>Self-assessment bias (self-report using pre-determined structured questionnaire).</td>
<td>Transferable to population addressed.</td>
</tr>
</tbody>
</table>

P&C, patients and carers; Pr, professionals

[H] = Hughes et al. (2005): UK study; patients, carers and professionals.
[B] = Borasio et al. (2001): European study (European ALS Research Group); professionals only.

2.5.3 Evidence to recommendations

The GDG agreed with the evidence overall, but stressed that the evidence needed to be utilised and adapted in order to strengthen the focus on information on respiratory function and the provision of non-invasive ventilation, rather than general information and support, for patients with MND and their families and carers.

The GDG agreed that communication among healthcare professionals is important to ensure that key decisions reached with patients and their families and carers are shared consistently among the healthcare professionals. The GDG also agreed with the concept of ‘staged discussions’ suggested by the evidence for sensitive discussions about the possible use of non-invasive ventilation, and suggested four key stages: soon after diagnosis of MND; when monitoring respiratory function; when respiratory function deteriorates; and if the patient asks for information. The GDG also agreed that
recommendations on the information and support needs of patients and their families and carers (or carers specifically) should be based on the evidence, with a specific focus on respiratory function and the use of non-invasive ventilation (evidence profiles 24 and 25).

The GDG acknowledged that there is a lack of evidence on providing information on non-invasive ventilation in relation to end-of-life care for patients with MND. The GDG discussed and came to the consensus that the principle of 'staged discussions' should also be adopted to offer sensitive discussions about end-of-life care to patients and their families and carers. The GDG also came to a consensus regarding the four key stages for the end-of-life staged discussions: around the time that MND is first diagnosed (but only if requested by the patient explicitly, or if the patient’s clinical condition indicates that ventilator support will be needed in the immediate future); when non-invasive ventilation is accepted or declined; when there is increasing dependence on ventilation; and if the patient asks for information. The GDG further discussed the key elements of discussions about end-of-life care, and came to the consensus that these should include: overall planning of end-of-life care; considering advance decisions to refuse treatment; what to do if non-invasive ventilation fails; strategies to withdraw ventilation if the patient wishes; and the involvement of families and carers in decision making (with the patient’s consent if they have the capacity to give it).

### 2.5.4 Recommendations

<table>
<thead>
<tr>
<th>Recommendation 1.1.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer to discuss the possible use of non-invasive ventilation with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times:</td>
</tr>
<tr>
<td>- soon after MND is first diagnosed</td>
</tr>
<tr>
<td>- when monitoring respiratory impairment</td>
</tr>
<tr>
<td>- when respiratory function deteriorates</td>
</tr>
<tr>
<td>- if the patient asks for information.</td>
</tr>
</tbody>
</table>
**Recommendation 1.1.3**
Discussions should be appropriate to the stage of the patient’s illness, carried out in a sensitive manner and include information on:

- the possible symptoms and signs of respiratory impairment (see table 1 in recommendation 1.1.7)
- the natural progression of MND and what to expect in the future
- the purpose, nature and timing of respiratory function tests, and explanations of the test results
- available interventions for managing respiratory impairment, including the benefits and limitations of each intervention
- accessing and using respiratory equipment, including that for non-invasive ventilation
- how non-invasive ventilation (as a treatment option) can improve symptoms associated with respiratory impairment and can be life prolonging, but does not stop progression of the underlying disease
- how non-invasive ventilation can be withdrawn
- palliative strategies as an alternative to non-invasive ventilation.

**Recommendation 1.1.4**
Inform all relevant healthcare professionals about key decisions reached with the patient and their family and carers.
Recommendation 1.1.5
Provide the patient and their family and carers with support and assistance to manage non-invasive ventilation. This should include:

- training on using non-invasive ventilation and ventilator interfaces, for example:
  - emergency procedures
  - night-time assistance if the patient is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)
  - how to use the equipment with a wheelchair or other mobility aids if required
  - what to do if the equipment fails
- assistance with secretion management
- information on general palliative strategies
- an offer of ongoing emotional and psychological support\(^{11}\) for the patient and their family and carers.

Recommendation 1.1.6
Ensure that families and carers:

- have an initial assessment if the patient they care for decides to use non-invasive ventilation, which should include:
  - their ability and willingness to assist in providing non-invasive ventilation
  - their training needs
- have the opportunity to discuss any concerns they may have with members of the multidisciplinary team and/or other healthcare professionals.

