Motor neurone disease: the use of non-invasive ventilation in the management of motor neurone disease

Full guideline

Draft for consultation, February 2010

This guideline was developed following the NICE short clinical guideline process. This document includes all the recommendations, details of how they were developed and summaries of the evidence they were based on.
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## Disclaimer

NICE clinical guidelines are recommendations about the treatment and care of people with specific diseases and conditions in the NHS in England and Wales.

This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are...
expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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. The clinical approach to using non-invasive ventilation for managing respiratory
impairment in patients with a diagnosis of MND is summarised in a care pathway (see section 1.2).

**Patient-centred care**

This guideline offers best practice advice on 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 guidelines – ‘Reference guide to consent for examination or treatment’ (2001) (available from www.dh.gov.uk). Healthcare professionals should also follow the code of practice that accompanies the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

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 patients with MND, including regular respiratory assessment and provision of non-invasive ventilation. The members of the multidisciplinary team who provide non-invasive ventilation should have the appropriate competencies. The team should:

- include a neurologist, a respiratory physician, an MND specialist nurse, a respiratory specialist nurse, a physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist, and have access to other healthcare professionals as needed
- be led by a healthcare professional with a specific interest in MND, who should ensure that the patient’s multidisciplinary care plan (see recommendation 1.1.19) is coordinated and communicated to relevant healthcare and social care professionals, including the patient’s primary care team.
Information and support needs of patients with MND and their families and carers

1.1.2 Ensure that all relevant healthcare professionals are informed about the key decisions reached with the patient and their family and carers.

1.1.3 Offer to discuss the possible use of non-invasive ventilation with the patient and their family and carers (if the patient agrees), 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 of respiratory impairment is started (see recommendation 1.1.9)
- when respiratory function deteriorates
- if the patient asks for information.

1.1.4 Provide the patient and their family and carers with information during discussions that is appropriate to the stage of the patient’s illness. This should be provided in a sensitive manner and include information on:

- the possible symptoms and signs of respiratory impairment (see table 1 in recommendation 1.1.7), including the natural progression of MND and what to expect in the future
- the purpose and nature of respiratory function tests, why the patient may be referred for the tests, when the tests will take place and explanations of the test results
- the interventions that are available for managing respiratory impairment, including the benefits and limitations of each intervention
- the use of, and how to access, respiratory equipment, including that for non-invasive ventilation
- alternative palliative strategies.
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 interfaces, such as:
  - emergency procedures
  - night-time assistance if the patient is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)
  - what to do if the equipment fails
- information on general palliative strategies
- assistance with secretion management
- an offer of ongoing emotional and psychological support\(^1\) for the patient and their family and carers.

1.1.6 Ensure that families and carers:

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

The identification and assessment of respiratory impairment in patients with MND

Symptoms and signs

1.1.7 Ensure that the symptoms and signs listed in table 1 are routinely monitored to detect potential respiratory impairment. Perform

respiratory function tests (see recommendations 1.1.8 and 1.1.13)
if any of these clinical symptoms and signs are present.

Table 1 Symptoms and signs of potential respiratory impairment

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

Respiratory function tests

Patients without severe bulbar impairment and without severe cognitive problems

1.1.8 At initial diagnosis of probable MND, a healthcare professional from the multidisciplinary team with the appropriate competencies should perform respiratory function tests to establish baseline respiratory function (or arrange for these to be performed). These tests should comprise:

- oxygen saturation measured by pulse oximetry (SpO₂)² – this should be a single measurement of SpO₂ with the patient at rest and breathing room air
- forced vital capacity (FVC)³

² If it is not possible to perform pulse oximetry and/or arterial blood gas analysis locally, refer the patient to a specialist respiratory service.
• sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP).

1.1.9 A healthcare professional with the appropriate competencies should perform respiratory function tests (see recommendation 1.1.8) every 3 months to assess and monitor respiratory impairment (although tests could be performed more or less often depending on the rate of disease progression and the patient’s preference and circumstances).

1.1.10 If one or more of the results listed in table 2 is obtained when respiratory assessments are performed, discuss with the patient the impact of respiratory impairment, treatment options and possible referral to a specialist respiratory service for further assessment.

Table 2 Results of respiratory assessments

<table>
<thead>
<tr>
<th>Forced vital capacity (FVC)</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>
</thead>
<tbody>
<tr>
<td>• FVC less than 50% of predicted</td>
<td>• SNIP or MIP less than 40 cmH₂O</td>
</tr>
<tr>
<td>• FVC less than 80% of predicted 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>• If repeated regular tests show a decrease in SNIP or MIP of more than 10 cmH₂O within 3 months</td>
<td></td>
</tr>
</tbody>
</table>

3 The GDG agreed that the difference between the measurement of vital capacity and forced vital capacity is very subtle and that, based on current practice, the guideline should refer to the test as (forced) vital capacity (FVC).
1.1.11 If the patient’s SpO₂ (measured at rest and breathing room air) is less than or equal to 94%, perform arterial blood gas analysis.

1.1.12 If arterial blood gas analysis shows that 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 their family and carers (if the patient agrees).

Patients with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment

1.1.13 If the patient cannot undergo all of the recommended respiratory function tests (see recommendation 1.1.8) because of severe bulbar symptoms and signs or cognitive problems, ensure that SpO₂ is measured (at rest and breathing room air).

1.1.14 If the patient’s SpO₂ is less than or equal to 94%, perform arterial blood gas analysis.

1.1.15 If the patient’s 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 their family and carers (if the patient agrees).

1.1.16 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:

- 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 their family and carers (if the patient agrees).
Patients with a diagnosis of dementia

1.1.17 When making decisions on routine respiratory function tests for patients with MND and a diagnosis of dementia, base these on considerations specific to the patient’s needs and circumstances, such as:

- their ability to give consent
- their understanding of the respiratory function tests
- their tolerance of, and willingness to undertake, the respiratory function tests
- 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

1.1.18 Consider a trial of non-invasive ventilation based on the patient’s symptoms and signs and the results of the respiratory function tests (see recommendations 1.1.8 to 1.1.16):

- For patients without severe bulbar impairment and without severe cognitive problems, offer a trial of non-invasive ventilation after an informed discussion with the patient and their family and carers (if the patient agrees) of both the benefits and limitations of the intervention.
- For patients with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment, consider a trial of non-invasive ventilation if the patient may benefit from an improvement in sleep-related symptoms or correction of hypoventilation, after an informed discussion.

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*From ‘Dementia’ (NICE clinical guideline 42; available from [www.nice.org.uk(CG42)]): Health and social care professionals should always seek valid consent from people with dementia. This should entail informing the person of options, and checking that he or she understands, that there is no coercion and that he or she continues to consent over time. If the person lacks the capacity to make a decision, the provisions of the Mental Capacity Act 2005 must be followed.*
discussion with the patient and their family and carers (with the
patient’s consent if they have the capacity to give it) of both the
benefits and limitations of the intervention.

1.1.19 Before starting non-invasive ventilation, the multidisciplinary team
should carry out and coordinate a patient-centred risk assessment
and prepare a comprehensive care plan.

- the risk assessment should consider:
  - which type of non-invasive ventilator and interfaces are
    appropriate for the patient, based on their needs and lifestyle
    factors
  - the patient’s tolerance of the treatment
  - the risk of ventilator failure
  - the power supply required, including battery back-up
  - how easily the patient can get to hospital
  - whether a humidifier is required
  - secretion management, including cough-assisted therapy (if
    required)
  - availability of carers.

- The comprehensive care plan should identify:
  - long-term support provided by the multidisciplinary team (see
    recommendation 1.1.1)
  - the initial frequency of respiratory function tests and
    monitoring of respiratory impairment
  - the frequency of clinical reviews of symptomatic and
    physiological changes
  - arrangements for the maintenance of devices and for 24-hour
    emergency clinical and technical support
  - training in and support for the use of non-invasive ventilation.
1.1.20 Trial non-invasive ventilation at night initially, before and during sleep. Gradually build up the patient’s hours of use as necessary, including daytime use if this is required for symptomatic relief.

1.1.21 Only continue non-invasive ventilation if clinical reviews show:

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

Patients with a diagnosis of dementia

1.1.22 The neurologist from the multidisciplinary team should carry out an assessment before a decision is made on the use of non-invasive ventilation. The assessment should include:

- the patient’s capacity to make decisions and to give consent\(^5\)
- 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 carer (with the patient’s consent if they have the capacity to give it).

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\(^5\) From ‘Dementia’ (NICE clinical guideline 42; available from www.nice.org.uk/CG42): Health and social care professionals should always seek valid consent from people with dementia. This should entail informing the person of options, and checking that he or she understands, that there is no coercion and that he or she continues to consent over time. If the person lacks the capacity to make a decision, the provisions of the Mental Capacity Act 2005 must be followed.
Planning end-of-life care

1.1.23 Offer to discuss end-of-life care with the patient and their family and carers (if the patient agrees), 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 non-invasive ventilation is accepted or declined
- when the patient is becoming increasingly dependent on the non-invasive ventilation
- if the patient asks for information.

1.1.24 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 pathway

**Diagnosed Probable MND Patients**

Ensure that the symptoms and signs (table 1) are routinely monitored to detect respiratory impairment. Perform respiratory function tests if any of the symptoms and signs are present.

A competent healthcare professional from the MDT should arrange or perform respiratory function tests to establish baseline respiratory function. Perform the respiratory function tests every 3 months to assess and monitor respiratory impairment (tests could be more or less often depending on the patient’s preferences, circumstances and disease progression).

Discuss with the patient the impact of respiratory impairment, treatment options and possible referral to a specialist respiratory service for further assessment.

#### Patients with MND without severe bulbar impairment or without severe cognitive problems:

Respiratory function tests should include:
- oxygen saturation measured by pulse oximetry (SpO2) – this should be a single measurement with the patient at rest and breathing room air.
- forced vital capacity (FVC)
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)

And one of both of the following:
- forced vital capacity (FVC)
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP)

#### Patients with MND without severe bulbar impairment or without severe cognitive problems:

1. forced vital capacity (FVC) is:
   - less than 50% of predicted
   - less than 40% of predicted plus any symptoms and signs of respiratory impairment, particularly orthopnoea
   - less than 65 cmH2O for men or 55 cmH2O for women, plus any symptoms and signs of respiratory impairment, particularly orthopnoea
   - if repeated regular tests show a decline of more than 10 cmH2O within 3 months.
2. the patient’s SpO2 is less than or equal to 94% at rest and breathing room air.
3. if the person’s PaCO2 (measured at rest and breathing room air) is less than 40 cmH2O
4. the patient’s PaCO2 is greater than 6 kPa, but have symptoms of signs of respiratory impairment

For (1) and (2) above, discuss with the patient the impact of respiratory impairment, treatment options and possible referral to a specialist respiratory service for further assessment.

For (3) above, refer the patient urgently to a specialist respiratory service (to be seen within 1 week).

For (4) above, consider a trial of non-invasive ventilation based on symptoms, signs and the results of respiratory function tests, after an informed discussion with the patient and their family and carers (if the patient agrees).

Offer a trial non-invasive ventilation after a discussion with the patient of both the benefits and limitations of intervention.

Trial non-invasive ventilation at night initially, when the patient is sleeping. Gradually build up the hours of use as necessary, including daytime use if required for symptomatic relief.

For people with MND and a diagnosis of dementia:

- When making decisions on routine respiratory assessments for patients with MND and a diagnosis of dementia, base these on considerations specific to the patient’s needs and circumstances, such as:
  - their ability to give consent
  - their understanding of the respiratory assessments and respiratory function tests
  - their tolerance of, and willingness to undertake, the respiratory function tests
  - the impact on their family and carers
  - their capability to receive non-invasive ventilation

People with MND and a diagnosis of dementia:

- The neuropsychiatric from the multidisciplinary team should carry out an assessment before a decision is made on the use of non-invasive ventilation. The assessment should include:
  - the patient’s ability to give consent
  - the severity of dementia and cognitive problems
  - whether the patient is likely to accept treatment
  - the patient’s capacity to make decisions
  - 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 carer (with patient’s consent if capable)

### Planning end-of-life care

- Offer sensitive discussions about end-of-life care to patient and their family and carers (if the patient agrees) at an appropriate time. This may be one or more of the following: when MND is first diagnosed; when NIV is accepted or declined; when the patient is becoming increasingly dependent on the ventilator; if the patient asks for information.
- Discussions about end-of-life care should include: planning of end-of-life care; considering advance decisions to refuse treatment; considering what to do when NIV fails; strategies to withdraw NIV if the patient wishes; the involvement of family and carers in decision making (if the patient agrees, providing they are capable of giving consent).
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 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 United Kingdom.

The clinical features of MND are the result of the degeneration of both the upper and lower motor neurones. Those 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. Dysarthria, dysphagia, fatigability and respiratory insufficiency are usually caused by a combination of lower and upper motor neurone degeneration (Andrews 2009; Jackson and Bryan 1998).

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 are limited for the treatment of MND (Phukan and Hardiman 2008). Although MND is considered incurable, many of the symptoms arising during the course of the disease are treatable, and all efforts should be made to improve quality of life and help maintain the patient'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 the arterial 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 1999; Lyall 2001a). Measures of respiratory muscle weakness are poor predictors of respiratory failure in patients with bulbar symptoms (Lyall 2001a).
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 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-limited ventilator (bilevel positive airway pressure ventilator), a volume-limited ventilator, or a newer non-invasive ventilator such as a proportional assist ventilator (PAV). Bilevel positive airway pressure ventilator devices are commonly used by people with MND in the UK.