Recommendation 1.1.24
Offer to discuss end-of-life care with the patient and (if the patient agrees) their family and carers, at an appropriate time and in a sensitive manner. This may be at one or more of the following times:

- around the time that MND is first diagnosed (but only if requested by the patient explicitly, or if the patient’s clinical condition indicates that ventilator support will be needed in the immediate future)
- when non-invasive ventilation is accepted or declined
- when the patient is becoming increasingly dependent on non-invasive ventilation
- if the patient asks for information.

Recommendation 1.1.25
Discussions about end-of-life care should include:

- planning of end-of-life care
- considering advance decisions to refuse treatment
- considering what to do if non-invasive ventilation fails because of either:
  - an acute, but potentially reversible, deterioration in health or
  - irreversible disease progression
- strategies to withdraw non-invasive ventilation if the patient wishes
- the involvement of family and carers in decision making (with the patient’s consent if they have the capacity to give it).

3 Research recommendations

We have made the following recommendations for research, based on our review of evidence, to improve NICE guidance and patient care in the future.

3.1 Cost effectiveness of non-invasive ventilation for patients with MND

Is non-invasive ventilation or standard care more cost effective for improving survival and quality of life for patients with MND?

NICE clinical guideline 105 – Non-invasive ventilation for motor neurone disease 95
Why this is important
More than half of patients with MND have respiratory symptoms and need some form of respiratory management. There is evidence to suggest that non-invasive ventilation improves the quality of life of patients with MND. However, there is a lack of evidence relating to the costs associated with non-invasive ventilation. Despite this lack of robust evidence with regard to cost analyses, the use of non-invasive ventilation by patients with MND is perceived to be cost effective compared with standard care. A prospective study enrolling only patients with MND receiving non-invasive ventilation is required to assess the costs associated with this intervention. The primary outcome measures should be: (i) a thorough cost record at each visit or assessment; and (ii) the duration of overall survival. Secondary outcome measures should include any adverse events and related costs.

3.2 Withdrawing non-invasive ventilation at the end of life
What is the most effective and acceptable method of treatment withdrawal for patients with MND who wish to stop using non-invasive ventilation as their disease progresses, and how should this be facilitated and managed?

Why this is important
As more patients receive non-invasive ventilation, there will be a corresponding increase in the numbers of patients who wish to withdraw from this treatment when they become more disabled and dependent. This is a very difficult decision for patients and their families and carers, and can also cause distress, conflict and difficulty for members of professional teams. A mixed-design longitudinal qualitative and quantitative study is an appropriate research design to address this question. Such a study should enrol patients with MND who are receiving non-invasive ventilation (and who have the cognitive ability to participate in interviews and complete structured questionnaires), their families and carers, and healthcare professionals. The outcome measures should be: (i) the experiences of patients, their family and carers and healthcare professionals on how withdrawal was managed (through case notes reviews and interviews); and (ii) assessment of quality of
life, locus of control and mood (through structured questionnaires and analysed by structural equation modelling).

3.3 Communication with patients, families and carers

What communication should take place when discussing the use of non-invasive ventilation – in particular, what information do patients and their families and carers want to be included in these discussions?

Why this is important

As guidelines on non-invasive ventilation are implemented across services, there will be an increased need to discuss with patients and their families and carers the positive and negative aspects of non-invasive ventilation in the management of MND. There is very little evidence about what occurs in these discussions or about what patients, family members and carers want to be included. This research would enable clearer ideas to be developed about the best methods of communication. A mixed-design longitudinal qualitative and quantitative study is an appropriate research design to address this question. Such a study should enrol patients with MND who are about to start or who are already receiving non-invasive ventilation (and who have the cognitive ability to participate in interviews and complete structured questionnaires), and their families and carers. The outcome measures should be: (i) experiences of the discussions; (ii) how decisions are reached; (iii) what patients and their families and carers want to discuss; and (iv) patient and carer views on how to undertake these discussions.

3.4 Non-invasive ventilation for patients with MND with severe bulbar impairment

What is the impact of non-invasive ventilation on quality of life and survival in patients with MND with severe bulbar impairment?

Why this is important

One randomised controlled trial (RCT) suggests that non-invasive ventilation does not improve survival in patients with MND with severe bulbar impairment, but can improve some aspects of their quality of life. This is low-grade evidence based on subgroup analysis of a secondary endpoint. Further
research is a priority, as the current practice of treating patients with bulbar impairment may not be based on secure evidence. An RCT with a long follow-up period should enrol patients with MND with severe bulbar impairment who have respiratory impairment. The patients should be randomised to one of two arms: severe bulbar receiving non-invasive ventilation, and severe bulbar without non-invasive ventilation. Outcome measures should include survival, quality of life, respiratory function, cognitive function and other sleep-related symptoms.

3.5 Training and education needs

What are the training and education needs and the requirements for ongoing support of carers and healthcare professionals in managing the care of patients with MND who are using non-invasive ventilation?

Why this is important

Many patients with MND become dependent on a family member to manage their care and equipment. Patients entering another care setting (for example, respite care or in an emergency) feel very vulnerable, particularly because staff may not be familiar with MND or non-invasive ventilation. A mixed-design longitudinal qualitative and quantitative study should enrol family members and carers, healthcare professionals and social care professionals who are involved in delivering treatment and care to patients with MND (for example, in care homes and respite care, as well as home carers). Outcome measures should be: (i) current level of knowledge of MND; (ii) training received and current skills in providing non-invasive ventilation; and (iii) the types of training, education and support that participants think they need in order to deliver non-invasive ventilation.

4 Other versions of this guideline

This is the full guideline. It contains details of the methods and evidence used to develop the guideline. It is available from our website (www.nice.org.uk/guidance/CG105/Guidance).
Quick reference guide
A quick reference guide for healthcare professionals is available from
www.nice.org.uk/guidance/CG105/QuickRefGuide

For printed copies, phone NICE publications on 0845 003 7783 or email
publications@nice.org.uk (quote reference number N2228).

‘Understanding NICE guidance’
A summary for patients and carers (‘Understanding NICE guidance’) is
available from www.nice.org.uk/guidance/CG105/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email
publications@nice.org.uk (quote reference number N2229).

We encourage NHS and voluntary sector organisations to use text from this
booklet in their own information about motor neurone disease.

5 Related NICE guidance

Published
• Dementia. NICE clinical guideline 42 (2006). Available from
  www.nice.org.uk/guidance/CG42
• Improving supportive and palliative care for adults with cancer. NICE

6 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into
account important new information. New evidence is checked 3 years after
publication, and healthcare professionals and patients are asked for their
views; we use this information to decide whether all or part of a guideline
needs updating. If important new evidence is published at other times, we
may decide to do a more rapid update of some recommendations.
7 References, glossary and abbreviations

7.1 References


Ara R, Brazier J. (2008) Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). Value in Health 11: 1131–43


NICE clinical guideline 105 – Non-invasive ventilation for motor neurone disease 102


Kleopa KA, Sherman M, Neal B et al. (1999) Bipap improves survival and rate of pulmonary function decline in patients with ALS. Journal of the Neurological Sciences 164: 82–8


Pinto AC, Evangelista T, Carvalho M et al. (1995) Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. Journal of the Neurological Sciences 129 (Suppl.): 19–26


7.2 Glossary

Absolute risk reduction
The difference in the risk of an event occurring between two groups (one subtracted from the other) in a comparative study.

Absolute risk
Measures the probability of an event or outcome occurring (for example, an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the absolute risk reduction.
Apnoea
Temporary cessation of breathing lasting 10 seconds or longer.

Arterial blood gas
A blood test that is performed using blood taken from an artery.

Atrophy
The partial or complete wasting away of a part of the body.

Autoimmune disease
A type of disease that arises from an overactive immune response of the body against substances and tissues normally present in the body.

Baseline
An initial set of measurements (after a run-in period where applicable), with which subsequent values are compared.

Bias
Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way in which the study is designed or conducted.

Blinding (masking)
The practice of keeping the investigators and/or subjects of a study ignorant of the group to which a subject has been assigned. The purpose of blinding or masking is to protect against bias.

Body mass index (BMI)
A statistical measure that compares a person's weight and height (body weight in kilograms (kg) divided by square of height in metres (m²)).

Brainstem
The lower part of the brain, which adjoins and is structurally continuous with the spinal cord.

Bulbar muscles
Muscles in the head and neck that control speech, chewing and swallowing.
Bulbar symptoms
Symptoms involving the impairment of speech and swallowing.

Case–control study
A comparative observational study in which the investigator selects people who have experienced an event (for example, have developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Cognitive impairment (cognitive problems)
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.

Cohort study
A retrospective or prospective follow-up study. Groups of people to be followed up are defined on the basis of the presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

Competency
The ability to perform a specific task, action or function successfully.