The use of non-invasive ventilation by patients with MND varies greatly across North America and Europe (Melo 1999; Bradley 2001; Borasio 2001; Cedarbaum 2001; Chio 2001; Bourke 2002). Evidence from several retrospective and some prospective studies indicates that non-invasive ventilation may be associated with a gain in survival (Pinto 1995; Aboussouan 1997; Kleopa 1999; Bach 2002), improved quality of life (Hein 1997, 1999; Aboussouan 2001; Bourke 2003; Jackson 2001; Lyall 2001b) and improved cognitive function (Newsom-Davis 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 (Cazzoli 1996; Aboussouan 1997).

This short clinical guideline aims to produce evidence-based recommendations on the use of non-invasive ventilation in the management of MND, in order to improve the care and quality of life of people with 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 [XX]) 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. From the 1009 studies, only one study met the inclusion and exclusion criteria (for review protocol and inclusion/exclusion criteria, see appendix 7.7). 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 7.7) 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-Functional Rating Scale (ALS-FRS)  &lt;br&gt; Appel ALS Rating Scale (AARS)  &lt;br&gt; Forced vital capacity (FVC)  &lt;br&gt; Gender  &lt;br&gt; Age  &lt;br&gt; Body mass index  &lt;br&gt; Time since ALS onset  &lt;br&gt; Duration of disease</td>
<td>Chronic hypoventilation</td>
</tr>
</tbody>
</table>

### 2.1.2 Evidence statements

#### 2.1.2.1 There was mixed-quality evidence that gender, age, time since 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 hypersomnolence and/or one of the following:(i) FVC < 50% of predicted value; (ii) PaCO$_2$ $\geq$ 45 mmHg; (iii) arterial oxygen saturation (SaO$_2$) < 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 hypersomnolence and/or one of the following:(i) FVC < 50% of predicted value; (ii) PaCO$_2$ $\geq$ 45 mmHg; (iii) SaO$_2$ < 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) PaCO₂ ≥45 mmHg; iii) nocturnal desaturation (SaO₂ <88% for 5 consecutive mins).

<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>Predictor/variable: Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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 (b)</td>
<td>N</td>
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<tr>
<td>Predictor/variable: Age</td>
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</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>
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<tr>
<td>Predictor/variable: ALS onset (bulbar or spinal)</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 (b)</td>
<td>N</td>
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<tr>
<td>Predictor/variable: BMI</td>
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<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>
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<tr>
<td>Predictor/variable: ALS-Functional Rating Scale score (ALS-FRS)</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>1.16 (0.98, 1.37)</td>
<td>0.9826</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td>Predictor/variable: Appel ALS Rating Scale score (AARS)</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>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>Predictor/variable: Appel ALS Rating Scale (AARS) subgroups* – Rapid group</td>
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<td></td>
</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 (c)</td>
<td>S (d)</td>
</tr>
<tr>
<td>Predictor/variable: Duration of disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [LC]</td>
<td>38</td>
<td>0.98 (0.96, 1.12)</td>
<td>0.0652</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Predictor/variable: FVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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 (mths – median, IQR) = 15 (10-36)
All the patients were followed up to 26 months and the occurrence of chronic hypoventilation was recorded as study endpoint.

[LC] = Lo Coco et al. (2006)
BMI = body mass index
CI = confidence interval
FVC = forced vital capacity
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. (2006) 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 guidance 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**

Ensure that the symptoms and signs listed in table 1 are routinely monitored to detect potential respiratory impairment. Perform respiratory function tests (see recommendations 1.1.8 and 1.1.13) if any of these clinical symptoms and signs are present.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopnoea</td>
<td>Increased respiratory rate</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>Shallow breathing</td>
</tr>
<tr>
<td>Non-refreshing sleep</td>
<td>Weak cough</td>
</tr>
<tr>
<td>Nightmares</td>
<td>Weak sniff</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>Abdominal paradox (inward movement of the abdomen during inspiration)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Use of accessory muscles of respiration</td>
</tr>
<tr>
<td>Poor concentration and/or memory</td>
<td>Reduced chest expansion on maximal inspiration</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Morning headache</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Poor appetite</td>
<td></td>
</tr>
<tr>
<td>Nocturia</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. From the 1009 studies, only five studies met the inclusion and exclusion criteria (for the review protocol and inclusion/exclusion criteria, see appendix 7.7). 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.
impairment in patients with MND with cognitive impairment and/or a diagnosis of dementia. 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&lt;br&gt;VC (seated)&lt;br&gt;MIP&lt;br&gt;MEP</td>
<td>Hypercapnia (defined as PaCO₂ ≥ 6 kPa)</td>
</tr>
<tr>
<td>Pinto (2009)</td>
<td>FVC (sitting)&lt;br&gt;Plmax (sitting)&lt;br&gt;PEmax (sitting)&lt;br&gt;MOP at 100 ms (P0.1)&lt;br&gt;PNamp</td>
<td>Hypercapnia (defined as pCO₂ &gt; 45 mmHg)</td>
</tr>
<tr>
<td>Lyall et al. (2001)</td>
<td>FVC (seating)&lt;br&gt;MIP and MEP&lt;br&gt;Sniff Pdi&lt;br&gt;Sniff Poes&lt;br&gt;SNP&lt;br&gt;Cough Pgas&lt;br&gt;CMS Pdi</td>
<td>Hypercapnia (defined as ELBG CO₂ tension &gt; 6 kPa)</td>
</tr>
<tr>
<td>Lechtzin et al. (2002)</td>
<td>Upright spirometry&lt;br&gt;Supine spirometry&lt;br&gt;Supine and upright FVC&lt;br&gt;MIP&lt;br&gt;MEP&lt;br&gt;PaCO₂,&lt;br&gt;Pdi-sniff&lt;br&gt;Accessory muscle use&lt;br&gt;Abdominal paradox</td>
<td>Abnormal diaphragmatic strength, defined as Pdi-sniff &lt; 70 cmH₂O</td>
</tr>
<tr>
<td>Pinto et al. (1999)</td>
<td>MOP</td>
<td>Nocturnal &lt; 90% O₂ saturation</td>
</tr>
</tbody>
</table>

2 Abbreviations: CMS Pdi, transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; Cough Pgas, cough gastric pressure; ELBG, earlobe blood gas; FVC, forced vital capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; MOP, mouth occlusion pressure; PaCO₂, partial pressure of CO₂ in the arterial blood; Pdi-sniff, maximal sniff transdiaphragmatic pressure; PEmax, maximal expiratory pressure; Plmax, maximal inspiratory pressure; PNamp, 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

From the GDG’s discussion and agreement, RS = reference standard in the evidence statements, and definitions for sensitivity, specificity and positive predictive value are as follows:

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

Detecting hypercapnia in MND patients overall

Evidence statements 2.2.2.1 and 2.2.2.2 refer to GRADE profile 2.

\[ \text{PaCO}_2 \geq 6 \text{ kPa (RS) vs VC + SNIP} \]

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 low positive predictive value for detecting hypercapnia in patients with MND (high-quality evidence).

\[ \text{PaCO}_2 \geq 6 \text{ kPa (RS) vs MIP/MEP} \]

2.2.2.2 Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were not significant tests 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.

\[ \text{ELBG CO}_2 \text{ tension} > 6 \text{ kPa (RS) vs CMS Pdi} \]

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

2.2.2.5 Maximal sniff transdiaphragmatic pressure (Sniff Pdi) at a cut-off of 40 cmH₂O has poor sensitivity, specificity and positive predictive value for detecting hypercapnia in patients with MND [bulbar patients] (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 has good sensitivity, specificity and 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 has good sensitivity, 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 has reasonably good sensitivity and specificity but poor positive predictive value for detecting hypercapnia in patients with MND (moderate-quality evidence).

ELBG CO₂ tension > 6 kPa (RS) vs %VC

2.2.2.9 Vital capacity (VC) at a cut-off of 50% of predicted has poor sensitivity but 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 has 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 has 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 has 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 power) (high-quality evidence).

pCO$_2$ $> 45$ mmHg (RS) vs PImax

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

pCO$_2$ $> 45$ mmHg (RS) vs PEmax

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

pCO$_2$ $> 45$ mmHg (RS) vs MOP

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

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

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

Detecting hypoxaemia in MND patients overall

Nocturnal ≤ 90% \( O_2 \) saturation (RS) vs MOP (refer to GRADE profile 5)

2.2.17 Mouth occlusion pressure (MOP) at a cut-off of 100% has 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 MND patients overall

Evidence statements 2.2.2.18 to 2.2.2.25 refer to GRADE profile 6.

\[ Pdi-sniff < 70 \text{ cmH}_2\text{O (RS) vs supine FVC} \]

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

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

\[ Pdi-sniff < 70 \text{ cmH}_2\text{O (RS) vs upright FVC} \]

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

Pdi-sniff < 70 cmH\textsubscript{2}O (RS) vs MIP

2.2.2.22 Maximal inspiratory pressure (MIP) at a cut-off of < −80 cmH\textsubscript{2}O has good sensitivity and very good specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (very-low-quality evidence).

Pdi-sniff < 70 cmH\textsubscript{2}O (RS) vs PaCO\textsubscript{2}

2.2.2.23 Partial pressure of CO\textsubscript{2} in the arterial blood (PaCO\textsubscript{2}) at a cut-off of > 45 mmHg has very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (very-low-quality evidence).

Pdi-sniff < 70 cmH\textsubscript{2}O (RS) vs accessory muscle use

2.2.2.24 Accessory muscle use (visible contractions of the sternocleidomastoid or scalene muscles in the supine position) has good sensitivity and very good specificity and positive predictive value for detecting abnormal diaphragmatic strength in patients with MND (very-low-quality evidence).

Pdi-sniff < 70 cmH\textsubscript{2}O (RS) vs abdominal paradox

2.2.2.25 Abdominal paradox (the presence of inward movement of the abdomen during inspiration in the supine position) has very good specificity and positive predictive value but poor sensitivity for detecting abnormal diaphragmatic strength in patients with MND (very-low-quality evidence).

Subgroup analysis: detecting hypercapnia in MND patients with bulbar symptoms

Evidence statements 2.2.2.26 to 2.2.2.33 refer to GRADE profile 7.
pCO₂ > 45 mmHg (RS) vs FVC

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

pCO₂ > 45 mmHg (RS) vs PImax

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

pCO₂ > 4  mmHg (RS) vs PEmax

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

pCO₂ > 45 mmHg (RS) vs MOP

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

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

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

2.2.2.33 Forced vital capacity (FVC) at a cut-off of 63.4\% of predicted
together with phrenic nerve motor response amplitude (PNampl) at
a cut-off of −0.25 mV has good sensitivity and reasonably good
specificity but poor positive predictive value for detecting
hypercapnia in MND patients with bulbar symptoms (AUC showed
good discriminative power) (moderate-quality evidence).

Subgroup analysis: detecting hypercapnia in MND patients with spinal
symptoms

Evidence statements 2.2.2.34 to 2.2.2.39 refer to GRADE profile 8.

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

2.2.2.34 Forced vital capacity (FVC) at a cut-off of 80\% of predicted has
reasonably good specificity but poor sensitivity and positive
predictive value for detecting hypercapnia in MND patients with
spinal symptoms (AUC showed poor discriminative power)
(moderate-quality evidence).

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

2.2.2.35 Maximal inspiratory pressure (Plmax) at a cut-off of 60\% of
predicted has very good sensitivity but poor specificity and positive
predictive value for detecting hypercapnia in MND patients with
spinal symptoms (AUC showed fair discriminative power) (high-
quality evidence).
2.2.2.35 \( p_{CO_2} > 45 \text{ mmHg (RS)} \) vs \( P_{Emax} \)

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

2.2.2.36 \( p_{CO_2} > 45 \text{ mmHg (RS)} \) vs MOP

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

2.2.2.37 \( p_{CO_2} > 45 \text{ mmHg (RS)} \) vs \( P_{Nampl} \)

Phrenic nerve motor response amplitude (\( P_{Nampl} \)) at a cut-off of \(-0.4 \text{ mV} \) has good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed fair discriminative power) (moderate-quality evidence).

2.2.2.38 Phrenic nerve motor response amplitude (\( P_{Nampl} \)) at a cut-off of \(-0.37 \text{ mV} \) has good sensitivity and reasonably good specificity but poor positive predictive value for detecting hypercapnia in MND patients with spinal symptoms (AUC showed fair discriminative power) (moderate-quality evidence from one study).