Confidence interval (CI)
A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.
Consensus methods
Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.

Consistency
The extent to which the conclusions of a collection of studies used to support a guideline recommendation are in agreement with each other.

Control group
A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment), in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Cost-effectiveness analysis (CEA)
A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in 'health-related units', for example, the cost of preventing one additional heart attack.

Cough-assist therapy
A non-invasive therapy that safely and consistently removes secretions in patients with an ineffective ability to cough.

Critical appraisal
The process of appraising a piece of research or a systematic review for the quality of its methods and content, generally used in order to make judgements about the quality of the research or review, and the effectiveness of the intervention under study.
Cross-sectional study
The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.)

Declaration of interest
A process by which members of a working group or committee 'declare' any personal or professional involvement with a company that might affect their objectivity (for example, if their position or department is funded by a pharmaceutical company).

Dementia
A group of symptoms that is characterised by a decline in a person’s intellectual functioning (such as thinking or memory) that is severe enough to interfere with their ability to perform routine activities.

Diagnostic study
A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.

Double-blind/masked study
A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.

Dysarthria
A motor speech disorder resulting from neurological injury, characterised by poor articulation.

Dysphagia
Difficulty swallowing.

Dyspnoea
Difficulty breathing.
Economic evaluation
A comparison of alternative courses of action in terms of both their costs and consequences. In health economic evaluations the consequences should include health outcomes.

Effect (as in effect measure, treatment effect, estimate of effect, effect size)
The observed association between interventions and outcomes, or a statistic to summarise the strength of the observed association.

Emotional lability
The pathological expression of laughter, crying or smiling.

Equity
The fair distribution of resources or benefits.

Evidence-based clinical practice
Evidence-based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence-based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.

Evidence statement
A brief summary of one finding from a review of evidence that a clinical guideline is based on.

Evidence table
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Exclusion criteria (clinical study)
Criteria that define who is not eligible to participate in a clinical study.
Exclusion criteria (literature review)
Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence.

Extensor plantar response
An important neurological examination based upon what the toes do when the sole (plantar surface) of the foot is stroked. Also known as the Babinski response

External validity
The degree to which the results of a study hold true in non-study situations, such as routine clinical practice. May also be referred to as the generalisability of study results to non-study patients or populations.

Fasciculation
A small, local, involuntary muscle contraction (twitching) visible under the skin arising from the spontaneous discharge of a bundle of skeletal muscle fibres.

Fatigue
Medical aspects of tiredness in humans.

Follow up
Observation over a period of time of a person, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.

Forced expiratory volume in 1 second (FEV₁)
The maximum volume of air that can forcibly blown out in the first 1 second during the forced vital capacity manoeuvre; measured in litres.

Gag reflex
A reflex contraction of the back of the throat that is evoked by touching the soft palate.
Generalisability
The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

GRADE (Grading of recommendations assessment, development and evaluation)
A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.

Guideline Development Group
The group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines technical team who developed the recommendations for the clinical guideline. The group wrote the draft guidance, and then revised it after a consultation with organisations registered as stakeholders.

Hallucinations
Perception in the absence of a stimulus.

Heterogeneity
A term used to illustrate the variability or differences between studies in the estimates of effects.

Hyperactive reflexes
Reflexes that persist for too long and may be too strong.

Hypercapnia
A condition in which the level of carbon dioxide (CO2) in the blood is too high.

Hypersomnolence
Excessive sleepiness.

Hyporeflexia
The condition of below normal or absent reflexes.

Hypoventilation
Occurs when ventilation is inadequate to perform necessary gas exchange.
Hypoxaemia
Decreased partial pressure of oxygen in the blood.

Hypoxia
A pathological condition in which the body as a whole, or a region of the body, is deprived of adequate oxygen supply.

Incidence
A measure of the number of new cases of a disease, divided by the total population at risk of getting the disease, during a certain time period.

Inclusion criteria (literature review)
Explicit criteria used to decide which studies should be considered as potential sources of evidence.

Incremental cost-effectiveness analysis
The analysis of additional costs and additional clinical outcomes that are associated with different interventions.

Incremental cost-effectiveness ratio (ICER)
The difference in the mean costs in the population of interest divided by the difference in the mean outcomes in the population of interest when comparing two interventions.

Index
In epidemiology and related sciences, this usually means a rating scale, for example a set of numbers derived from a series of observations of specified variables. Examples include the various health status indices, and scoring systems for severity or stage of cancer.

Index test
The test being evaluated in a study to compare it with the best available test (the reference standard).

Inspiration
The movement of air into the lungs.
**Interface**
The means by a patient’s airway is connected to a ventilator or to a machine used to carry out respiratory function tests. Examples include face masks, mouthpieces, nasal masks, and nasal pillows or plugs.

**Life years gained**
Average years of life gained per person as a result of the intervention.

**Literature review**
A process of collecting, reading and assessing the quality of published (and unpublished) articles on a given topic.

**Locus of control**
A term in psychology that refers to the extent to which a person believes that they can control events that affect them.

**Longitudinal study**
A study of the same group of people at more than one point in time. (This type of study contrasts with a cross-sectional study, which observes a defined set of people at a single point in time.)

**Maximal expiratory pressure** (MEP, 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** (MIP, Plmax)
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.

**Mortality rate**
The proportion of deaths in a defined population.

**Motor cortex**
A term that describes the regions of the cerebral cortex that are involved in the planning, control and execution of voluntary motor functions.
Multivariate model
A statistical model for analysis of the relationship between two or more predictor (independent) variables and the outcome (dependent) variable.

Negative predictive value
The proportion of people with negative test results who do not have the disease.

Neurotoxicity
Occurs when the exposure to natural or artificial toxic substances, which are called neurotoxins, alters the normal activity of the nervous system in such a way as to cause damage to nervous tissue.

Nocturia
The need to urinate in the middle of the night, thus interrupting sleep.

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.

Normocapnia
The state of having a normal arterial carbon dioxide pressure.

Observational study
A retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; examples include cohort studies and case–control studies.

Orthopnoea
Shortness of breath (dyspnoea) that occurs when the person is lying flat.

Oxygen saturation
A clinical measure of the amount of oxygen in a person's blood.
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.

Paralysis
The complete loss of muscle function for one or more muscle groups.

Partial pressure of carbon dioxide (PaCO₂)
A measure of how much carbon dioxide is dissolved in the blood and how well carbon dioxide is able to move out of the body.

Partial pressure of oxygen (PaO₂)
A measure of how much oxygen is dissolved in the blood and how well oxygen is able to move from the airspace of the lungs into the blood.

Placebo
An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.

Positive predictive value
The proportion of people with a positive test result who actually have the disease.

Prevalence
The proportion of people in a population with a particular characteristic. For example, smoking prevalence is the proportion of smokers in the population. Prevalence may be expressed by age, sex, socio-economic group, ethnic group, etc. See also Incidence.

Prospective study
A study in which people are entered into the research and then followed up over a period of time, with future events recorded as they happen. This contrasts with studies that are retrospective.
**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.

**Qualitative research**
Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.

**Quality-adjusted life year (QALY)**
A statistical measure, representing 1 year of life with full quality of life.

**Randomisation**
Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure that there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.

**Randomised controlled trial (RCT)**
A study to test the effectiveness of a treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The groups are followed up to compare differences in outcomes.

**Reference standard**
An agreed standard, for example for a test or treatment, against which other interventions can be compared.

**Relative risk (RR)**
The ratio of risk in the intervention group to risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total number of people in the group. A relative risk of 1 indicates no difference between comparison groups. For undesirable outcomes, a relative risk that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome. Also known as risk ratio.
Retrospective study
A type of study that deals with the present and/or past and does not involve studying future events. This contrasts with prospective studies.

Sample
A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.

Sampling
Refers to the way in which participants are selected for inclusion in a study.

Sensitivity
In diagnostic testing, this refers to the chance of having a positive test result if you have the disease. Sensitivity of 100% means that all people with the disease will test positive. However, a person could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all people who have a negative test result do not have the disease. To fully judge the accuracy of a test, its specificity must also be considered.

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 exploration of the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. Different types of sensitivity analysis are:

- 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): two or more parameters are varied at the same time and the overall effect on the results is evaluated.

• Threshold sensitivity analysis: the critical values 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).

Sleep study
A multi-parametric test used in the study of sleep and as a diagnostic tool in sleep medicine. Also known as polysomnography (PSG).

Sniff nasal inspiratory pressure (SNIP)
One of the newer measures of inspiratory muscle strength. Peak nasal pressure is measured in one nostril during a maximal sniff performed through the other nostril.

Spasticity
A disorder of the central nervous system in which certain muscles continually receive a message to tighten and contract.