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 MND patients with cognitive impairment and/or a diagnosis of dementia.
### GRADE profile 2: Detecting hypercapnia (defined as PaCO₂ ≥ 6 kPa)

#### Outcome (reference standard): Hypercapnia (defined as PaCO₂ ≥ 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> VC &lt; 49% and SNIP &lt; 26% [n=69]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [C]</td>
<td>16.9</td>
<td>90 (55–99)</td>
<td>73.5 (59–85)</td>
<td>40.9 (23–61)</td>
<td>97.3 (86–99)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>High</td>
</tr>
</tbody>
</table>

**Index test: Maximal inspiratory pressure (MIP)**

| 1 Cohort [C]                  | 16.9           | N/A                         | N/A                         | N/A                | N/A                | Regression analysis p > 0.05 | N           | S (b)        | N            | S (c)        | N                     | Low     |

**Index test: Maximal expiratory pressure (MEP)**

| 1 Cohort [C]                  | 16.9           | N/A                         | N/A                         | N/A                | N/A                | Regression analysis p > 0.05 | N           | S (b)        | N            | S (c)        | N                     | Low     |

Mean (SD) duration of disease (mths) at study entry: Bulbar = 26.3 (23.7); Nonbulbar = 23.7 (11.4)

---

1. [C] = Chaudri et al. (2000)
2. NPV = negative predictive value
3. SD = standard deviation
4. SNIP = sniff nasal inspiratory pressure
5. N = no serious limitation; S = serious limitation; VS = very serious limitation
6. a = cut-off values derived from receiver operating characteristic (ROC) analysis.
7. b = unable to assess inconsistency as diagnostic accuracy not reported, downgrade 1 level.
8. c = unable to assess imprecision as confidence interval not reported, downgrade 1 level.
GRADE profile 3: detecting ventilatory failure (hypercapnia) [defined as earlobe blood gas (ELBG) CO₂ tension of > 6 kPa]

<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 consider.</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test: 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>Index test: 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>Index test: 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>S (b)</td>
<td>N</td>
<td>N</td>
<td>S (c)</td>
<td>N</td>
<td>Low</td>
</tr>
<tr>
<td>Index test: 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 (77–96)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>N</td>
<td>Moderate</td>
</tr>
<tr>
<td>Index test: %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>S</td>
<td>(c)</td>
<td>N</td>
</tr>
<tr>
<td>Index test: Cough Pgas (cut-off: 55 cmH₂O) [n=65]</td>
<td>29.2</td>
<td>68 (43–87)</td>
<td>78 (64–89)</td>
<td>57 (37–74)</td>
<td>86 (71–95)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>(c)</td>
<td>N</td>
</tr>
<tr>
<td>Index test: %VC (cut-off: 50% predicted) [n=65]</td>
<td>29.2</td>
<td>53 (29–76)</td>
<td>89 (76–96)</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>S</td>
<td>(c)</td>
<td>N</td>
</tr>
<tr>
<td>Index test: %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>S</td>
<td>(c)</td>
<td>N</td>
</tr>
<tr>
<td>Index test: Maximal inspiratory pressure (%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>S</td>
<td>(c)</td>
<td>N</td>
</tr>
</tbody>
</table>

Mean duration of disease not reported.

[L] = Lyall et al. (2001)
1. CMS Pdi = transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation
2. Cough Pgas = cough gastric pressure
3. FEV₁ = forced expiratory volume in 1 second
4. MIP, MEP = static inspiratory and expiratory mouth pressures
5. VC = vital capacity
6. Sniff Pdi = maximal sniff transdiaphragmatic pressure
7. Sniff Poes = maximal sniff oesophageal pressure
8. N = no serious limitation; S = serious limitation; VS = very serious limitation
9. a = cut-off values derived from ROC analysis.
10. b = risk of bias as small number study sample, downgrade 1 level.
11. c = wide confidence intervals for estimates of test accuracy (any CIs that covered the range of ≥ 40%), downgrade 1 level.

## GRADE profile 4: detecting 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 (%)</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><strong>Index test</strong>: FVC (cut-off: 80% predicted) [n=199]</td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [P]</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>AUC = 0.723</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Index test</strong>: PImax (cut-off: 60% predicted) [n=199]</td>
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<td></td>
</tr>
<tr>
<td>1 Cohort [P]</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>AUC = 0.671</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Index test</strong>: PEmax (cut-off: 60% predicted) [n=199]</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [P]</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>AUC = 0.626</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Index test</strong>: Mouth occlusion pressure at 100ms (P0.1) [n=199]</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [P]</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 (81–94)</td>
<td>AUC = 0.546</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (b)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Index test</strong>: Phrenic nerve motor response amplitude at -0.4mV (PNamp) [n=199]</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Cohort [P]</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>AUC = 0.772</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

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

[P] = Pinto et al. (2009)

MIP, MEP or PImax, PEmax = static inspiratory and expiratory mouth pressures

FVC = forced vital capacity

N = no serious limitation; S = serious limitation; VS = very serious limitation

a = cut-off values were based on normative limits commonly used in clinical practice.
**GRADE profile 5: detecting hypoxaemia [defined as nocturnal ≤ 90% O₂ saturation measured by pulse oximetry]**

<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>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>S (b)</td>
<td>N</td>
<td>S (c)</td>
<td>S (d)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

*Index test: Mouth occlusion pressure (MOP) (cut-off: MOP 100%) [n=14]*

<table>
<thead>
<tr>
<th>[P] = Pinto et al. (1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a = cut-off values derived from ROC analysis.</td>
</tr>
<tr>
<td>b = unable to assess inconsistency as full details of diagnostic accuracy not reported, downgrade 1 level.</td>
</tr>
<tr>
<td>c = unable to assess imprecision as full details for calculation confidence intervals not available, downgrade 1 level.</td>
</tr>
<tr>
<td>d = pre-test probabilities (prevalence) not reported, risk of bias, downgrade 1 level.</td>
</tr>
</tbody>
</table>
**GRADE profile 6: detecting Abnormal diaphragmatic strength [defined as transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) < 70 cmH₂O]**

<table>
<thead>
<tr>
<th>Outcome (reference standard): Abnormal diaphragmatic strength [defined as transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No. of studies (study design)</th>
<th>[95%CI] (%)</th>
<th>N/A</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>S (f)</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>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>
</tr>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>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>
</tr>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>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>
</tr>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>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>
</tr>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>92</td>
<td>33 (15–55)</td>
<td>100 (16–100)</td>
<td>100 (66–100)</td>
<td>14 (1–36)</td>
<td>N/A</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Index test: Transdiaphragmatic pressure during maximal sniffing (Pdi-sniff) &lt; 70 cmH₂O</td>
<td>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>
</tr>
</tbody>
</table>

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

4  
5  
6  
7  

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4  
5  
6  
7  

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NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 39 of 126
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 confidence intervals for estimates of test accuracy (any CIs that covered the range of \( \geq 40\% \)), downgrade 1 level.
f = high pre-test probabilities, risk of bias, downgrade 1 level.
### GRADE profile 7: Subgroups analysis: detecting hypercapnia [defined as pCO₂ > 45 mmHg]

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 (%) [95%CI] (%)</th>
<th>Specificity (%) [95%CI] (%)</th>
<th>PPV (%) [95%CI] (%)</th>
<th>NPV (%) [95%CI] (%)</th>
<th>Other Analysis (%) [95%CI] (%)</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>BULBAR GROUP: Index test: FVC (cut-off: 80% predicted) [n=68]</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Moderate</td>
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<tr>
<td><strong>BULBAR GROUP: Index test: PImax (cut-off: 60% predicted) [n=68]</strong></td>
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<td></td>
<td></td>
<td></td>
<td>Moderate</td>
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</tr>
<tr>
<td><strong>BULBAR GROUP: Index test: PEmax (cut-off: 60% predicted) [n=68]</strong></td>
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<td></td>
<td></td>
<td></td>
<td>Moderate</td>
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<tr>
<td><strong>BULBAR GROUP: Index test: Mouth occlusion pressure at 100ms (P0.1) (cut-off: 80% predicted) [n=68]</strong></td>
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<td></td>
<td></td>
<td>Moderate</td>
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</tr>
<tr>
<td><strong>BULBAR GROUP: Index test: Phrenic nerve motor response amplitude (PNampl) (cut-off: -0.40mV) [n=68]</strong></td>
<td></td>
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<td></td>
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<td></td>
<td>Moderate</td>
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</tr>
<tr>
<td><strong>BULBAR GROUP: Further logistic regression model: Index test: FVC (cut-off: 63.4% predicted) [n=68]</strong></td>
<td></td>
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<td>Moderate</td>
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<tr>
<td><strong>BULBAR GROUP: Further logistic regression model: Index test: PNampl (cut-off: -0.25mV) [n=68]</strong></td>
<td></td>
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<td></td>
<td>Moderate</td>
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<tr>
<td><strong>BULBAR GROUP: Further logistic regression model: Index test: FVC+PNampl (cut-off: unclear) [n=68]</strong></td>
<td></td>
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<td></td>
<td>Moderate</td>
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<tr>
<td><strong>SPINAL GROUP: Index test: FVC (cut-off: 80% predicted) [n=131]</strong></td>
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<td></td>
<td></td>
<td>Moderate</td>
<td></td>
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</tr>
<tr>
<td>1. Cohort [P]</td>
<td>10.7</td>
<td>50 [23–77] 73.5 [64–81] 18.4 [9–33] 92.5 [85–97]</td>
<td></td>
<td></td>
<td></td>
<td>AUC = 0.680</td>
<td>N N N S (d)</td>
<td>N</td>
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<tr>
<td><strong>SPINAL GROUP: Index test: PImax (cut-off: 60% predicted) [n=131]</strong></td>
<td></td>
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<td></td>
<td>High</td>
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</tr>
<tr>
<td>1. Cohort [P]</td>
<td>10.7</td>
<td>100 [77–100] 35 [26–44] 15.6 [9–24] 100 [91–100]</td>
<td></td>
<td></td>
<td></td>
<td>AUC = 0.730</td>
<td>N N N N N</td>
<td>N</td>
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</tbody>
</table>
**SPINAL GROUP**: Index test: PEmax (cut-off: 60% predicted) \[n=131\]

1 Cohort \[P\] 10.7 71.4 (42–92) 62.4 (53–71) 18.5 (10–31) 94.8 (87–99) AUC = 0.687 N N N N S (d) N Moderate

**SPINAL GROUP**: Index test: Mouth occlusion pressure at 100ms (P0.1) (cut-off: 80% predicted) \[n=131\]

1 Cohort \[P\] 10.7 42.9 (18–71) 52.1 (43–61) 9.7 (5–19) 88.4 (78–95) AUC = <0.5 N N N N S (d) N Moderate

**SPINAL GROUP**: Index test: Phrenic nerve motor response amplitude (PNampl) (cut-off: -0.40mV) \[n=131\]

1 Cohort \[P\] 10.7 71.4 (42–92) 65 (56–74) 19.6 (11–33) 95 (87–98) AUC = 0.797 N N N N S (d) N Moderate

**SPINAL GROUP**: Further logistic regression model: Index test: PNampl (cut-off: -0.37mV) \[n=131\]

1 Cohort \[P\] 10.7 71.4 (42–92) 65 (56–73) 19.6 (11–33) 95 (87–98) AUC = 0.768 N N N N S (d) N Moderate

Mean (SD) duration of disease at study entry [bulbar group] = 12.3 months (7.5) (range: 1-45)
Mean (SD) duration of disease at study entry [spinal group] = 19.76 months (18) (range: 1-72)

1 \[P\] = Pinto et al. (2009)
2 MIP, MEP or PImax, PEmax = static inspiratory and expiratory mouth pressures
3 FVC = forced vital capacity
4 N = no serious limitation; S = serious limitation; VS = very serious limitation
5 a = cut-off values were based on normative limits commonly used in clinical practice.
6 b = further logistic regression model was carried out in the bulbar group 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.
7 c = further logistic regression model was carried out in the spinal group 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.
8 d = wide confidence intervals for estimates of test accuracy (any CIs that covered the range of ≥ 40%), downgrade 1 level.
### Table 5 Summary matrix of GRADE profiles

**HYPERCAPNIA**

<table>
<thead>
<tr>
<th>PaCO$_2$</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
<th>Q</th>
<th>PPV</th>
<th>Spe</th>
<th>Sen</th>
<th>Q</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO$_2$ &gt; 6 kPa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC &lt; 49%+SNIP &lt; 26%</td>
<td>90</td>
<td>73.5</td>
<td>40.9</td>
<td>H</td>
<td>VC</td>
<td>67</td>
<td>89</td>
<td>53</td>
<td>M</td>
<td>VC</td>
<td>50%</td>
</tr>
<tr>
<td>FEV$_1$</td>
<td>58</td>
<td>88</td>
<td>50</td>
<td>M</td>
<td>MIP</td>
<td>56</td>
<td>83</td>
<td>55</td>
<td>M</td>
<td>MIP</td>
<td>25%</td>
</tr>
<tr>
<td>SNP</td>
<td>68</td>
<td>85</td>
<td>81</td>
<td>M</td>
<td>Sniff Pdi</td>
<td>74</td>
<td>87</td>
<td>90</td>
<td>H</td>
<td>Sniff Pdi</td>
<td>30cmH$_2$O</td>
</tr>
<tr>
<td>MIP</td>
<td>56</td>
<td>83</td>
<td>55</td>
<td>M</td>
<td>Sniff Poes</td>
<td>78</td>
<td>91</td>
<td>74</td>
<td>M</td>
<td>Sniff Poes</td>
<td>32cmH$_2$O</td>
</tr>
<tr>
<td>Cough Pgas</td>
<td>57</td>
<td>78</td>
<td>68</td>
<td>M</td>
<td>CMS Pdi</td>
<td>63</td>
<td>78</td>
<td>89</td>
<td>H</td>
<td>CMS Pdi</td>
<td>7cmH$_2$O</td>
</tr>
</tbody>
</table>

Abbreviations: CMS Pdi, transdiaphragmatic pressure after bilateral cervical magnetic phrenic nerve stimulation; Cough Pgas, cough gastric pressure; FEV$_1$, forced expiratory volume in 1 second FVC, forced vital capacity; H, high; L, low; M, moderate; MIP, maximal inspiratory pressure; MOP, mouth occlusion pressure; PaCO$_2$, partial pressure of CO$_2$ in the arterial blood; PEmax, maximal expiratory pressure; Plmax, maximal inspiratory pressure; PNamp, 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; VL, very low
### ABNORMAL DIAPHRAGMATIC STRENGTH

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

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Q Value</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>44</td>
<td>66</td>
<td>80</td>
<td>MOP (100%)</td>
</tr>
</tbody>
</table>

H = high; L = low; M = moderate; MIP, maximal inspiratory pressure; MOP, mouth occlusion pressure; PaCO2, partial pressure of CO2 in the 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

### HYPOXAEMIA

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Q Value</th>
<th>Sen</th>
<th>Spe</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>44</td>
<td>66</td>
<td>80</td>
<td>MOP (100%)</td>
</tr>
</tbody>
</table>

#### 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, 2.2.2.12, 2.2.2.4 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 that baseline respiratory function should be established at the initial
diagnosis of probable MND, and that respiratory function tests should be
carried out every 3 months (although the tests could be performed more or
less often depending on the rate of disease progression and the patient’s
preferences and circumstances).

**Using pulse oximetry to measure oxygen saturation and arterial blood
gas analysis to measure arterial partial pressure of carbon dioxide**

There was an absence of clear evidence on which respiratory function tests
were 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 hypoxaemia) and measurement of the arterial
partial pressure of carbon dioxide (PaCO₂) by arterial blood gas analysis
(used as the reference standard in GRADE profiles 2 and 3 for 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). Hence the GDG agreed that
SpO₂ should be recommended as the first routine respiratory function test,
with a cut-off value of equal to or less than 94% (although a cut-off of ≤ 90%
was used as the reference standard in GRADE profile 5, the GDG felt that the
threshold should be higher in order to be able identify patients earlier)]. The
GDG further agreed that if the patient’s SpO₂ is equal to or less than 94%,
arterial blood gas analysis to measure PaCO₂ should be performed (with a
cut-off value of 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 who cross this threshold should
be seen urgently (within 1 week) by a specialist respiratory service in order to
prevent the possibility of sudden respiratory failure.

**(Forced) vital capacity**
The GDG agreed that there was high-quality evidence that measurement of
vital capacity (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, based on current practice, the guideline should refer to the test as (forced) vital capacity (FVC). Based on the evidence, the GDG agreed that if the patient’s FVC 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 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 and MIP (also called PImax) (evidence statements 2.2.2.1, 2.2.2.4 and 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 discussed and agreed that cmH2O is the actual unit of measurement provided by the machine for both SNIP and MIP, and that to try to provide a formula to calculate % of predicted value in the recommendations 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. Since 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 came to the consensus that, where possible, both tests should be recommended as an option 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 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.


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):

- less than 40 cmH₂O
- less than 65 cmH₂O for men or 55 cmH₂O for women with any symptoms
  or signs of respiratory impairment (see table 1 in recommendation 1.1.7),
  particularly orthopnoea
- if repeated regular tests show a decrease of more than 10 cmH₂O within
  3 months.

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

The GDG agreed that there was high-quality evidence that transdiaphragmatic
pressure (CMS Pdi), maximal sniff transdiaphragmatic pressure (Sniff Pdi)
and phrenic nerve motor response (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 to that obtained using pulse oximetry, arterial blood gas analysis,
and measurement of SNIP and 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 severe bulbar impairment. The GDG noted that
the interfaces used for measuring vital capacity and SNIP/MIP may not be
suitable for patients with severe bulbar impairment. Therefore the GDG came
to the consensus that, as for patients without severe bulbar impairment,
measurement of SpO₂ should be recommended as the first routine respiratory
function test. This should be followed by arterial blood gas analysis to
measure PaCO₂ for patients with SpO₂ of equal to or less than 94%, and
patients with a PaCO₂ greater than 6 kPa should be seen urgently (within
NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 47 of 126
1 week) by a specialist respiratory service. Furthermore, in order to detect respiratory impairment as early as possible for this subgroup with severe bulbar impairment, the GDG also came to the consensus that such patients should be referred for nocturnal (overnight) pulse oximetry and/or a limited sleep study if their PaCO$_2$ is less than 6 kPa but they have any symptoms or signs of respiratory impairment (see table 1 in recommendation 1.1.7), particularly orthopnoea. Both the impact of respiratory impairment and treatment options should also be discussed with the patient and their family and carers (if the patient agrees).

**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 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 vital capacity, 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 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

Patients without severe bulbar impairment and without severe cognitive problems

Recommendation 1.1.8
At initial diagnosis of probable MND, a healthcare professional from the multidisciplinary team with the appropriate competencies should perform respiratory function tests to establish baseline respiratory function (or arrange for these to be performed). These tests should comprise:

- oxygen saturation measured by pulse oximetry (SpO₂)\textsuperscript{7} – this should be a single measurement of SpO₂ with the patient at rest and breathing room air
- forced vital capacity (FVC)\textsuperscript{8}
- sniff nasal inspiratory pressure (SNIP) and/or maximal inspiratory pressure (MIP).

Recommendation 1.1.9
A healthcare professional with the appropriate competencies should perform respiratory function tests (see recommendation 1.1.8) every 3 months to assess and monitor respiratory impairment (although tests could be performed more or less often depending on the rate of disease progression and the patient's preference and circumstances).

Recommendation 1.1.10
If one or more of the results listed in table 2 is obtained when respiratory assessments are performed, discuss with the patient the impact of respiratory impairment, treatment options and possible referral to a specialist respiratory service for further assessment.

Table 2 Results of respiratory assessments

| Forced vital capacity (FVC) | Sniff nasal inspiratory pressure (SNIP) |

\textsuperscript{7} If it is not possible to perform pulse oximetry and/or arterial blood gas analysis locally, refer the patient to a specialist respiratory service.

\textsuperscript{8} The GDG agreed that the difference between the measurement of vital capacity and forced vital capacity is very subtle and that, based on current practice, the guideline should refer to the test as (forced) vital capacity (FVC).
and/or maximal inspiratory pressure (MIP)  
(if both tests are performed, base the assessment on the better respiratory function reading)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC less than 50% of predicted</td>
<td>SNIP or MIP less than 40 cmH₂O</td>
</tr>
<tr>
<td>FVC less than 80% of predicted 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>If repeated regular tests show a decrease in SNIP or MIP of more than 10 cmH₂O within 3 months</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendation 1.1.11**

If the patient’s SpO₂ (measured at rest and breathing room air) is less than or equal to 94%, perform arterial blood gas analysis.

**Recommendation 1.1.12**

If arterial blood gas analysis shows that 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 their family and carers (if the patient agrees).

*Patients with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment*

**Recommendation 1.1.13**

If the patient cannot undergo all of the recommended respiratory function tests (see recommendation 1.1.8) because of severe bulbar symptoms and signs or cognitive problems, ensure that SpO₂ is measured (at rest and breathing room air).

**Recommendation 1.1.14**

If the patient’s SpO₂ is less than or equal to 94%, perform arterial blood gas analysis.
Recommendation 1.1.15
If the patient’s 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 their family and carers (if the patient agrees).

Recommendation 1.1.16
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:

- 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 their family and carers (if the patient agrees).

Patients with a diagnosis of dementia

Recommendation 1.1.17
When making decisions on routine respiratory function tests for patients with MND and a diagnosis of dementia, base these on considerations specific to the patient’s needs and circumstances, such as:

- their ability to give consent⁹
- their understanding of the respiratory function tests
- their tolerance of, and willingness to undertake, the respiratory function tests

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¹From ‘Dementia’ (NICE clinical guideline 42; available from www.nice.org.uk/CG42): Health and social care professionals should always seek valid consent from people with dementia. This should entail informing the person of options, and checking that he or she understands, that there is no coercion and that he or she continues to consent over time. If the person lacks the capacity to make a decision, the provisions of the Mental Capacity Act 2005 must be followed.
tests
- the impact on their family and carers
- whether they are capable of receiving non-invasive ventilation.

2.3 Clinical and cost effectiveness of non-invasive ventilation (NIV) for the treatment of respiratory impairment in patients with MND

2.3.1 Evidence review
A total of 2672 studies were retrieved by the systematic searches. From the 2672 studies, only 12 studies met the inclusion and exclusion criteria (for review protocol and inclusion/exclusion criteria, see appendix 7.7). 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 7.7) 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>
</table>
| Bourke et al. (2006) RCT     | Respiratory criteria (both treatment and control groups): orthopnoea with PImax < 60% of predicted, or symptomatic daytime hypercapnia; Comparison: NIV vs standard care without NIV (subgroup analysis available) | Quality of life: SF-36 (Mental Component Summary)  
Symptom improvement: SAQLI  
Survival (median days) |
| Pinto et al. (1995) Cohort   | Respiratory criteria (both treatment and control groups): onset of abnormalities in diurnal gas exchanges; Comparison: NIV (BiPAP) (group II) vs standard care (oxygen, bronchodilators and other palliative measures) (group I) | Respiratory muscle strength (6–12 months): FVC, VC, PO2, PCO2  
Survival: total survival, % survival from onset of diurnal disorder of gas exchange |
| Mustfa et al. (2006) Cohort   | 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 < 90% for > 55% of sleep time); Comparison: NIV vs no NIV (refused or intolerant) | Survival: mortality at 1 year; adjusted hazard ratio of survival |
| Carrat et al. (2009) Cohort   | Respiratory criteria (both treatment and control groups): FVC < 75%; nocturnal respiratory insufficiency at polysomnography; Comparison: NIV vs no NIV (refused or intolerant) | Survival: 1-year survival rates |
| Kleopa et al. (1999) Cohort   | Respiratory criteria (both treatment and control groups): FVC < 50% of predicted; or if FVC dropped more than 15% within a 3-month period; Comparison: NIV vs no NIV (refused) vs NIV intolerant (fewer hours) (subgroup analysis available) | Survival: in months from initiation/offer of NIV  
Respiratory muscle strength: % FVC decline before and after the initiation/offer of NIV |
| Sivori et al. (2007) Cohort   | Respiratory criteria (both treatment and control groups): symptomatic ventilation impairment (dyspnoea, morning headache, fatigue) plus one of the following: PaCO2 > 45 mmHg, or nocturnal oxygen saturation by pulse oximetry ≤ 88% for 5 continuous minutes, or PImax < 60 cmH2O or FVC < 50%; Comparison: NIV vs no NIV (refused) | Survival: at 10, 20 and 30 months |
| Lo Coco et al. (2006) Cohort   | Respiratory criteria (both treatment and control groups): dyspnoea, morning headache, daytime hypersomnolence, or one of the following: FVC < 50% of predicted, MIP < −60 cmH2O, PaCO2 ≥ 45 mmHg, nocturnal desaturation; Comparison: NIV vs NIV intolerant (fewer hours) | Survival: median (months) after initiation of NIV  
Factor influencing NIV tolerance |
| Aboussouan et al. (1997) Cohort | Respiratory criteria (both treatment and control groups): orthopnoea, hypercapnia or both; PCO2 ≥ 45 mmHg; Comparison: NIV vs NIV intolerant (fewer hours) | Survival: hazard ratios |
| Farrero et al. (2005) Cohort   | Respiratory criteria (both treatment and control groups): occurrence of any of the following: FVC ≤ 50% of predicted or a decrease in FVC of ≥ 500 ml on two consecutive visits, SpO2 < 90% during 5 consecutive minutes, or hypercapnia (PaCO2 > 45 mmHg); Comparison: NIV for patients with non-bulbar MND vs NIV for patients with bulbar MND | Survival of subgroups: mean survival (months) |
| Berlowitz et al. (2006) Cohort | Respiratory criteria (both treatment and control groups): respiratory failure (NIV or tracheostomy); Comparison: NIV vs tracheostomy | Survival: median (months) after initiation of treatment |
| Kaub-Wittemer et al. (2003) | Respiratory criteria (both treatment and control groups): patients recorded to be ventilated (NIV or tracheostomy); NIV vs. TV | Carer’s burden |
Cross-sectional survey

Newson-Davis et al. (2001)

Cohort

<table>
<thead>
<tr>
<th>Respiratory criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group: reduced vital capacity (&lt; 80% of predicted); nocturnal polysomnography showing episodes of nocturnal hypoventilation causing arousals; evidence of abnormal daytime blood gases (PCO₂ &gt; 49 mmHg); bicarbonate &gt; 28 mmol/l; daytime somnolence using Epworth sleepiness scale</td>
</tr>
<tr>
<td>Control group: matched for age and disease severity but with no respiratory difficulty</td>
</tr>
<tr>
<td>NIV vs no NIV</td>
</tr>
</tbody>
</table>

Cognitive performance: list learning, list recall verbal fluency, KOLT

Abbreviations: 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 the arterial blood; PCO₂, partial pressure of carbon dioxide; 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; TV, tracheostomy ventilation; VC, vital capacity

2.3.2 Evidence statements

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 There was very-low-quality evidence from an observational study that showed even patients who were less tolerant to 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 There was very-low-quality evidence from observational studies that showed a positive trend between survival and hours of NIV used. [GRADE profile 10]

2.3.2.4 One very-low-quality 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 There was low-quality evidence from a randomised controlled trial (main evidence) that showed NIV improved quality of life (SF-36 mental component summary) compared with patients who did not useNIV. [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. [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 MND patients with respiratory impairment.

- Some very-low-quality evidence from observational studies showed that NIV did not improve FVC (% of predicted), VC (% of predicted), PO$_2$ or PCO$_2$ compared with no NIV in MND patients after the onset of abnormalities in diurnal gas exchanges.

- Some very-low-quality evidence from observational studies showed that minimum NIV (less than 4 hours per day) significantly improved FVC (% of predicted) compared with no NIV in MND patients with respiratory impairment.