Specificity
In diagnostic testing, this refers to the chance of having a negative test result given that you do not have the disease. Specificity of 100% means that all people without the disease will test negative. However, a person could have a negative test result yet still have the disease – this is called a ‘false negative’. The specificity of a test is also related to its ‘positive predictive value’ (true positives) – a test with a specificity of 100% means that all people who have a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.

Spirometry
The most common of the pulmonary function tests used to measure lung function.
Standard deviation (SD)
A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.

Statistical power
The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a P value of less than 5% (0.05) in a statistical test (that is, a statistically significant treatment effect) if there really was an important difference (for example, 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power.

Systematic review
A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a meta-analysis.

Tracheostomy
A surgical procedure on the neck to open a direct airway through an incision in the trachea.

Utility
A measure of the strength of a person’s preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or ‘perfect’ health). Health states can be considered worse than death and thus have a negative utility value.

Validity
Assessment of how well a tool or instrument measures what it is intended to measure. See also External validity.
Variable
A measurement that can vary within a study (for example, the age of participants). Variability is present when differences can be seen between different people or within the same person over time, with respect to any characteristic or feature which can be assessed or measured.

Ventilator
Any machine designed to mechanically move breathable air into and out of a person’s lungs, to provide the mechanism of breathing for a patient who is physically unable to breathe, or is breathing insufficiently.

Vital capacity
The maximum amount of air that a person can expel from their lungs after a maximum inspiration.
### 7.3 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AARS</td>
<td>Appel ALS Rating Scale</td>
</tr>
<tr>
<td>ALS</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>ALS-FRS</td>
<td>ALS-Functional Rating Scale</td>
</tr>
<tr>
<td>ARI</td>
<td>Absolute risk increase</td>
</tr>
<tr>
<td>ARR</td>
<td>Absolute risk reduction</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the curve</td>
</tr>
<tr>
<td>BiPAP</td>
<td>Bilevel positive airway pressure ventilator</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CMS Pdi</td>
<td>Cervical magnetic phrenic nerve stimulation</td>
</tr>
<tr>
<td>Cough Pgas</td>
<td>Cough gastric pressure</td>
</tr>
<tr>
<td>ELBG</td>
<td>Earlobe blood gas</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<tr>
<td>MEP</td>
<td>Maximal expiratory pressure</td>
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<tr>
<td>MIP</td>
<td>Maximal inspiratory pressure</td>
</tr>
<tr>
<td>MND</td>
<td>Motor neurone disease</td>
</tr>
<tr>
<td>MNDAA</td>
<td>Motor Neurone Disease Association</td>
</tr>
<tr>
<td>MOP</td>
<td>Mouth occlusion pressure</td>
</tr>
<tr>
<td>NIV</td>
<td>Non-invasive ventilation</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OIS</td>
<td>Optimal information size</td>
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<tr>
<td>PaCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PCO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>Pdi-sniff</td>
<td>Maximal sniff transdiaphragmatic pressure</td>
</tr>
<tr>
<td>PEmax</td>
<td>Maximal expiratory pressure</td>
</tr>
<tr>
<td>PI&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximal inspiratory pressure</td>
</tr>
<tr>
<td>PNamp</td>
<td>Phrenic nerve motor response amplitude</td>
</tr>
<tr>
<td>PO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>RS</td>
<td>Reference standard</td>
</tr>
<tr>
<td>SaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Arterial oxygen saturation</td>
</tr>
<tr>
<td>SAQLI</td>
<td>Sleep apnoea quality-of-life index</td>
</tr>
<tr>
<td>SC</td>
<td>Standard care</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form-36</td>
</tr>
<tr>
<td>SFVC</td>
<td>Supine forced vital capacity</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sniff Pdi</td>
<td>Maximal sniff transdiaphragmatic pressure</td>
</tr>
<tr>
<td>Sniff Poes</td>
<td>Maximal sniff oesophageal pressure</td>
</tr>
<tr>
<td>SNIP</td>
<td>Sniff nasal inspiratory pressure</td>
</tr>
<tr>
<td>SNP</td>
<td>Maximal sniff nasal pressure</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Oxygen saturation measured by pulse oximetry</td>
</tr>
<tr>
<td>TV</td>
<td>Tracheostomy ventilation</td>
</tr>
<tr>
<td>UFVC</td>
<td>Upright forced vital capacity</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
</tbody>
</table>

8 Contributors

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