Key outcome: symptom improvement/relief

2.3.2.7 There was low-quality evidence from randomised controlled trial (main evidence) that showed NIV improved sleep quality (compared with no NIV) in MND patients with respiratory impairment, and there was very low-quality evidence from observational study showed that NIV improved cognitive performance (compared to no NIV) in MND patients. [GRADE profile 15]
Subgroup analysis: bulbar and non-bulbar impairment

Key outcome: survival

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

2.3.2.9 There was very-low-quality evidence from an observational study that showed that MND patients with respiratory impairment who had no bulbar impairment had longer survival compared to bulbar patient with respiratory impairment after the initiation of NIV. [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 normocapnia). [GRADE profile 17]

2.3.2.11 There was very-low-quality evidence from an observational study showing that NIV improved survival in both bulbar and limb groups (compared with patients who were less tolerant of NIV [treatment for less than 4 hours per day]). [GRADE profile 18]

Key outcome: quality of life

2.3.2.12 There was low-quality evidence from a randomised controlled trial (main evidence) showing that NIV improved quality of life (SF-36 mental component summary) in MND patients with good bulbar function but not in those with poor bulbar function. [GRADE profile 9]
Key outcome: Symptoms improvement/relief

2.3.2.13 Low-quality evidence from a randomised controlled trial (main
evidence) showed that NIV improved sleep quality in MND patients
regardless of bulbar function. [GRADE profile 20]

Other factors/outcomes

Key outcome: factors that influence tolerance of NIV

2.3.2.14 There was very-low-quality evidence from an observational study
that showed that bulbar involvement influenced tolerance of NIV.
[GRADE profile 21]

Key outcome: carers burden

2.3.2.15 There was very-low-quality evidence from observational study
showed that carers of MND patients 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
carer’s 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.

Key outcome: Survival

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

<table>
<thead>
<tr>
<th>NIV vs no NIV</th>
<th>Key outcome: Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>Design</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
</tr>
<tr>
<td>Outcome: Survival (days) after randomisation</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>[B]</td>
</tr>
<tr>
<td>Outcome: Survival at 6 months and 1 year after the onset of abnormalities in diurnal gas exchanges</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>[P]</td>
</tr>
</tbody>
</table>
### Outcome: Survival at the end of study period (Kaplan-Meier, hazard ratio)

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>NIV</th>
<th>No NIV</th>
<th>HR</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>N</th>
<th>Very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[A]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/18 (50.0%)</td>
<td>20/21 (95.2%)</td>
<td>3.4 (95%CI: 1.5 to 7.9)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

### Outcome: Survival at 1 year (adjusted hazard ratio)

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>NIV</th>
<th>No NIV</th>
<th>HR</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>N</th>
<th>Very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[M]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>4/13 (30.8%)</td>
<td>0/13 (0.0%)</td>
<td>24.9 (95%CI: 11.4 to 54.0)</td>
<td>p = 0.0001</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>N</td>
</tr>
</tbody>
</table>

### Outcome: Survival (months) from the initiation of NIV

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>NIV</th>
<th>No NIV</th>
<th>Mean (SD):</th>
<th>N</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>N</th>
<th>Very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[K]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>38</td>
<td>52</td>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

### Outcome: Survival at 21-30 months after the initiation of NIV

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>NIV</th>
<th>No NIV</th>
<th>RR</th>
<th>S</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>N</th>
<th>Very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5/29 (17.2%)</td>
<td>0/68 (0.0%)</td>
<td>infinity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Outcome: Survival at 11-20 months after the initiation of NIV

<table>
<thead>
<tr>
<th></th>
<th>Cohort</th>
<th>NIV</th>
<th>No NIV</th>
<th>RR</th>
<th>S</th>
<th>N</th>
<th>N</th>
<th>S</th>
<th>N</th>
<th>Very low</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10/29 (34.5%)</td>
<td>11/68 (16.2%)</td>
<td>2.13 (95%CI: 1.01 to 4.46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARI = absolute risk increase; HR = hazard ratio; N = No serious; S = Serious; SC = standard care; VS = Very serious; SC = 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.

Standard care (oxygen, bronchodilators and other palliative measures)

Patients who declined or intolerant to NIV.

In the NIV group, 18/29 were also on riluzole.

In the No NIV group, patients declined NIV but 26/68 were on riluzole.

(i) = study with no blinding.

(ii) = downgraded 1 level as 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).

(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, downgrade 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>Cohort</td>
<td>NIV less tolerant&lt;sup&gt;a&lt;/sup&gt; (38)</td>
<td>No NIV&lt;sup&gt;b&lt;/sup&gt; (52)</td>
<td>Mean (SD): NIV intolerant = 7.0 (6.7) No NIV = 4.6 (12.7) p = 0.038</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious

<sup>a</sup> Patients in the NIV less tolerant group received < 4 hours NIV per day.

<sup>b</sup> Patients who declined NIV.

(i) = unable to assess sample size (OIS), small study sample, downgraded 1 level.


---

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

The clinical effectiveness of NIV for respiratory impairment in patients with MND.

**Key outcome: Survival**

<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>Cohort</td>
<td>NIV (44)</td>
<td>NIV less tolerant&lt;sup&gt;a&lt;/sup&gt; (27)</td>
<td>Median (months) (IQR): NIV = 18 (7–28) NIV intolerant = 6 (3–12) p = 0.0001</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients in the NIV less tolerant group received < 4 hours NIV per day.

(i) = unable to assess sample size (OIS), small study sample, downgraded 1 level.

[LC] = Lo Coco et al. (2006)

### GRADE profile 11: Clinical effectiveness of NIV (NIV vs TV)

#### NIV vs TV

**Key outcome: Survival**

<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>1 [Be]</td>
<td>Cohort</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>

N = No serious; S = Serious; VS = Very serious

TV = tracheostomy ventilation

(i) = unable to assess sample size (OIS), 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)

#### NIV vs no NIV

**Key outcome: Quality of life**

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

<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>1 [B]</td>
<td>RCT</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) – time-weighted improvement (at 12-month 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>1 [B]</td>
<td>RCT</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>

N = No serious; S = Serious; VS = Very 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 above baseline divided by time from randomisation to death.

(i) = study with no blinding.

(ii) = downgraded 1 level as 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 OIS.

[B] = Bourke et al. (2006)
1 Key outcome: Respiratory muscle strength

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

NIV vs no NIV

Key outcome: Respiratory function

<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: Decline of %FVC after the initiation of NIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 [K]</td>
<td>Cohort</td>
<td>NIV (38)</td>
<td>No NIV(^a) (52)</td>
<td>Mean (SD): NIV = -3.5 (5.3) No NIV = -8.3 (5.0) (p &lt; 0.001)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>S (i)</td>
<td>N</td>
<td>Very low</td>
</tr>
</tbody>
</table>

| **Outcome: FVC (%predicted) after the onset of abnormalities in diurnal gas exchanges (at 6–12 months)** |
| 1 [P] | Cohort | NIV (10) | No NIV\(^a\) (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 the onset of abnormalities in diurnal gas exchanges (at 6–12 months)** |
| 1 [P] | Cohort | NIV (10) | No NIV\(^a\) (10) | Mean (SD): NIV = 40.0 (21.2) SC = 35.8 (5.11) \(p = 0.06\) | N | N | N | S (i) | N | Very low |

| **Outcome: PO\(_2\) (mmHg) after the onset of abnormalities in diurnal gas exchanges (at 6–12 months)** |
| 1 [P] | Cohort | NIV (10) | No NIV\(^a\) (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 the onset of abnormalities in diurnal gas exchanges (at 6–12 months)** |
| 1 [P] | Cohort | NIV (10) | No NIV\(^a\) (10) | Mean (SD): NIV = 46.0 (3.4) SC = 45.2 (4.5) \(p = 0.7\) | N | N | N | S (i) | N | Very low |

3 N = No serious; S = Serious; VS = Very serious

4 \(^a\) Patients who declined or intolerant to NIV.

5 Standard care (oxygen, bronchodilators and other palliative measures)

6 \((i)\) = unable to assess sample size (OIS), small study sample, downgraded 1 level.

7 [P] = Pinto et al. (1995)

8 [K] = Kleopa et al. (1999)

9

10 GRADE profile 14: Clinical effectiveness of NIV (NIV less tolerant vs no NIV)

The clinical effectiveness of NIV for respiratory impairment in patients with MND.

Key outcome: Respiratory function

<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: Decline of %FVC after the initiation of NIV</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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### Key outcome: Symptoms improvement/relief

#### GRADE profile 15: Clinical effectiveness of NIV (NIV vs no NIV)

<table>
<thead>
<tr>
<th>NIV vs no NIV</th>
<th>Key outcome: Symptoms improvement/relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of studies</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – duration (days) maintained &gt; 75% of baseline</td>
<td>[B]</td>
</tr>
<tr>
<td>Outcome: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – time-weighted improvement (from AUC)</td>
<td>[B]</td>
</tr>
<tr>
<td>Outcome: Change in cognitive performance – list learning (at 6 weeks)</td>
<td>[ND]</td>
</tr>
<tr>
<td>Outcome: Change in cognitive performance – list recall (at 6 weeks)</td>
<td>[ND]</td>
</tr>
<tr>
<td>Outcome: Change in cognitive performance – Kendrick object learning test (KOLT) (at 6 weeks)</td>
<td>[ND]</td>
</tr>
</tbody>
</table>

---

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

\(^b\) Patients in the NIV less tolerant group received < 4 hours NIV per day

\([K]\) = Kleopa et al. (1999)

N = No serious; S = Serious; VS = Very serious

8 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.

9 Patients in the control group: matched age and disease severity with treatment group but with no respiratory difficulty.

10 Data are median (range) values of AUC above baseline divided by time from randomisation to death.

11 (i) = study with no blinding.

12 (ii) = downgraded 1 level as 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 OIS.

13 (iii) = indirect comparator, as the control group had no respiratory difficulty, downgraded 1 level.
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)

| Outcome: GOOD BULBAR FUNCTION*: Survival (days) after randomisation |
|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration |
| 1 | [B] | RCT | NIV (11) | No NIV (9) | Median (range): NIV = 216 (94-681) SC = 11 (1-283) p = 0.0059 | N (i) | N | N | S (ii) | N | Low |

| Outcome: POOR BULBAR FUNCTION*: Survival (days) after randomisation |
|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision | Other consideration |
| 1 | [B] | RCT | NIV (11) | No NIV (10) | Median (range): NIV = 222 (75-1382) SC = 261 (6-878) p = 0.92 | N (i) | N | N | S (ii) | N | Low |

| Outcome: MODERATE OR SEVERE BULBAR: Survival (months) from the initiation of NIV |
|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision |
| 1 | [A] | Cohort | NIV (6) | No NIV (14) | Hazard ratio: HR = 2.7 (95%CI: 1.1 to 10.6) | N | N | N | S (iii) | S (iv) | Very low |

| Outcome: BULBAR ONSET*: Survival (months) from the initiation of NIV |
|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision |
| 1 | [K] | Cohort | NIV (14) | No NIV (17) | NIV had longer mean survival compared to No NIV (p = 0.01) *actual mean not reported | N | N | N | S (iii) | S (iv) | Very low |

| Outcome: LIMB ONSET*: Survival (months) from the initiation of NIV |
|---|---|---|---|---|---|---|---|---|
| No. of studies | Design | Treatment (n) | Control (n) | Results | Limitations | Inconsistency | Indirectness | Imprecision |
| 1 | [K] | Cohort | NIV (24) | No NIV (35) | NIV had longer mean survival compared to No NIV (p < 0.001) *actual mean not reported | N | N | N | S (iii) | S (iv) | Very low |

N = No serious; S = Serious; VS = Very serious

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

*b 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.

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

*d Patients who declined or intolerant to NIV.

(i) = study without blinding.

(ii) = downgraded 1 level as 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 OIS.

(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)

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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></td>
<td></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>

Outcome: BULBAR VS. NON-BULBAR\(^a\): Survival (months) from the initiation of NIV

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></td>
<td></td>
<td>NIV (14)</td>
<td>NIV less tolerant(^c) (12)</td>
<td>No significant difference between NIV and NIV intolerant (p = 0.07) *actual mean 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>

Outcome: BULBAR ONSET\(^d\): Survival (months) from the initiation of 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 (24)</td>
<td>NIV less tolerant(^c) (20)</td>
<td>NIV had longer mean survival compared to NIV intolerant (p = 0.006) *actual mean 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>

Outcome: LIMB ONSET\(^d\): Survival (months) from the initiation of NIV

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Subgroup analysis: bulbar and non-bulbar impairment

Key outcome: Quality of life

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

### NIV vs no NIV

**Key outcome: Quality of life (subgroup analysis - bulbar vs. non-poor 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: GOOD BULBAR FUNCTION</strong>: SF-36 (Mental component summary) – duration (days) maintained &gt; 75% of baseline</td>
<td>1</td>
<td>RCT</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>
</tr>
<tr>
<td><strong>Outcome: POOR BULBAR FUNCTION</strong>: SF-36 (Mental component summary) – duration (days) maintained &gt; 75% of baseline</td>
<td>1</td>
<td>RCT</td>
<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>
</tr>
<tr>
<td><strong>Outcome: GOOD BULBAR FUNCTION</strong>: SF-36 (Mental component summary) – time-weighted improvement (at 12-month or until death)</td>
<td>1</td>
<td>RCT</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>
</tr>
<tr>
<td><strong>Outcome: POOR BULBAR FUNCTION</strong>: SF-36 (Mental component summary) – time-weighted improvement (at 12-month or until death)</td>
<td>1</td>
<td>RCT</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>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious

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

* Patients in the NIV less tolerant group received < 4 hours NIV per day.

(i) = unable to assess sample size (OIS), small study sample, downgraded 1 level.

(ii) = only p-value was reported, median survival not reported, downgraded 1 level.


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Subgroup analysis: bulbar and non-bulbar impairment

Key outcome: Symptoms improvement/relief

GRADE profile 20: 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>: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – duration (days) maintained &gt; 75% of baseline</td>
<td>1</td>
<td>[B] RCT</td>
<td>NIV (11)</td>
<td>No NIVb (9)</td>
<td>Median (range): NIV = 205 (69–629) SC = 4 (0–143) p = 0.0004</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>: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – duration (days) maintained &gt; 75% of baseline</td>
<td>1</td>
<td>[B] RCT</td>
<td>NIV (11)</td>
<td>No NIVb (10)</td>
<td>Median (range): NIV = 143 (48–1357) SC = 100 (2–703) p = 0.26</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Outcome: GOOD BULBAR FUNCTION</strong>: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – time-weighted improvement (from AUC)</td>
<td>1</td>
<td>[B] RCT</td>
<td>NIV (11)</td>
<td>No NIVb (9)</td>
<td>Median (range): NIV = 1.73 (0.52–2.95) SC = 0 (0–0) p &lt; 0.0001</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>: Sleep apnoea quality-of-life index symptoms domain (SAQLI symptoms domain) – time-weighted improvement (from AUC)</td>
<td>1</td>
<td>[B] RCT</td>
<td>NIV (11)</td>
<td>No NIVb (10)</td>
<td>Median (range): NIV = 0.90 (0–3.20) SC = 0.04 (0–1.14) p = 0.018</td>
<td>N (i)</td>
<td>N</td>
<td>N</td>
<td>S (ii)</td>
<td>N</td>
</tr>
</tbody>
</table>

N = No serious; S = Serious; VS = Very serious

a Bulbar function was assessed with a simple six-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. 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.
c Data are median (range) values of AUC above baseline divided by time from randomisation to death.
(i) = study with no blinding.
(ii) = downgraded 1 level as 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 OIS.
[B] = Bourke et al. (2006)
Other factors/outcomes

Key outcome: Factors that influence NIV tolerance

GRADE profile 21: Clinical effectiveness of NIV (patients who tolerate vs less tolerant)

### Tolerant vs. less tolerant

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

<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>1 [LC]</td>
<td>Cohort</td>
<td>NIV (35/44)</td>
<td>NIV less tolerant (15/27)</td>
<td>Mild/moderate bulbar involvement (vs. severe bulbar involvement) OR = 6.09 (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>

N = No serious; S = Serious; VS = Very serious

*Patients in the NIV intolerant group received < 4 hours NIV per day.

(i) = unable to assess sample size (OIS), small study sample, downgraded 1 level.

[LC] = Lo Coco et al. (2006)

### Key outcome: Carer’s burden

GRADE profile 22: Carer’s burden (NIV vs. TV)

**NIV vs TV**

**Key outcome: Carer’s burden**

<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>1 [KW]</td>
<td>Cross-sectional</td>
<td>NIV (6/32) (19%)</td>
<td>TV (12/20) (60%)</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>
</tbody>
</table>

[NIV = non-invasive ventilation; TV = tracheostomy ventilation; ARR = absolute risk reduction; N = No serious; S = Serious; VS = Very serious]

(i) = unable to assess sample size (OIS), 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 7.12). 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 7.12).

Models

Two models were developed to estimate the cost effectiveness of NIV: the first was based on a Markov model while 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 GDG expert opinion, given the lack of quality clinical evidence.
- 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 and 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 7.12.

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 et al. 2000). This HTA report assumed that patients with MND can progress and regress in a stepwise manner through the model. However, the Guideline Development Group (GDG) considered that patients can only progress and cannot revert to an earlier health state in the model.

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Disease-specific health states were defined and transition probabilities were assigned for movement between these states over a discrete time period (or Markov cycle). Once the model structure (health states, transitions) was set, estimates of resource use and health outcome 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 MND progression.

Randomised control trial 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) and 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 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>

The analysis of the value of information was approximately £40 million. This infers to the amount of money that society would be willing to resolve uncertainty in the cost-effectiveness analysis by undertaking further research in the use of NIV in people with MND.

The incremental cost-effectiveness ratios (ICERs) results of RCT model were obtained by calculating the cost difference and QALY gain obtained using various QALYs with the ‘No NIV’ strategy. The base-case ICERs were between £13,327 and £30,439 per QALY gained when the No NIV quality-of-life profile was varied. Details relating to a deterministic sensitivity analysis in which cost and QALYs were varied for the No NIV strategy can be found in appendix 7.12.

The evidence presented shows 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 considered that because of the model structure and how the treatment effects had been implemented it may underestimate the quality-of-life benefits attributable to NIV. The GDG noted that the RCT model was based on poor data, in particular the absence of data for the standard care arm. The GDG was mindful that the results of the RCT model were highly speculative. The NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 70 of 126
GDG also noted that a limitation of both models were the limitations in 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 estimates obtained using the Markov model were on the higher side, though cost effective, since more accurate capturing of the quality of life would reduce the ICERs much further. Therefore, given the severity of the condition, the lack of alternative options and the difficulty in measuring quality of life in patients with MND, the GDG considered that NIV represented 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 to carry out. 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 because of the reasons mentioned above.

Based on the evidence on improved 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/or their family and carers (if the patient agrees) of both the benefits and limitations of the intervention. The GDG also agreed that treatment should be continued only if symptomatic and/or physiological improvements are achieved.

Although there was low-quality evidence showing that patients with bulbar involvement overall did not benefit 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...
DRAFT FOR CONSULTATION

subgroup analysis) demonstrating that non-invasive ventilation improved
sleep-related symptoms in patients with bulbar involvement. Hence the GDG
agreed that that a trial of non-invasive ventilation should also be considered
for patients with severe bulbar impairment if the patient may benefit from an
improvement in sleep-related symptoms or correction of hypoventilation.

Although the evidence on the improvement of 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 there may be cognitive
improvements with correction of hypoxia and/or hypercapnia. The GDG also
agreed that non-invasive ventilation should only be continued for patients with
severe bulbar impairment or severe cognitive problems if clinical reviews
show an improvement in sleep-related symptoms or 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 this
particular subgroup because of issues such as the patient’s capacity to make
decisions and give consent (see ‘Dementia’ [NICE clinical guideline 42]), the
severity of dementia and cognitive problems, the patient's ability to
understand the purpose of the interfaces and their acceptance of the
treatment, whether the patient is 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 for this subgroup. 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.
2.3.5 Recommendations

**Recommendation 1.1.18**
Consider a trial of non-invasive ventilation based on the patient’s symptoms and signs and the results of the respiratory function tests (see recommendations 1.1.8 to 1.1.16):

- For patients without severe bulbar impairment and without severe cognitive problems, offer a trial of non-invasive ventilation after an informed discussion with the patient and their family and carers (if the patient agrees) of both the benefits and limitations of the intervention.
- For patients with severe bulbar impairment or with severe cognitive problems that may be related to respiratory impairment, consider a trial of non-invasive ventilation if the patient may benefit from an improvement in sleep-related symptoms or correction of hypoventilation, after an informed discussion with the patient and their family and carers (with the patient’s consent if they have the capacity to give it) of both the benefits and limitations of the intervention.

**Recommendation 1.1.20**
Trial non-invasive ventilation at night initially, before and during sleep. Gradually build up the patient’s hours of use as necessary, including daytime use if this is required for symptomatic relief.

**Recommendation 1.1.21**
Only continue non-invasive ventilation if clinical reviews show:

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

*Patients with a diagnosis of dementia*

**Recommendation 1.1.22**
The neurologist from the multidisciplinary team should carry out an assessment before a decision is made on the use of non-invasive ventilation. The assessment should include:

- the patient’s capacity to make decisions and to give consent\textsuperscript{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 carer (with the patient’s consent if they have the capacity to give it).

\textbf{2.4 \textit{Key elements in the management of the use of non-invasive ventilation for patients with MND}}

\textbf{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.

\textbf{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.

\textbf{2.4.3 Evidence to recommendations}

The GDG acknowledged that there is no evidence on 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 key elements in the management of the use of non-invasive ventilation for patients with MND.

\textsuperscript{10} From ‘Dementia’ (NICE clinical guideline 42; available from www.nice.org.uk/CG42): Health and social care professionals should always seek valid consent from people with dementia. This should entail informing the person of options, and checking that he or she understands, that there is no coercion and that he or she continues to consent over time. If the person lacks the capacity to make a decision, the provisions of the Mental Capacity Act 2005 must be followed.
elements of care, including: risk assessment before offering non-invasive ventilation, ongoing monitoring and review of the effectiveness of the treatment, initial hours of 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 and with a comprehensive multidisciplinary care plan. The coordination of care should be led by a healthcare professional within the multidisciplinary team who has a specific interest in MND.

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 physiotherapist, a respiratory physiologist, a speech and language therapist and a specialist in palliative care.
2.4.4 Recommendations

Recommendation 1.1.1
A multidisciplinary team should coordinate and provide ongoing management and treatment for patients with MND, including regular respiratory assessment and provision of non-invasive ventilation. The members of the multidisciplinary team who provide non-invasive ventilation should have the appropriate competencies. The team should:

- include a neurologist, a respiratory physician, an MND specialist nurse, a respiratory specialist nurse, a physiotherapist, a respiratory physiologist, a specialist in palliative care and a speech and language therapist, and have access to other healthcare professionals as needed
- be led by a healthcare professional with a specific interest in MND, who should ensure that the patient's multidisciplinary care plan (see recommendation 1.1.19) is coordinated and communicated to relevant healthcare and social care professionals, including the patient’s primary care team.

Recommendation 1.1.19
Before starting non-invasive ventilation, the multidisciplinary team should carry out and coordinate a patient-centred risk assessment and prepare a comprehensive care plan.

- the risk assessment should consider:
  - which type of non-invasive ventilator and interfaces are appropriate for the patient, based on their needs and lifestyle factors
  - the patient’s tolerance of the treatment
  - the risk of ventilator failure
  - the power supply required, including battery back-up
  - how easily the patient can get to hospital
  - whether a humidifier is required
  - secretion management, including cough-assisted therapy (if required)
  - availability of carers.
• The comprehensive care plan should identify:
  − long-term support provided by the multidisciplinary team (see recommendation 1.1.1)
  − the initial frequency of respiratory function tests and monitoring of respiratory impairment
  − the frequency of clinical reviews of symptomatic and physiological changes
  − arrangements for the maintenance of devices and for 24-hour emergency clinical and technical support
  − training in and support for the use of non-invasive ventilation.

2.5 Information and support needs of patients with MND and their families and carers

2.5.1 Evidence review

A total of 616 studies were retrieved by the systematic searches. From the 616 studies, 11 studies were relevant to the review question, and hence were included. One topic-specific website was also identified (www.healthtalkonline.org) and 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 7.11), 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 qualitative research types (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 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 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 MND patients, and hence patients who had NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 78 of 126
progressive MND with severe disability and 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</td>
<td>Total number of patients and caregivers in study = 46</td>
<td>Information needs from patients and their carers</td>
</tr>
<tr>
<td>(2009) Interview</td>
<td>UK study</td>
<td></td>
</tr>
<tr>
<td>Silverstein et al. (1991)</td>
<td>Total number of patients in study = 38</td>
<td>Preferences for specific evidence; wishes for participating in decisions.</td>
</tr>
<tr>
<td>Structured questionnaire</td>
<td>US study</td>
<td></td>
</tr>
<tr>
<td>Bolmsjo et al. (2003)</td>
<td>Total number of families/close relatives in study = 16</td>
<td>Information on the disease, communication, knowledge of healthcare professionals,</td>
</tr>
<tr>
<td>Interview</td>
<td>Swedish study</td>
<td>information on equipment and assistance.</td>
</tr>
<tr>
<td>Chio et al. (2008)</td>
<td>Total number of participants in study = 120 (60 patients; 60</td>
<td>Information on the disease, research and treatment; communication.</td>
</tr>
<tr>
<td>Structured questionnaire</td>
<td>carers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Italian study</td>
<td></td>
</tr>
<tr>
<td>Hughes et al. (2005)</td>
<td>Total number of participants in study = 29 (9 patients; 5</td>
<td>Experiences of services and suggestions for changes.</td>
</tr>
<tr>
<td>Interview</td>
<td>carers; 15 professionals)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK study</td>
<td></td>
</tr>
<tr>
<td>Johnston et al. (1996)</td>
<td>Total number of patients in study = 50</td>
<td>Information needs; ways of communication.</td>
</tr>
<tr>
<td>Interview</td>
<td>UK study</td>
<td></td>
</tr>
<tr>
<td>McCluskey et al. (2004)</td>
<td>Total number of participants in study = 257 (144 patients; 113</td>
<td>Information needs; end-of-life care.</td>
</tr>
<tr>
<td>Structured questionnaire</td>
<td>carers)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>US study</td>
<td></td>
</tr>
<tr>
<td>Williams et al. (1996)</td>
<td>Total number of carers in study = 19</td>
<td>Carer-specific Information and support needs.</td>
</tr>
<tr>
<td>Interview</td>
<td>US study</td>
<td></td>
</tr>
<tr>
<td>Borasio et al. (1996)</td>
<td>Total number of professionals (neurologists) in study = 74</td>
<td>Communication; structure for delivering information; end-of-life care.</td>
</tr>
<tr>
<td>Structured questionnaire</td>
<td>EU study</td>
<td></td>
</tr>
<tr>
<td>Moss et al. (1996)</td>
<td>Total number of patients in study = 50</td>
<td>End-of-life care.</td>
</tr>
<tr>
<td>Interview</td>
<td>US study</td>
<td></td>
</tr>
<tr>
<td>Wicks et al. (2008)</td>
<td>Total number of participants in study = 334 (247 patients; 87</td>
<td>Information needs; preferences for information.</td>
</tr>
<tr>
<td>Semi-structured questionnaire</td>
<td>US study</td>
<td></td>
</tr>
<tr>
<td>Cox (1992)</td>
<td>Total number of participants in study = 28 (10 patients; 10</td>
<td>Knowledge of services; information and support needs.</td>
</tr>
<tr>
<td>Interview</td>
<td>carers; 8 professionals)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UK study</td>
<td></td>
</tr>
</tbody>
</table>
2.5.2 Evidence statements

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

2.5.2.1 There was mixed-quality qualitative evidence that showed 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 There was mixed-quality qualitative evidence that showed patients and carers need information on 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; and the risk of developing cognitive dysfunction and emotional lability. [Evidence profile 24]

2.5.2.3 There was moderate-quality qualitative evidence that showed patients and carers need support for general domestic care including financial support; use of different equipments; physical or mobility assistance; psychological and emotional support. [Evidence profile 24]

Key outcome: Information and support needs (carer-specific)

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

2.5.2.5 There was mixed-quality qualitative evidence that showed carers need support on the use and maintenance of equipment; respite care; carer coping strategies; counselling; and be able to communicate with healthcare professionals. [Evidence profile 25]

Key outcome: Decision making and end-of-life care

2.5.2.6 There was mixed-quality qualitative evidence that showed patients wanted shared decision making regarding end-of-life care, and NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 80 of 126
end-of-life care should be discussed and planned when appropriate. [Evidence profile 26]

Key outcome: Knowledge and communication among healthcare professionals

2.5.2.7 There was mixed-quality qualitative evidence that showed some healthcare professionals (those who were not specialised in MND but involved in care provision) lacked knowledge of MND and peer communication, including communication between primary and secondary care. [Evidence profile 27]

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 in the studies</th>
<th>Themes 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 individuals and be person-centred.</td>
<td>Overall comments: • Good quality. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total = 46</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x interviews [H][J]</td>
<td>P&amp;C = 64 \ Pr = 15</td>
<td>However, healthcare professionals should aim to give/discuss information as soon as possible.</td>
<td>Overall comments: • [H] Good quality. • [J] No report of data analysis and synthesis methods. • Both studies were transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total = 79</td>
<td></td>
<td></td>
<td></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: • Self-assessment bias (ie. self-report per-determined structured questionnaire). • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x interviews [BH][J]</td>
<td>P&amp;C = 66 \ Total = 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/carers to ask questions</td>
<td>Overall comments: • [B] Good quality. • [J] No report data of analysis and synthesis methods. • Both studies were transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


[BH] = Bolmsjo & Hermerén (2003), Swedish study. Carers only.

P&C = patients and carers; Pr = professionals
### Evidence profile 24: Information and support needs (patients and carers)

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample in the studies</th>
<th>Themes emerged</th>
<th>Study limitations</th>
<th>Indirectness (Transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: Information needs (patients and carers)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 x interviews [HT][H][BH][Co][U] 2 x structured questionnaires [S][C] 1 x structured questionnaire (self-report) [B]</td>
<td>P&amp;C = 304 Pr = 97 Total = 373</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, communication.</td>
<td>Overall comments: Mixed quality as: • Some studies subjected to self-assessment bias or lack of details in methodology. Transferability: not all studies were UK/European studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 x interviews [HT][BH][W] 1 x structured questionnaire [S]</td>
<td>P&amp;C = 119 Total = 119</td>
<td>Information on aids and equipments (eg. for mobility, eating, breathing, communication) and how to access it.</td>
<td>Overall comments: • Good quality interviews and structured questionnaire. • Transferability: not all studies were UK/European studies</td>
<td></td>
<td></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 are the tests/investigations for, at what point they should be carried out, and explaining the results.</td>
<td>Overall comments: Mixed quality as: • 2 studies of good quality [HT][C], [B] was subjected to self-assessment bias or lack of details in methodology. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 x interviews [HT][W][Co] 1 x structured questionnaire (self-report) [MC]</td>
<td>P&amp;C = 332 Total = 322</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 OT, support groups.</td>
<td>Overall comments: Mixed quality as: • Some good quality studies, some were subjected to self-assessment bias or lack of details in methodology. Transferability: not all studies were UK/European studies</td>
<td></td>
<td></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>Overall comments: Mixed quality as: • 3 studies of good quality [HT][H][C], [B] was subjected to self-assessment bias or lack of details in methodology. • Transferable to population addressed.</td>
<td></td>
<td></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>Overall comments: Mixed quality as: • [HT] was of good quality, [B] was subjected to self-assessment bias or lack of details in methodology. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x interview [HT]</td>
<td>P&amp;C = 46 Total = 46</td>
<td>Information on social and financial support ie. benefits</td>
<td>Overall comments: • Good quality. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x semi-structured questionnaire (self-report) [WF]</td>
<td>P&amp;C= 334</td>
<td>Information about, and the risk of developing cognitive dysfunction and emotional lability.</td>
<td>Overall comments: • Self-assessment bias (ie. self-report per-determined structured questionnaire). • Transferability: non-UK study.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Outcome: Support needs (or assistance required) (patients and carers)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sample Size</th>
<th>Support Needs</th>
<th>Overall Comments</th>
</tr>
</thead>
</table>
| 1 x interview [Co] | P&C = 20, Pr = 8, Total = 28 | Support needs or assistance required to manage daily living:  
  - Care support, including domestic assistance and nighttime assistance  
  - Physical/mobility assistance  
  - Use of different equipment, including ventilator support.  
  - Psychological and emotional support  
  - Carry out activities to improve ability  
  - Use of emergency call alarm  
  - OT support  
  - Financial support |  
  - Lack of details on synthesis methods.  
  - Transferable to population addressed. |

Evidence profile 25: Information and support needs (carers specific)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Sample Size</th>
<th>Themes 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></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1 x interview [W] | C = 19, Total = 19 | Support needs or assistance required to manage daily living:  
  - To be able to speak to healthcare professionals alone (without the patients) about their concerns and needs of the patients.  
  - How to use and maintain the aids and equipments. |  |  |  |
| 1 x interview [Co] | C = 10, Pr = 8, Total = 18 | Support needs or assistance required to manage daily living:  
  - Psychological/emotional support and counselling due to strain, stress, frustration and isolation.  
  - Support from respite care  
  - Education and coping strategies as a carer |  |  |  |

Overall comments:
- Self-assessment bias (ie. self-report per-determined structured questionnaire).
- Transferability: non-UK/EU study.

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Evidence profile 26: Decision making and end-of-life care

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample in the studies</th>
<th>Themes emerged</th>
<th>Study limitations</th>
<th>Indirectness (Transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
</table>
| 1 x structured questionnaire [S] | P = 38 Total = 38          | 26/37 patients wanted shared decision-making. Quote: “I prefer to participate in decisions about my own medical care”.
Patients’ preference was stable at 6 months follow up. | Overall comments: • Good quality. • Transferability: non-UK/EU 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.
• 78% of neurologist (out of 74) believed advance directives are useful, and 55% discussed them with patients regularly.
• When advance directives should be discussed:
  - When patients asked for it
  - When respiratory insufficiency is imminent, or
  - When the present of the first respiratory symptoms.
| Overall comments: • Self-assessment bias (ie. self-report per-determined structured questionnaire).
• Transferability: one EU and one US study. |
| 1 x interview [MO] | P = 50 Total = 50 | • 48/50 patients answered questions about advance directives. The topics that were discussed are:
  - 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 to those who had not completed an advance directive. | Overall comments: • Lack of details and incomplete reporting of methodology, unsure whether all analyses were reported.
• Transferability: Non-UK study (it is a US study). |

Evidence profile 27: Knowledge and communication among healthcare professionals

<table>
<thead>
<tr>
<th>No. of studies and study design</th>
<th>Study sample in the studies</th>
<th>Themes emerged</th>
<th>Study limitations</th>
<th>Indirectness (Transferability)</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 x 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 MDT or supportive care staff) who are not specialists (ie. neurologists).</td>
<td>Overall comments: • Both good quality. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x interview [H]</td>
<td>P&amp;C = 14 Pr = 15 Total = 29</td>
<td>There should be better communication and coordination among the MDT, and between primary and secondary care.</td>
<td>Overall comments: • Good quality. • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x structured questionnaire (self-report) [B]</td>
<td>Pr = 74 Total = 74</td>
<td>A plan for follow-up and support should be communicated to patients/carers after diagnosis.</td>
<td>Overall comments: • Self-assessment bias (ie. self-report per-determined structured questionnaire). • Transferable to population addressed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[BH] = Bolmsjo & Hermeren (2003), Swedish study. Carers only.
P&C = patients and carers; Pr = professionals

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 was 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: at the time of or soon after diagnosis of MND; at the point when respiratory monitoring is started; when NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 85 of 126
respiratory function deteriorates; and when the patient asks for information.

The GDG also agreed that recommendations on 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. The GDG discussed and came to the consensus that the principle of ‘staged discussion’ should 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: at the time of or soon after diagnosis of MND; when non-invasive ventilation is accepted or declined; when there is increasing dependence on ventilation; and when the patient asks for information. The GDG further discussed the key elements of discussions about end-of-life care, and they 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 are capable of giving it).
2.5.4 Recommendations

**Recommendation 1.1.2**
Ensure that all relevant healthcare professionals are informed about the key decisions reached with the patient and their family and carers.

**Recommendation 1.1.3**
Offer to discuss the possible use of non-invasive ventilation with the patient and their family and carers (if the patient agrees), 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 of respiratory impairment is started (see recommendation 1.1.9)
- when respiratory function deteriorates
- if the patient asks for information.

**Recommendation 1.1.4**
Provide the patient and their family and carers with information during discussions that is appropriate to the stage of the patient’s illness. This should be provided in a sensitive manner and include information on:

- the possible symptoms and signs of respiratory impairment (see table 1 in recommendation 1.1.7), including the natural progression of MND and what to expect in the future
- the purpose and nature of respiratory function tests, why the patient may be referred for the tests, when the tests will take place and explanations of the test results
- the interventions that are available for managing respiratory impairment, including the benefits and limitations of each intervention
- the use of, and how to access, respiratory equipment, including that for non-invasive ventilation
- alternative palliative strategies.
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 interfaces, such as:
  - emergency procedures
  - night-time assistance if the patient is unable to use the equipment independently (for example, emergency removal or replacement of interfaces)
  - what to do if the equipment fails
- information on general palliative strategies
- assistance with secretion management
- 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; this assessment should include:
  - their ability and willingness to assist in providing non-invasive ventilation
  - their training needs
  - their capability in applying non-invasive ventilation
- have the opportunity to discuss any concerns they may have with members of the multidisciplinary team and/or other healthcare professionals.

Recommendation 1.1.23
Offer to discuss end-of-life care with the patient and their family and carers (if the patient agrees), 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

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

**Recommendation 1.1.24**
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 NIV for MND patients**

Is NIV or standard care more cost effective at improving survival and quality of life in MND patients?

**Why this is important**

More than 50% of patients diagnosed with MND have respiratory symptoms and need some form of respiratory management. Despite the lack of robust evidence for QoL assessment, and a cost analysis for MND patients on NIV, NIV compared with standard care is perceived to be cost effective. A prospective study is required to compare the cost effectiveness of standard NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 89 of 126
care and NIV. The trial should enrol adults aged 60–75 years and classified according to Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS). The primary outcome measures should be quality of life (reported preferably in EQ5D), a thorough cost record at each visit/assessment and the duration of overall survival. Secondary outcome measures should include any adverse events.

3.2 Withdrawing NIV at end of life

What is the most effective and acceptable method for MND patients who wish to discontinue the use of NIV during the course of the disease trajectory and how should this be facilitated and managed?

Why this is important

As more patients receive NIV, there will be increasing numbers of patients who wish to withdraw from treatment when they become more disabled and dependent. This is a very difficult decision for patients and their families, and can also cause distress, conflict and difficulty for professional teams. A mixed-design longitudinal qualitative and quantitative study should be designed to enrol MND patients who are having NIV (and have cognitive ability to participate in interviews and structured questionnaires), their families and carers, as well as healthcare professionals. The outcome measures for the study should be: i) experiences from patients, their family/carers and healthcare professionals on how withdrawals were managed (through case notes review and interviews); ii) quality of life, locus of control and mood (through structured questionnaires and analysed by Structural Equation Modelling).

3.3 Communication

What communication should occur when discussing the use of NIV, particularly what would patients and families wish to be discussed in this communication?

Why this is important
As the guidelines on NIV are developed and used across services there will be the need for increased discussion of the positive and negative aspects of NIV in the management of a patient with MND. There is very little evidence about what occurs in these discussions or what patients and families would wish to be included. This research would enable clearer ideas of the best methods of communication to be developed. A mixed-design longitudinal qualitative and quantitative study should be designed to enrol MND patients are about to commence or are receiving NIV (cognitive ability to participate in interviews and structured questionnaires), and their family and carers. The outcome measures for the study should be: i) experiences of the discussion; ii) how decisions are reached; iii) what would patients and families wish to be discussed; and iv) how to undertake these discussions.

### 3.4 Respiratory function tests

What are the appropriate respiratory function tests to predict and/or diagnose respiratory impairment in MND patients, and how often respiratory function tests should be performed to ensure optimal monitoring?

### 3.5 NIV and MND patients with severe bulbar impairment

What are the effects of NIV on quality of life and survival in patients with severe bulbar impairment?

**Why this is important**

Existing evidence suggests that patients with severe bulbar impairment do not achieve survival benefit from NIV but may benefit in some aspects of 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 bulbar patients may not be based on secure evidence. A randomised controlled trial with long follow-up period should be designed to enrol MND patients with respiratory impairment, both with and without severe bulbar impairment. The enrolled MND patients should be randomised to one of four arms: severe bulbar receiving NIV, severe bulbar without NIV, non-bulbar receiving NIV, and non-bulbar without NIV). Outcomes should include
survival, quality of life, respiratory function, cognitive function, and other sleep-related symptoms.

3.6 Training and education needs

What are the training, education needs and requirements for ongoing support of carers in managing the care for MND patients who are using NIV?

Why this is important

Many patients become dependent on a family member to manage care and equipment. Patients entering another care setting (for example, on respite or in an emergency) feel very vulnerable, particularly as staff may not be familiar with MND or the use of NIV. A mixed-design longitudinal qualitative and quantitative study should be designed to enrol family/carers of MND patients, healthcare professionals, and social care professionals who are involved in delivering the treatment and care to MND patients (eg: in care home, respite, home carers, etc.). The outcomes of the study should be: i) current level of knowledge of MND; ii) training received and current skills to provide NIV; iii) what kind of training, education and support the participants think they need in order to deliver appropriate NIV.

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/CG[XX]FullGuideline). [Note: these details will apply to the published full guideline.]

Quick reference guide

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). [Note: these details will apply when the guideline is published.]

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

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N1[XXX]). [Note: these details will apply when the guideline is published.]

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

5 Related NICE guidance

Published

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


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7.2 Glossary

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

Absolute risk
Measures the probability of an event or outcome occurring (e.g. 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.

Abstract
Summary of a study, which may be published alone or as an introduction to a full scientific paper.

Apnoea
Temporary cessation of breathing lasting 10 seconds or longer.

Appetite
Is the desire to eat food, felt as hunger.

Arterial Blood Gas
Is a blood test that is performed using blood from an artery.

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

Autoimmune disease
Arise from an overactive immune response of the body against substances and tissues normally present in the body.

Baseline
The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are
Best available evidence
The strongest research evidence available to support a particular guideline recommendation.

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

Blinding (masking)
Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.

Body mass index
Is a statistical measure which compares a person's weight and height.

Brainstem
Is the lower part of the brain, adjoining and 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
Comparative observational study in which the investigator selects individuals who have experienced an event (For example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Cognitive impairment
A reduction in intellectual functioning, such as a reduced ability to think, reason or remember. It is not necessarily severe enough to interfere with everyday life.

Cohort study
A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of 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.

Comorbidity
Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

Comparability
Similarity of the groups in characteristics likely to affect the study results (such as health status or age).

Competence
Is the ability to perform a specific task, action or function successfully.

Confidence intervals
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.
Confounding
In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the „confounding variable“) that can influence the outcome independently of the intervention under study.

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. See also Homogeneity.

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)
An economic study design in which consequences of different interventions are measured using a single outcome, usually in „natural” units (For example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

Cough-assisted therapy
Is 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 method 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 (or related to a technology) that might affect their objectivity e.g. if their position or department is funded by a pharmaceutical company.

Dementia
Group of symptoms that is characterised by a decline in intellectual functioning (such as thinking or memory) that is severe enough to interfere with the 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.
Dominance
A term used in health economics describing when an option for treatment is both less clinically effective and more costly than an alternative option. The less effective and more costly option is said to be 'dominated'.

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

Drop-out
A participant who withdraws from a clinical trial before the end.

Drowsiness
Is a state of near-sleep, a strong desire for sleep, or sleeping for unusually long periods.

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

Dysphagia
Difficulty in swallowing.

Dyspnoea
Difficulty breathing.

Economic evaluation
Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and consequences.

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
1 Refers to the pathological expression of laughter, crying, or smiling.

Epidemiological study
3 The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (For example, infection, diet) and interventions.

Equity
7 Fair distribution of resources or benefits.

Evidence based clinical practice
9 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
16 A brief summary of one finding from a review of evidence that a clinical guideline or piece of public health guidance is based on.

Evidence table
19 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)
24 Criteria that define who is not eligible to participate in a clinical study.

Exclusion criteria (literature review)
25 Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Extensor plantar responses
Also known as the Babinski response, is an important neurologic examination based upon what the toes do when the sole (the plantar surface) of the foot is stroked.

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

False negative
A negative result in a diagnostic test when the person being tested does possess the attribute for which the test is conducted.

False positive
A positive result in a diagnostic result when the person being tested does not possess the attribute for which the test is conducted.

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

Fatigue
Medical aspects of tiredness in humans.

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

Forced expiratory volume in 1 second (FEV₁)
This is the maximum volume of air that can forcibly blow out in the first second during the FVC manoeuvre, measured in litres.
Frequency
In media campaigns: the average number of times an audience could see or hear a specific media message during a specific period of time, based on its planned placement.

Gag reflex
Is a reflex contraction of the back of the throat, 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.

Genetics
The science of genes, heredity, and the variation of organisms.

Guideline Development Group
A group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines Technical Team who develop the recommendations for a clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Hallucinations
Is a perception in the absence of a stimulus.

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

Homogeneity
This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hyperactive reflexes
Reflexes that persist too long and may be too strong.

Hypercapnia
Is a condition where there is too much carbon dioxide (CO2) in the blood.

Hyper-somnolence
Is excessive sleepiness.

Hyporeflexia
Is the condition of below normal or absent reflexes.

Hypoventilation
Occurs when ventilation is inadequate (hypo means "below") to perform needed gas exchange.

Hypoxaemia
Is generally defined as decreased partial pressure of oxygen in blood

Hypoxia
A pathological condition in which the body as a whole or 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. It is the number of instances of persons falling ill during a given time in a specified population. It is often expressed as rates per million population.

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

Incremental analysis
The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost
The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost effectiveness ratio (ICER)
The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Incremental net benefit (INB)
The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Index
In epidemiology and related sciences, this word 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.

Indication (specific)
The defined use of a technology as licensed by the Medicines and Healthcare products Regulatory Agency (MHRA).

Inspiration
The movement of air into the lungs.

Intention-to-treat analysis (ITT analysis)
An analysis of the results of a clinical study in which the data are analysed for all study participants as if they had remained in the group to which they were randomised, regardless of whether or not they remained in the study until the end, crossed over to another treatment or received an alternative intervention.
Internal validity
The degree to which the results of a study are likely to approximate the "truth" for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and is a prerequisite for applicability (external validity) of a study’s findings.

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.

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
Measure of the strength of respiratory muscles, obtained by having the patient exhale as strongly as possible against a mouthpiece; the maximum value is near total lung capacity.

Maximal inspiratory pressure
A measure of the strength of 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 rates
The proportion of deaths in a defined population.

Motor cortex
Is a term that describes regions of the cerebral cortex involved in the planning, control, and execution of voluntary motor functions.
Motor neurone disease
A term covering a number of progressive conditions involving the selective
degeneration of motor neurones; other types of nerves are not affected.

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.

Nightmares
Also known as a "bad dream", is an unpleasant dream.

Nocturia
Is the need to get up during the night in order to urinate, 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 a mouth-piece, which is connected to a ventilator by tubing. The
ventilator senses when the patient tries to take a breath in and delivers an
extra flow of air to increase the volume of air inhaled

Normocapnia
Is a state of normal arterial carbon dioxide pressure.
Number needed to treat to benefit (NNTB)

NNTB is an epidemiological measure used in assessing the effectiveness of a health-care intervention, typically a treatment with medication. The NNTB is the number of patients who need to be treated in order to prevent one additional bad outcome (i.e. the number of patients that need to be treated for one to benefit compared with a control in a clinical trial). It is defined as the inverse of the absolute risk reduction. The ideal NNTB is 1, where everyone improves with treatment and no-one improves with control. The higher the NNTB, the less effective is the treatment.

Number needed to treat to harm (NNTH)

NNTH is an epidemiological measure that indicates how many patients need to be exposed to a risk-factor to cause harm in one patient that would not otherwise have been harmed. It is defined as the inverse of the attributable risk. Intuitively, the lower the number needed to harm, the worse the risk-factor.

Observational study

Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.

Orthopnoea

Is shortness of breath (dyspnoea) which occurs when lying flat.

Oxygen saturation

A clinical measure of the amount of oxygen in a patient's blood.

Palliative care

Treatment to relieve the symptoms of a serious illness. It aims to keep patients comfortable, improve quality of life and provide support rather than to treat the disease itself.

Paralysis

Is the complete loss of muscle function for one or more muscle groups.
Partial pressure of Carbon dioxide (PaCO₂)
This measures 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)
This measures the pressure of oxygen 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
Used to describe 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. 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
Is a non-invasive method allowing the monitoring of the oxygenation of a patient's hemoglobin.

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 there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.

Randomised controlled trial
A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

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

Relative risk
Also known as risk ratio; the ratio of risk in the intervention group to the 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 in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Retrospective study
A retrospective study deals with the present/past and does not involve studying future events. This contrasts with studies that are prospective.

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 participants are selected for inclusion in a study.

Selection bias (also allocation bias)

A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.

Selection criteria

Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Semi-structured interview

Structured interviews involve asking people pre-set questions. A semi-structured interview allows more flexibility than a structured interview. The interviewer asks a number of open-ended questions, following up areas of interest in response to the information given by the respondent.

Sensitivity

In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient 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 those who get 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 for exploring the generalisability of results to other settings. The analysis is repeated using NIV for MND: NICE clinical guideline DRAFT (February 2010) Page 116 of 126
different assumptions to examine the effect on the results. One-way simple
sensitivity analysis (univariate analysis): each parameter is varied individually
in order to isolate the consequences of each parameter on the results of the
study. Multi-way simple sensitivity analysis (scenario analysis): two or
more parameters are varied at the same time and the overall effect on the
results is evaluated. Threshold sensitivity analysis: the critical value of
parameters above or below which the conclusions of the study will change are
identified. Probabilistic sensitivity analysis: probability distributions are
assigned to the uncertain parameters and are incorporated into evaluation
models based on decision analytical techniques (For example, Monte Carlo
simulation).

Sign
Is an objective indication of some medical fact or characteristic that may be
detected by a physician during a physical examination of a patient.

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

Sniff nasal inspiratory pressure
Is one of the newer measures of inspiratory muscle strength.

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

Specificity
In diagnostic testing, it refers to the chance of having a negative test result
given that you do not have the disease. 100% specificity means that all those
without the disease will test negative, but this is not the same the other way
around. A patient 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 those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its Sensitivity must also be considered.

**Spinal cord**
Is a long, thin, tubular bundle of nervous tissue and support cells that extends from the brain.

**Spirometry**
Is the most common of the Pulmonary Function Tests (PFTs), measuring lung function.

**Standard deviation**
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% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 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. See also P value.

**Structured interview**
A research technique where the interviewer controls the interview by adhering strictly to a questionnaire or interview schedule with pre-set questions.

**Synthesis of evidence**
A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
**Systematic error**
Refers to the various errors or biases inherent in a study. See also Bias.

**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.

**Systemic**
Involving the whole body.

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

**Treatment allocation**
Assigning a participant to a particular arm of the trial.

**Utility**
A measure of the strength of an individual’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 value.

**Validity**
Assessment of how well a tool or instrument measures what it is intended to measure. See also External validity, Internal validity.

**Variable**
A measurement that can vary within a study, e.g. 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.
1 **Ventilator**
2 May be defined as any machine designed to mechanically move breathable air into and out of the lungs, to provide the mechanism of breathing for a patient who is physically unable to breathe, or breathing insufficiently.

5 **Vital capacity**
6 Is the maximum amount of air a person can expel from the 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>BDI</td>
<td>Baseline dyspnoea index</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$_1$</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>MEP</td>
<td>Maximal expiratory pressure</td>
</tr>
<tr>
<td>MIP</td>
<td>Maximal inspiratory pressure</td>
</tr>
<tr>
<td>MND</td>
<td>Motor neurone disease</td>
</tr>
<tr>
<td>MNDA</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>
</tr>
<tr>
<td>PaCO$_2$</td>
<td>Partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PAV</td>
<td>Proportional assist ventilator</td>
</tr>
<tr>
<td>PCO$_2$</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>Plmax</td>
<td>Maximal inspiratory pressure</td>
</tr>
<tr>
<td>PNamp</td>
<td>Phrenic nerve motor response amplitude</td>
</tr>
<tr>
<td>PO$_2$</td>
<td>Partial pressure of oxygen</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
</tbody>
</table>
8 Contributors

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8.2 The short clinical guidelines technical team

A short clinical guidelines technical team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments. The following NICE employees made up the technical team for this guideline.

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8.3 The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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8.4 Declarations of interest

A full list of all declarations of interest made by this Guideline Development Group is available on the NICE website (www.nice.org.uk).

8.5 Authorship and citation

Authorship of this document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the Guideline Development Group under group authorship.

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